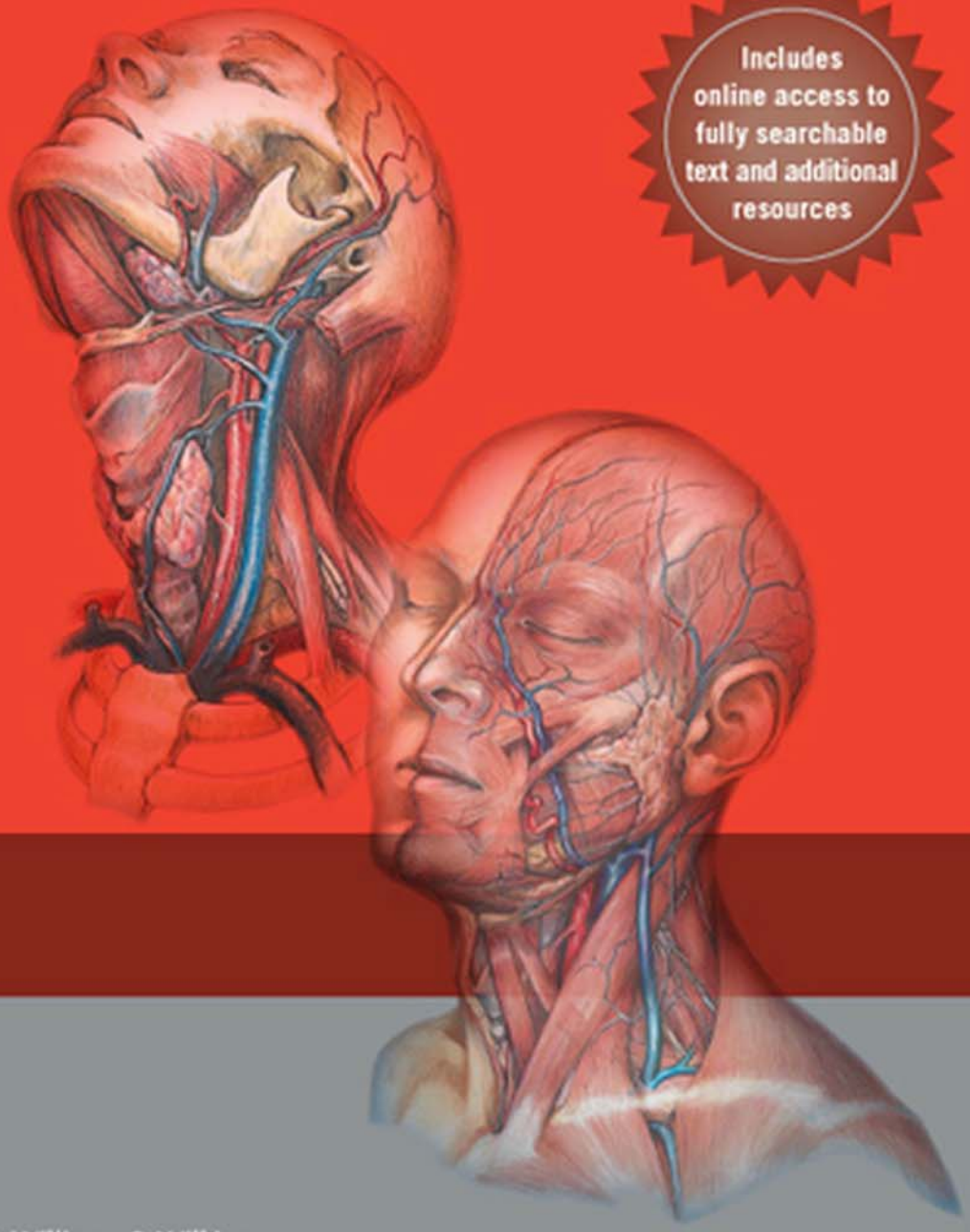
VOLUME ONE

Bailey's Head & Neck Surgery
OTOLARYNGOLOGY

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Milan Amin
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Berrylin Ferguson
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Radiology

Barton F. Branstetter

VOLUME ONE

Bailey's Head and Neck Surgery—OTOLARYNGOLOGY

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JONAS T. JOHNSON, MD

Professor and Chairman, Department of Otolaryngology
The Dr. Eugene N. Myers Professor and Chairman of Otolaryngology
Professor, Department of Radiation Oncology, University of Pittsburgh School of Medicine
Professor, Department of Oral and Maxillofacial Surgery, University of Pittsburgh School of Dental Medicine
Pittsburgh Pennsylvania

CLARK A. ROSEN, MD

Professor, Department of Otolaryngology
University of Pittsburgh Medical Center
Director, University of Pittsburgh Voice Center
Professor, Department of Communication Sciences Disorders
University of Pittsburgh
Pittsburgh, Pennsylvania

380 Contributors

Illustrations by Victoria J. Forber, Anthony Pazos and Christine Gralapp



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Manufacturing Manager: Beth Welsh
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CONTRIBUTING AUTHORS

MEREDITH E. ADAMS, MD Assistant Professor, Departments of Otolaryngology–Head and Neck Surgery and Neurosurgery, University of Minnesota; Attending Surgeon, Departments of Otolaryngology–Head and Neck Surgery and Neurosurgery, University of Minnesota Medical Center, Fairview, Minneapolis, Minnesota

PETER A. ADAMSON, BSc, MD, FRCSC, FACS Professor, Head, Division of Facial Plastic and Reconstructive Surgery, Department of Otolaryngology–Head and Neck Surgery, University of Toronto, Toronto, Ontario, Canada

ROBERT T. ADELSON, MD Chief, Division of Facial Plastic and Reconstructive Surgery, Assistant Professor, Department of Otolaryngology, University of Florida College of Medicine, Gainesville, Florida

OLIVER F. ADUNKA, MD Associate Professor, Department of Otolaryngology–Head and Neck Surgery, University of North Carolina at Chapel Hill; Attending Physician, Department of Otolaryngology–Head and Neck Surgery, UNC Health Care, Chapel Hill, North Carolina

AMIT AGRAWAL, MD Associate Professor, Department of Otolaryngology–Head and Neck Surgery, The Ohio State University; Attending Surgeon, Department of Otolaryngology–Head and Neck Surgery, Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, The Ohio State University Wexner Medical Center, Columbus, Ohio

YURI AGRAWAL, MD Assistant Professor, Division of Otology, Neurotology and Skull Base Surgery, Department of Otolaryngology–Head and Neck Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland

EUGENIO A. AGUILAR III, MD Professor, Division of Plastic Surgery, Department of Surgery, Baylor College of Medicine, Houston, Texas

CUNEYT M. ALPER, MD Professor, Departments of Otolaryngology, University of Pittsburgh School of Medicine; Pediatric Otolaryngologist, Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania

H. ALEXANDER ARTS, MD Professor, Department of Otolaryngology and Neurosurgery, University of Michigan, Ann Arbor, Michigan

MILAN R. AMIN, MD Associate Professor, Department of Otolaryngology–Head and Neck Surgery, New York University School of Medicine; Associate Professor, Department of Otolaryngology–Head and Neck Surgery, NYU Langone Medical Center, New York, New York

SAMANTHA ANNE, MD, MS Assistant Professor of Surgery, Head and Neck Institute, Cleveland Clinic Foundation, Cleveland, Ohio

PATRICK J. ANTONELLI, MD, MS Professor and Chair, Department of Otolaryngology, University of Florida; Chair, Department of Otolaryngology, Shands at the University of Florida, Gainesville, Florida

ABBAS A. ANWAR, MD Resident Physician, PGY-1, Department of Otolaryngology–Head and Neck Surgery, New York University Langone Medical Center, New York, New York

ALFREDO S. ARCHILLA, MD Director, Center for Advanced Sinus and Nasal Care, Otolaryngology Consultants, PA, Boynton Beach, Florida

BEHRAD B. AYNEHCHI, MD Assistant Clinical Instructor, Department of Otolaryngology–Head and Neck Surgery, SUNY Downstate Medical Center, Brooklyn, New York

ALESSANDRO DE ALARCÓN, MD, MPH Assistant Professor, Department of Otolaryngology, University of Cincinnati College of Medicine; Assistant Professor, Department of Otolaryngology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

CRISTINA M. BALDASSARI, MD, FAAP Assistant Professor, Department of Pediatric Otolaryngology, Eastern Virginia Medical School; Assistant Professor, Department of Pediatric Otolaryngology, Children's Hospital of the King's Daughters, Norfolk, Virginia

DAVID M. BARRS, MD Consultant, Department of Otolaryngology, Mayo Clinic Arizona, Phoenix, Arizona

PETE S. BATRA, MD, FACS Associate Professor, Department of Otolaryngology–Head and Neck Surgery, University of Texas Southwestern Medical Center; Co-Director, Comprehensive Skull Base Program, University Hospitals, Dallas, Texas

REGINALD BAUGH, MD Professor, Department of Surgery, The University of Toledo; Chief, Division of Otolaryngology–Head and Neck Surgery, University of Toledo Medical Center, Toledo, Ohio

ADAM M. BECKER, MD Assistant Professor of Surgery, Division of Otolaryngology, Department of Surgery, Duke University Medical Center, Durham, North Carolina

PETER C. BELAFSKY, MD, MPD, PhD Professor, Department of Otolaryngology–Head and Neck Surgery, University of California, Davis Medical Center, Sacramento, California

JOHN P. BENT, MD Associate Professor, Department of Otolaryngology–Head and Neck Surgery, Albert Einstein College of Medicine; Director, Division of Pediatric Otolaryngology, Children's Hospital at Montefiore, Bronx, New York

AARON J. BERGER, MD, PhD Chief Resident, Division of Plastic Surgery, Department of Surgery, Stanford Hospital and Clinics, Palo Alto, California; Chief Resident, Division of Plastic Surgery, Department of Surgery, Stanford Hospital and Clinics, Stanford, California

ARNAUD F. BEWLEY, MD Head and Neck/Microvascular Fellow, Department of Otolaryngology–Head and Neck Surgery, Medical University of South Carolina, Charleston, South Carolina

MIHIR KIRAN BHAYANI, MD Clinical Assistant Professor, Department of Surgery, Pritzker School of Medicine, University of Chicago, Chicago, Illinois; Otolaryngologist, Department of Surgery, Kellogg Cancer Center, North Shore University Health System, Evanston, Illinois

BENJAMIN S. BLEIER, MD Assistant Professor, Department of Otology and Laryngology, Harvard Medical School, Boston, Massachusetts

JOEL H. BLUMIN, MD, FACS Associate Professor and Chief, Division of Laryngology and Professional Voice, Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin, Milwaukee, Wisconsin

A. BRADLEY BOLAND, MD Professor, Department of Surgery, University of Mississippi Medical Center, Jackson, Mississippi

MARK BOSTON, MD Pediatric Otolaryngologist, San Antonio Military Medical Health System, San Antonio, Texas

MATTHEW A. BOWEN, MD Resident Physician, Department of Otolaryngology–Head and Neck Surgery, Louisiana State University Health Sciences Center, New Orleans, Louisiana

SUSAN BAKER BREHM, PhD Associate Professor, Department of Speech Pathology and Audiology, Miami University, Oxford, Ohio; Research Associate, Department of Speech Language Pathology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

D. BRADLEY WELLING, MD, PhD, FACS Professor and Chair, Department of Otolaryngology–Head and Neck Surgery, The Ohio State University; Professor, Department of Otolaryngology–Head and Neck Surgery, The Ohio State University Wexner Medical Center, Columbus, Ohio

BARTON F. BRANSTETTER, MD Professor of Radiology, Otolaryngology, and Biomedical Informatics, Department of Radiology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

JEAN BRERETON, MBA Senior Director, Research and Quality, American Academy of Otolaryngology–Head and Neck Surgery, Alexandria, Virginia

HILARY A. BRODIE, MD, PhD Professor and Chairman, Division of Otology and neurotology, Department of Otolaryngology, UC Davis Health System, Sacramento, California

CRAIG A. BUCHMAN, MD, FACS Harold C. Pillsbury Distinguished Professor, Department of Otolaryngology and Head and Neck Surgery, University of North Carolina at Chapel Hill; Physician Service Leader, Department of Otolaryngology–Head and Neck Surgery, UNC Health Care, Chapel Hill, North Carolina

JEFFREY M. BUMPOUS, MD Professor and Chief, Division of Otolaryngology–Head and Neck Surgery, School of Medicine, University of Louisville, Louisville, Kentucky

MATTHEW L. BUSH, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, University of Kentucky; Chief of Otolaryngology, Department of Surgery, Veterans Affairs Medical Center, Lexington, Kentucky

STEVEN B. CANNADY, MD Assistant Professor, Department of Otolaryngology, SUNY Downstate Medical Center; Chief, Head and Neck Surgery at University Hospital Brooklyn, Department of Otolaryngology, SUNY Downstate Medical Center, Brooklyn, New York

RANDOLPH B. CAPONE, MD Director, Baltimore Center for Facial Plastic Surgery, Baltimore, Maryland

JOHN P. CAREY, MD Professor, Chief, Division of Otology, Neurotology, and Skull Base Surgery, Department of Otolaryngology–Head and Neck Surgery, Johns Hopkins Hospital, Baltimore, Maryland

RICARDO L. CARRAU, MD Professor, Department of Otolaryngology, The Ohio State University College of Medicine; Director of the Comprehensive Skull Base Surgery Program, Department of Otolaryngology, The Ohio State University Wexner Medical Center, Columbus, Ohio

RYAN CASE, MD Resident, Department of Otolaryngology and Communicative Sciences, University of Mississippi Medical Center, Jackson, Mississippi

MARGARETHA L. CASSELBRANT, MD, PhD Eberly Professor of Pediatric Otolaryngology, Department of Otolaryngology, University of Pittsburgh School of Medicine; Director, Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania

MOHAMAD RAAFAT CHAABAN, MD Rhinology Fellow/Instructor, Division of Otolaryngology–Head and Neck Surgery, Department of Surgery, University of Alabama at Birmingham, Birmingham, Alabama; Director, Lanier Nasal & Sinus Institute, Valley, Alabama

ZAHI ABOU CHACRA, MD Surgeon, Department of Otolaryngology, Westmount Square Medical Center, Westmount, Quebec, Canada

RAYMOND L. CHAI, MD Resident, Department of Otolaryngology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

JAMES CHAN, MD Department of Otolaryngology–Head and Neck Surgery, Providence Medical Center, Portland, Oregon

TERESA V. CHAN, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, University of Texas Southwestern Medical Center; Chief, Department of Otolaryngology–Head and Neck Surgery, Parkland Health and Hospital System, Dallas, Texas

KAY W. CHANG, MD Associate Professor, Department of Otolaryngology, Stanford University, Stanford, California

HENRY HAIPEI CHEN, MD, MBA Attending Physician, Department of Otolaryngology–Head and Neck Surgery, Cedars-Sinai Medical Center, Los Angeles, California

ALAN G. CHENG, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, Stanford University School of Medicine, Stanford, California

DOUGLAS B. CHEPEHA, MD, MSPH, FRCSC Professor and Director of Microvascular, Reconstructive Surgery, Department of Otolaryngology–Head and Neck Surgery, University of Michigan, Ann Arbor, Michigan

DAVID H. CHI, MD Assistant Professor, Department of Otolaryngology, University of Pittsburgh School of Medicine; Pediatric Otolaryngologist, Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania

ALEXANDER G. CHIU, MD Professor and Chief, Division of Otolaryngology–Head and Neck Surgery, Arizona Health Science Center, University of Arizona, Tucson, Arizona

RAYMOND I. CHO, MD, FACS Assistant Professor, Department of Surgery, Uniformed Services University of the Health Sciences; Director, Oculoplastic and Orbital Surgery, Department of Ophthalmology, Walter Reed National Military Medical Center, Bethesda, Maryland

RICHARD A. CHOLE, MD, PHD Lindburg Professor and Head, Department of Otolaryngology, Washington University School of Medicine; Chief, Department of Otolaryngology, Barnes-Jewish Hospital, St Louis, Missouri

DANIEL T. T. CHUA, MBCHB, MD, FRCR, FHKCR, FHKAM Associate Director, Comprehensive Oncology Centre, Associate Director, Department of Radiotherapy, Department of Medicine, Department of Radiotherapy, Hong Kong Sanatorium and Hospital, Hong Kong SAR

WILLIAM L. CHUNG, DDS, MD Associate Professor, Department of Oral and Maxillofacial Surgery, School of Dental Medicine, University of Pittsburgh; Associate Professor, Department of Oral and Maxillofacial Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

ALIZA P. COHEN, MA Medical Writer, Division of Pediatric Otolaryngology–Head and Neck Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

DAVID E. CONRAD, MD Resident, Department of Otorhinolaryngology–Head and Neck Surgery, Albert Einstein College of Medicine–Montefiore Medical Center, Bronx, New York

MAURA K. COSETTI, MD Assistant Professor, Departments of Otolaryngology–Head and Neck Surgery and Neurosurgery, Shreveport, Louisiana

MARK S. COUREY, MD Professor, Department of Otolaryngology–Head and Neck Surgery, University of California, San Francisco; Director, Division of Laryngology, University of California, San Francisco, San Francisco, California

BENJAMIN T. CRANE, MD, PHD Assistant Professor, Department of Otolaryngology, Bioengineering, Neurobiology and Anatomy, University of Rochester; Assistant Professor, Department of Otolaryngology, Strong Memorial Hospital, Rochester, New York

BRIANNA K. CRAWLEY, MD Chief Resident, Department of Surgery, University of New Mexico; Department of Surgery, University of New Mexico Health Sciences Center, Albuquerque, New Mexico

MICHAEL CUNNINGHAM, MD Professor, Department of Otology and Laryngology, Harvard Medical School; Otolaryngologist in Chief, Department of Otolaryngology and Communication Enhancement, Boston Children's Hospital, Boston, Massachusetts

J. DAVID KRIET, MD, FACS WS and EC Jones Chair in Craniofacial Reconstruction, Associate Professor, Director, Division of Facial Plastic and Reconstructive Surgery, Department of Otolaryngology–Head and Neck Surgery, University of Kansas School of Medicine, Kansas City, Kansas

RICHARD E. DAVIS, MD Voluntary Professor of Otolaryngology, Department of Otolaryngology, University of Miami, Miller School of Medicine, Miami, Florida

ALEXANDER J. DAVIT III, MD Assistant Professor, Department of Plastic Surgery, University of Pittsburgh School of Medicine; Attending, Department of Plastic Surgery, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania

SAMANTHA DEMAURO-JABLONSKI, MD Clinical Assistant Professor, Internal Medicine, University of Pittsburgh; Clinical Assistant Professor, Internal Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

CRAIG S. DERKAY, MD, FACS Professor, Department of Otolaryngology–Head and Neck Surgery, Eastern Virginia Medical School; Director, Department of Pediatric Otolaryngology, Children's Hospital of the King's Daughters, Norfolk, Virginia

DANIEL G. DESCHLER, MD, FACS Professor, Department of Otology and Laryngology, Harvard Medical School; Director, Division of Head and Neck Surgery, Department of Otolaryngology–Head and Neck Surgery, Massachusetts Eye and Ear Infirmary/Massachusetts General Hospital, Boston, Massachusetts

RODNEY C. DIAZ, MD Assistant Professor, Department of Otolaryngology, UC Davis Health System, Sacramento, California

HENRY R. DIGGELMANN, MD Chief Resident, Department of Otolaryngology–Head and Neck Surgery, University of Iowa Hospitals and Clinics, Iowa City, Iowa

TATIANA K. DIXON, MD Fellow, Division of Facial Plastic and Reconstructive Surgery, Department of Otolaryngology–Head and Neck Surgery, University of Illinois at Chicago, Chicago, Illinois

ROBERT A. DOBIE, MD Clinical Professor, Department of Otolaryngology, University of Texas Health Science Center at San Antonio, San Antonio, Texas

TIMOTHY D. DOERR, MD, FACS Associate Professor and Program Director, Department of Otolaryngology–

Head and Neck Surgery, University of Rochester School of Medicine; Director of Facial Plastic Surgery, Department of Otolaryngology, University of Rochester Medical Center, Rochester, New York

JOSEPH E. DOHAR, MD, MS Professor, Department of Otolaryngology, University of Pittsburg School of Medicine; Professor, Staff Otolaryngologist, Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania

KIMBERLY A. DONNELLAN, MD Adjunct Professor, Department of Surgery, University of South Alabama School of Medicine; Adjunct Professor, IMC Otolaryngology and Facial Plastic Surgery, Mobile Infirmary Medical Center, Mobile, Alabama

JOHN L. DORNHOFFER, MD, FACS Professor and Vice-Chair of Adult Services, Department of Otolaryngology, University of Arkansas for Medical Sciences; Professor and Vice-Chair of Adult Services, Department of Otolaryngology, University Hospital, Little Rock, Arkansas

UMAMAHESWAR DUVVURI, MD, PHD Assistant Professor, Department of Otolaryngology, University of Pittsburgh School of Medicine; Director of Head and Neck Robotic Surgery, Eye and Ear Institute, Pittsburgh, Pennsylvania

ANTHONY ECHO, MD Staff Physician, Division of Plastic Surgery, Department of Surgery, Methodist Institute for Reconstructive Surgery, Houston, Texas

DAVID E. EIBLING, MD, FACS Professor, Department of Otolaryngology–Head and Neck Surgery, University of Pittsburgh School of Medicine; Assistant Chief of Surgery, Surgery Service Line, VA Pittsburgh Healthcare System, University Drive C SSSL, Pittsburgh, Pennsylvania

DAVID W. EISELE, MD, FACS Andelot Professor and Director, Department of Otolaryngology–Head and Neck Surgery, Johns Hopkins University School of Medicine; Department of Otolaryngologist–Head and Neck Surgeon in Chief, The Johns Hopkins Hospital, Baltimore, Maryland

RAVINDHRA G. ELLURU, MD, PHD Associate Professor, Department of Otolaryngology–Head and Neck Surgery, University of Cincinnati College of Medicine; Associate Professor, Department of Pediatric Otolaryngology, Cincinnati Children's Hospital, Cincinnati, Ohio

AUDREY B. ERMAN, MD Assistant Professor, Co-director, Head and Neck Oncology Program, Division of Otolaryngology–Head and Neck Section, University of Arizona College of Medicine, Tucson, Arizona

RAMON M. ESCLAMADO, MD Richard H. Chaney Sr., Professor and Chief, Division of Otolaryngology–Head and Neck Surgery, Department of Surgery, Duke University, Durham, North Carolina

NEDA ESMAILI, MD Clinical Instructor, Section of Oculofacial and Orbital Surgery, Department of Ophthalmology, Medical College of Wisconsin, Milwaukee, Wisconsin

JOSEPH JOHN J. FANTUZZO, DDS, MD Associate Professor, Department of Oral and Maxillofacial Surgery, University of Rochester; Chair and Program Director, Department of Oral and Maxillofacial Surgery, University of Rochester Medical Center, Strong Memorial Hospital, Rochester, New York

A. STEWART FERGUSON, PHD Chief Information Officer (CIO), Health Information Technology, Alaska Native Tribal Health Consortium, Anchorage, Alaska

BERRYLIN J. FERGUSON, MD Professor of Otolaryngology, Director, Division of Sino-Nasal Disorders and Allergy; Assistant Professor, Department of Otolaryngology, University of Pittsburgh School of Medicine, UPMC Mercy, Pittsburgh, Pennsylvania

ROBERT L. FERRIS, MD, PHD, FACS UPMC Endowed Professor, Department of Medicine, Immunology, University of Pittsburgh School of Medicine; Chief, Head and Neck Surgery, Department of Otolaryngology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

ARLENE A. FORASTIERE, MD Professor, Department of Oncology, Johns Hopkins University; Active Staff, The Johns Hopkins Hospital, Baltimore, Maryland

ELLEN M. FRIEDMAN, MD Otolaryngology Center Staff Physician, Texas Children's Hospital, Bobby Alford Chair in Pediatric Otolaryngology; Professor and Chief of Service, Baylor College of Medicine, Houston, Texas

MICHAEL A. FRITZ, MD Staff Member, Department of Otolaryngology, Cleveland Clinic, Cleveland, Ohio

STEVEN GABEL, MD, FACS Gabel Hair Restoration Center, Hillsboro, Oregon

ANURAG GANDHI, MD Fellow, Infectious Disease Division, University of Rochester Medical Center, Rochester, New York; Physician, Infectious Disease, Gadsden Regional Medical Center, Gadsden, Alabama

PAUL A. GARDNER, MD Assistant Professor, Department of Neurology Surgery, University of Pittsburgh School of Medicine; Co-Director, Center for Cranial Base Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

JACKIE GARTNER-SCHMIDT, PHD Associate Professor, Department of Otolaryngology, University of Pittsburgh; Associate Director/Speech Language Pathologist, UPMC Voice Center, UPMC Mercy, Pittsburgh, Pennsylvania

NEAL C. GEHANI, MD Staff Physician, Department of Otolaryngology, Milford Regional Medical Center, Milford, Massachusetts

CARLA M. GIANNONI, MD Associate Professor, Department of Otolaryngology, Baylor College of Medicine; Associate Professor, Department of Pediatric Otolaryngology, Texas Children's Hospital, Houston, Texas

GRANT S. GILLMAN, MD, FRCS Associate Professor, Director, Division of Facial Plastic Surgery, Department of Otolaryngology–Head and Neck Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

MICHAEL B. GLUTH, MD Assistant Professor, Division of Otolaryngology–Head and Neck Surgery, Department of Surgery, Pritzker School of Medicine University of Chicago; Director, University of Chicago Listening Center, Division of Otolaryngology–Head and Neck Surgery, University of Chicago Medical Center, Chicago, Illinois

JOEL A. GOEBEL, MD, FACS, FRCS Professor and Vice Chairman, Department of Otolaryngology–Head and Neck

Surgery, Washington University School of Medicine; Attending Surgeon, Barnes-Jewish Hospital, St Louis, Missouri

CHRISTINE G. GOURIN, MD, MPH, FACS Associate Professor, Department of Otolaryngology–Head and Neck Surgery, Johns Hopkins University; Active Staff, The Johns Hopkins Hospital, Baltimore, Maryland

JENNIFER R. GRANDIS, MD, FACS Fulltime Faculty, Department of Otolaryngology and Pharmacology, University of Pittsburgh; Fulltime Faculty, Department of Otolaryngology and Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

JOHN GREINWALD, MD, FAAP Professor, Department of Otolaryngology and Pediatrics, University of Cincinnati College of Medicine; Professor, Department of Otolaryngology–Head and Neck Surgery, Auditory Genetics Lab (Director), Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

ROXANN DIEZ GROSS, PhD Director of Research, The Children's Institute, Pittsburgh, Pennsylvania

JESSICA L. GUSTAFSON, Esq Partner, The Health Law Partners, PC, Southfield, Michigan

DANA E. HABERS, MPH Chief Operating Officer, USC Care Faculty Practice Plan, Keck Medical Center of USC, Los Angeles, California

TESSA A. HADLOCK, MD Director, Facial Nerve Center, Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts

JOSEPH E. HALL, MD Resident, Department of Otolaryngology, Vanderbilt University Medical Center, Nashville, Tennessee

JAMES W. HALL III, PhD Extraordinary Professor, Department of Communication Pathology, University of Pretoria, Pretoria, South Africa

GRANT S. HAMILTON III, MD Assistant Professor, Department of Otorhinolaryngology, Mayo Clinic; Senior Associate Consultant, Department of Otorhinolaryngology, Mayo Clinic, Rochester, Minnesota

JAYNEE A. HANDELSMAN, PhD Clinical Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, University of Michigan Medical School; Director, Pediatric Audiology, Department of Otolaryngology–Head and Neck Surgery, University of Michigan C.S. Mott Children's Hospital, Ann Arbor, Michigan

MAUREEN HANNLEY, PhD Clinical Associate Professor, Department of Otolaryngology–Head and Neck Surgery, University of Arizona Medical Center, Tucson, Arizona

GADY HAR-EL, MD, FACS Professor, Department of Otolaryngology and Neurosurgery, SUNY Downstate Medical Center, Brooklyn, New York; Chairman, Department of Otolaryngology–Head and Neck Surgery, Lenox Hill Hospital, New York, New York

CATHERINE HART, MD Assistant Professor, Department of Pediatric Otolaryngology, University of Cincinnati College of Medicine; Assistant Professor, Department of Pediatric Otolaryngology–Head and Neck Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

GEORGE T. HASHISAKI, MD Associate Professor, Department of Otolaryngology–Head and Neck Surgery, University of Virginia Health System, Charlottesville, Virginia

BRUCE H. HAUGHEY, MBChB, FACS, FRACS Kimbrough Professor and Director, Head and Neck Surgical Oncology, Department of Otolaryngology–Head and Neck Surgery, Washington University School of Medicine; Kimbrough Professor and Director, Head and Neck Surgical Oncology, Department of Otolaryngology–Head and Neck Surgery, Barnes-Jewish Hospital, St. Louis, Missouri

DAVID S. HAYNES, MD, FACS Professor of Otolaryngology, Neurosurgery and Hearing and Speech Sciences, Neurotology Division/Fellowship Program/Cochlear Implant Program Director, Department of Otolaryngology, Vanderbilt University Medical Center, The Otology Group of Vanderbilt; Vanderbilt University Hospital, Vanderbilt University Medical Center, Nashville, Tennessee

STEFAN HELLER, PhD Professor, Department of Otolaryngology–Head and Neck Surgery, Stanford University School of Medicine, Stanford, California

SELENA E. HEMAN-ACKAH, MD, MBA Clinical Instructor, Division of Otolaryngology, Department of Surgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts

KATHRYN HICKNER-CRUZ, Esq Partner, The Health Law Partners, PC, Southfield, Michigan

BARRY E. HIRSCH, MD Professor, Department of Otolaryngology, Neurological Surgery, and Communication Science and Disorders, University of Pittsburgh, Eye and Ear Institute; Director, Division of Otology/Neurotology, Department of Otolaryngology, Neurological Surgery, and Communication Science and Disorders, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

JENNY K. HOANG, MD Assistant Professor of Radiology and Radiation Oncology, Department of Radiology, Duke University, Durham, North Carolina

ELIZABETH K. HODDESON, MD Resident Physician, Department of Otolaryngology–Head and Neck Surgery, Emory University; Resident Physician, Department of Otolaryngology–Head and Neck Surgery, Emory University Hospital, Atlanta, Georgia

STEPHEN R. HOFF, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, Northwestern University, Feinberg School of Medicine, Chicago, Illinois

JOHN F. HOFFMANN, MD, FACS Spokane Center for Facial Plastic Surgery, Spokane, Washington

ERIC H. HOLBROOK, MD Assistant Professor, Department of Otology and Laryngology, Harvard Medical School; Surgeon; Co-Director of the Sinus Center, Department of Otolaryngology–Head and Neck Surgery, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts

G. RICHARD HOLT, MD, D Bioethics Professor Emeritus, Department of Otorhinolaryngology–Head and Neck Surgery, University of Texas Health Science Center at San Antonio, San Antonio, Texas

J. CHRISTOPHER HOLT, PhD Assistant Professor, Department of Otolaryngology and Neurobiology and Anatomy, University of Rochester Medical Center, Rochester, New York

JEAN EDWARDS HOLT, MD, MPH Clinical Professor, Department of Ophthalmology, University of Texas Health Science Center at San Antonio, San Antonio, Texas

RUNHUA HOU, MD Assistant Professor, Division of Endocrinology and Metabolism, Department of Medicine, University of Rochester Medical Center, Rochester, New York

STEVEN M. HOUSER, MD, FAAOA Associate Professor of Otolaryngology, Department of Otolaryngology, Case Western Reserve University School of Medicine; Director of Rhinology, Allergy, and Sinus, Department of Otolaryngology, MetroHealth Medical Center, Cleveland, Ohio

CLINTON D. HUMPHREY, MD, FACS Assistant Professor, Division of Facial Plastic and Reconstructive Surgery, Department of Otolaryngology–Head and Neck Surgery, University of Kansas School of Medicine, Kansas City, Kansas

PETER H. HWANG, MD Professor, Department of Otolaryngology–Head and Neck Surgery, Stanford University School of Medicine; Chief, Division of Rhinology and Endoscopic Skull Base Surgery, Department of Otolaryngology–Head and Neck Surgery, Stanford University School of Medicine, Stanford, California

JOHN W. INGLE, MD Clinical Instructor, Department of Otolaryngology, University of Pittsburgh; Laryngologist/Surgeon, UPMC Voice Center, UPMC Mercy, Pittsburgh, Pennsylvania

BRANDON ISAACSON, MD Associate Professor, Department of Otolaryngology–Head and Neck Surgery, University of Texas Southwestern Medical Center, Dallas, Texas

AKIRA ISHIYAMA, MD Professor, Department of Head and Neck Surgery, UCLA, David Geffen School of Medicine; Surgeon, Department of Head & Neck Surgery, Ronald Reagan UCLA Medical Center, Los Angeles, California

GAIL ISHIYAMA, MD Associate Professor in Residence, Department of Neurology, UCLA, David Geffen School of Medicine; Attending Neurologist, Department of Neurology, Ronald Reagan UCLA Medical Center, Los Angeles, California

STACEY L. ISHMAN, MD, MPH Associate Professor, Department of Otolaryngology–Head and Neck Surgery, Pediatrics, Internal Medicine–Division of Pulmonary and Critical Care, Anesthesia and Critical Care Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland

ROBERT S. IWREY, Esq Partner, The Health Law Partners, PC, Southfield, Michigan

ROBERT K. JACKLER, MD Sewall Professor and Chair, Department of Otolaryngology–Head and Neck Surgery, Stanford University School of Medicine, Stanford, California

ABRAHAM JACOB, MD Associate Professor of surgery and Director of the UA Ear Institute, Division of Otolaryngology, Department of Surgery, The University of Arizona, Tucson, Arizona

KRISTEN L. JANKY, PhD Coordinator, Vestibular Services; Director, Vestibular Lab, Department of Audiology, Boys Town National Research Hospital, Omaha, Nebraska

GINA D. JEFFERSON, MD, MS Assistant Professor, Department of Otolaryngology and Communicative Sciences, University of Mississippi Medical Center, Jackson, Mississippi

BRIAN JEWETT, MD Assistant Professor, Department of Otolaryngology, University of Miami Health Systems, Miami, Florida

ANITA JEYAKUMAR, MD Assistant Professor, Department of Otorhinolaryngology, Louisiana State University Health Science Center; Faculty, Department of Otorhinolaryngology, Children's Hospital New Orleans, New Orleans, Louisiana

MICHAEL M. JOHNS III, MD Associate Professor–Otolaryngology, Director–Emory Voice Center, Emory University, Atlanta, Georgia

KAREN J. JOHNSON, MD Associate Clinical Professor, Department of Dermatology, University of Colorado Health Sciences Center, Denver, Colorado

JONAS T. JOHNSON, MD Professor and Chairman, Department of Otolaryngology; The Dr. Eugene N. Myers Professor and Chairman of Otolaryngology; Professor, Department of Radiation Oncology, University of Pittsburgh School of Medicine; Professor, Department of Oral and Maxillofacial Surgery, University of Pittsburgh School of Dental Medicine, Pittsburgh, Pennsylvania

NIKKI JOHNSTON, PhD Assistant Professor, Director of Airway, Digestive and Voice Research, Division of Research, Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin, Milwaukee, Wisconsin

J. RANDALL JORDAN, MD, FACS Professor and Vice Chair, Department of Otolaryngology Head and Neck Surgery and Communicative Sciences, University of Mississippi Medical Center, Jackson, Mississippi

JEB M. JUSTICE, MD Assistant Professor, Department of Otolaryngology, University of Florida, Gainesville, Florida

SARAH H. KAGAN, PhD, RN Professor–Clinician Educator, University of Pennsylvania School of Nursing; Clinical Nurse Specialist, Abramson Cancer Center at the University of Pennsylvania, Philadelphia, Pennsylvania

SALLY M. KAMAL, MD Resident Physician, Department of Otolaryngology, UC Davis Health System, Sacramento, California

AMIR M. KARAM, MD Director, Carmel Valley Facial Plastic Surgery, San Diego, California

SVETA KARELSKY, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, University of Rochester Medical Center, Rochester, New York

KIAN KARIMI, MD Cosmetic and Reconstructive Facial Plastic Surgeon, Pacific Eye and Ear Specialists, Los Angeles, California

ROBERT M. KELLMAN, MD Professor and Chair, Department of Otolaryngology, SUNY Upstate Medical University, Syracuse, New York

MARGARET A. KENNA, MD, MPH Professor, Department of Otology and Laryngology, Harvard Medical School; Director of Clinical Research, Department of Otolaryngology and Communication Enhancement, Boston Children's Hospital, Boston, Massachusetts

ROBERT C. KERN, MD Professor and Chairman, Department of Otolaryngology–Head and Neck Surgery, Northwestern University; Chairman, Department of Otolaryngology–Head and Neck Surgery, Northwestern Memorial Hospital, Chicago, Illinois

ERIC JAMES KEZIRIAN, MD, MPH Associate Professor in Residence, Department of Otolaryngology–Head and Neck Surgery, University of California, San Francisco, San Francisco, California

SAMIR KHARIWALA, MD Assistant Professor, Department of Otolaryngology, University of Minnesota Medical Center, Minneapolis, Minnesota

SEUNGWON KIM, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania

DAVID W. KIM, MD, FACS Associate Clinical Professor, Facial Plastic and Reconstructive Surgery, Department of Otolaryngology–Head and Neck Surgery, University of California, San Francisco, San Francisco, California

JOHN KOKESH, MD Chief, Department of Otolaryngology, Alaska Native Medical Center, Anchorage, Alaska

PETER J. KOLTAI, MD, FACS Professor of Otolaryngology and Pediatrics, Department of Otolaryngology–Head and Neck Surgery and Pediatrics, Stanford University School of Medicine, Stanford, California; Chief, Department of Pediatric Otolaryngology, Lucile Packard Children's Hospital, Palo Alto, California

RAYMOND J. KONIOR, MD Clinical Professor, Department of Otolaryngology–Head and Neck Surgery, Loyola University Medical Center, Maywood, Illinois

KAREN M. KOST, MD Assistant Professor, Department of Otolaryngology, McGill University Health Center, Montreal, Quebec, Canada

PAUL KRAKOVITZ, MD, Section Head, Head and Neck Institute, Department of Otolaryngology, Cleveland Clinic, Cleveland, Ohio

RUSSELL W. H. KRIDEL, MD, FACS Clinical Professor and Chief of Division of Facial Plastic Surgery, Department of Otolaryngology–Head and Neck Surgery, University of Texas–Health Science Center at Houston; Facial Plastic Surgeon, Facial Plastic Surgery Associates, Houston, Texas

GREGORY J. KUBICEK, MD Assistant Professor, Department of Radiation Oncology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

MAGGIE A. KUHN, MD Fellow, Laryngology and Broncho-esophagology, Department of Otolaryngology, University of California, Davis Medical Center, Sacramento, California

MELDA KUNDUK, PHD, CCC-SLP Associate Professor, Department of Communication Science and Disorder, Louisiana State University, Baton Rouge, Louisiana

JOE WALTER KUTZ JR, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, University of Texas Southwestern Medical Center, Dallas, Texas

ANIL K. LALWANI, MD Professor and Vice Chairman, Department of Otolaryngology–Head and Neck Surgery, Columbia University College of Physicians and Surgeons; Chief, Division of Otology, Neurotology, and Skull Base Surgery, Director, Columbia Cochlear Implant Program, Department of Otolaryngology–Head and Neck Surgery, New York-Presbyterian Hospital, New York, New York

SAMUEL M. LAM, MD, FACS Director, Willow Bend Wellness Center, Plano, Texas

PAUL R. LAMBERT, MD Professor and Chair, Department of Otolaryngology–Head and Neck Surgery, Medical University of South Carolina, Charleston, South Carolina

CATHY L. LAZARUS, PHD Associate Professor, Department of Otorhinolaryngology–Head and Neck Surgery, Albert Einstein College of Medicine, Bronx, New York; Research Director, THANC Foundation Research Center, Department of Otolaryngology–Head and Neck Surgery, Beth Israel Medical Center, New York, New York

DONALD A. LEOPOLD, MD Professor, Department of Surgery, Division of Otorhinolaryngology–Head and Neck Surgery, University of Vermont; Surgery, Fletcher Allen Health Care, Burlington, Vermont

RANDY M. LEUNG, MD, FRCSC Clinical Lecturer, Department of Otolaryngology–Head and Neck Surgery, University of Toronto; Rhinologist, Department of Otolaryngology–Head and Neck Surgery, Royal Victoria Hospital, Barrie, Ontario, Canada

STEPHEN R. LEVINSON, MD ASA, LLC, Easton, Connecticut

TIMOTHY S. LIAN, MD, FACS Associate Professor, Department of Otolaryngology–Head and Neck Surgery, Louisiana State University-Health, Shreveport; Vice-Chairman, Department of Otolaryngology–Head and Neck Surgery, Louisiana State University-Health, Shreveport, Shreveport, Louisiana

JONATHAN LIANG, MD Resident Physician, Department of Otolaryngology, UC Davis Health System, Sacramento, California

JERRY W. LIN, MD, PHD Otolaryngology Associates, PC, Fairfax, Virginia

CHRISTOPHER J. LINSTROM, MD, CM Professor, Department of Otolaryngology–Head and Neck Surgery, New York Medical College, Valhalla, New York; Surgeon Director, Department of Otolaryngology–Head and Neck Surgery, New York Eye and Ear Infirmary, New York, New York

CATHERINE REES LINTZENICH, MD Associate Professor, Department of Otolaryngology, Wake Forest School of Medicine, Medical Center Boulevard, Winston Salem, North Carolina

BRIDGET C. LOEHN, MD Resident, Department of Otolaryngology, Louisiana State University Health Sciences Center, New Orleans, Louisiana

JOSEPH E. LOSEE, MD, FACS, FAAP Professor and Vice Chair, Department of Plastic Surgery, University of Pittsburgh

Medical Center; Chief, Division of Plastic Surgery, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania

FRANK E. LUCENTE, MD Professor and Former Chairman, Department of Otolaryngology, SUNY Downstate Medical Center, Brooklyn, New York

RODNEY P. LUSK, MD Director: ENT Institute, Boys Town National Research Center, ENT, Boys Town National Research Center; Boys Town National Research Hospital, ENT, Boys Town National Research Center, Omaha, Missouri

STEWART J. LUSTIK, MD, MBA Professor, Department of Anesthesiology, University of Rochester Medical Center; Department of Anesthesiology, Strong Memorial Hospital, Rochester, New York

CHRISTINA KENNEY MAGILL, MD Surgeon, Department of Otolaryngology, Alyeska Facial Plastic Surgery ENT, Anchorage, Alaska

LI-XING MAN, MSc, MD, MPA Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, University of Rochester–School of Medicine and Dentistry; Attending Physician, Department of Otolaryngology–Head and Neck Surgery, University of Rochester Medical Center, Rochester, New York

ELLEN M. MANDEL, MD Associate Professor, Department of Otolaryngology, University of Pittsburgh School of Medicine; Research Pediatrician, Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania

DEVINDER S. MANGAT, MD Mangat-Kuy-Holzapfel Plastic Surgery, Edgewood, Kentucky

BRANNON D. MANGUS, MD Resident Physician, Department of Otolaryngology–Head and Neck Surgery, Vanderbilt University Medical Center, Nashville, Tennessee

SPIROS MANOLIDIS, MD Associate Professor, Department of Otolaryngology, Albert Einstein School of Medicine; Faculty, Department of Otolaryngology, Beth Israel Hospital, New York, New York

VALENTIN D. MARIAN, MD Administrator Department of Rheumatology, Department of Medicine, Jersey City Medical Center, Jersey City, New Jersey

BRADLEY F. MARPLE, MD Professor, Vice Chairman, Department of Otolaryngology–Head and Neck Surgery, University of Texas Southwestern Medical Center, Dallas, Texas

STEPHEN C. MATURO, MAJ, USAF, MC, FS Assistant Professor, Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, Maryland; Pediatric Otolaryngologist, Department of Otolaryngology, San Antonio Military Medical Center, Fort Sam Houston, Texas

TED MAU, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, University of Texas Southwestern Medical Center, Dallas, Texas

MICHAEL D. MAVES, MD Executive Vice President and Chief Executive Officer, American Medical Association, Chicago, Illinois

JESUS E. MEDINA, MD Paul and Ruth Jonas Professor, Department of Otorhinolaryngology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

DEEPAK K. MEHTA, MD Assistant Professor, Department of Otolaryngology, University of Pittsburgh School of Medicine; Assistant Professor, Staff Otolaryngologist, Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania

THUY-ANH N. MELVIN, MD Instructor, Department of Otolaryngology–Head and Neck Surgery, Johns Hopkins University School of Medicine; Department of Otolaryngology–Head and Neck Surgery, The Johns Hopkins Hospital, Baltimore, Maryland

ALBERT L. MERATI, MD, FACS Professor and Chief, Division of Laryngology, Department of Otolaryngology–Head and Neck Surgery, University of Washington School of Medicine; Chief, Laryngology Service, Department of Otolaryngology–Head and Neck Surgery Center, University of Washington Medical Center, Seattle, Washington

TED A. MEYER, MD Assistant Professor, Director, Cochlear Implant Center, Department of Otolaryngology–Head and Neck Surgery, Medical University of South Carolina, Charleston, South Carolina

TANYA K. MEYER, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, University of Washington; Attending Surgeon, Department of Otolaryngology–Head and Neck Surgery, University of Washington Medical Center, Seattle, Washington

BRETT A. MILES, DDS, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, Mount Sinai School of Medicine, New York, New York

CHASE H. MILLER, MD Associate Professor of Clinical Otolaryngology, Department of Otolaryngology, University of Rochester; Attending, Department of Otolaryngology, Strong Memorial Hospital, Rochester, New York

MATTHEW C. MILLER, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery and Neurosurgery, University of Rochester; Attending Surgeon, Department of Otolaryngology–Head and Neck Surgery and Neurosurgery, University of Rochester Medical Center, Rochester, New York

SEAN MILLER, MD Resident, Department of Otolaryngology, Saint Louis University, St Louis, Missouri

JAMES W. MIMS, MD Associate Professor, Department of Otolaryngology, Wake Forest School of Medicine, Medical Center Boulevard; Medical Staff Member, Department of Otolaryngology, Wake Forest Baptist Health, Medical Center Boulevard, Winston Salem, North Carolina

LLOYD B. MINOR, MD Professor of Otolaryngology-Head and Neck Surgery, Andelot Professor and Director, Department of Otolaryngology–Head and Neck Surgery, Johns Hopkins Outpatient Center, Baltimore, Maryland

NATASHA MIRZA, MD Professor, Department of Otolaryngology, University of Pennsylvania; Department of Otolaryngology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

RON B. MITCHELL, MD Professor, Departments of Otolaryngology–Head and Neck Surgery and Pediatrics, William Beckner Distinguished Chair in Otolaryngology,

University of Texas Southwestern Medical Center; Chief, Department of Pediatric Otolaryngology, Children's Medical Center Dallas, Dallas, Texas

STEVEN ROSS MOBLEY, MD Associate Professor, Division of Otolaryngology–Head and Neck Surgery, University of Utah; Attending Physician, Division of Otolaryngology–Head and Neck Surgery, University of Utah Hospitals and Clinics, Salt Lake City, Utah

CRAIG S. MURAKAMI, MD Clinical Associate Professor, Department of Facial Plastic Surgery and Otolaryngology, University of Washington, Virginia Mason Medical Center, Seattle, Washington

ANDREW H. MURR, MD, FACS Professor and Interim Chairman, Roger Boles, M.D. Endowed Chair in Otolaryngology Education, Department of Otolaryngology–Head and Neck Surgery, University of California, San Francisco School of Medicine; Chief of Service, Department of Otolaryngology–Head and Neck Surgery, San Francisco General Hospital, San Francisco, California

SUSAN J. MURR, JD Vice President, Commercial Assurance and Privacy, Becton Dickinson and Company, Franklin Lakes, New Jersey

CHARLES M. MYER III, MD Professor-Vice-Chairman, Department of Otolaryngology–Head and Neck Surgery, University of Cincinnati–Academic Health Center; Residency Program Director, Department of Otolaryngology–Head and Neck Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

JEFFREY N. MYERS, MD, PhD, FACS Hubert L. and Olive Stringer Distinguished Professor in Cancer Research Professor and Director of Research Deputy Chair for Academic Programs, Department of Head and Neck Surgery, University of Texas M.D. Anderson Cancer Center, Houston, Texas

RICHARD K. McHUGH, MD, PhD Assistant Professor, Division of Otolaryngology–Head and Neck Surgery, Department of Surgery, University of Alabama at Birmingham; Assistant Professor of Surgery, Division of Otolaryngology–Head and Neck Surgery, Department of Surgery, UAB Hospital, Birmingham, Alabama

ANDREW J. McWHORTER, MD Associate Professor, Director OLOL/LSU Voice Center, Department of Otolaryngology–Head and Neck Surgery, Louisiana State University Health Sciences Center, New Orleans, Louisiana

ROBERT M. NACLERIO, MD, FACS Professor and Chief, Department of Otolaryngology–Head and Neck Surgery, Surgery, University of Chicago, Chicago, Illinois

YURESH S. NAIDOO, BE, MBBS, FRACS Rhinology and Skull Base Surgeon, Department of Otorhinolaryngology Head and Neck Surgery, Australian School of Advanced Medicine, Macquarie University, Sydney, Australia

CHERIE-ANN O. NATHAN, MD, FACS Professor, Department of Otolaryngology–Head and Neck Surgery, Louisiana State University-Health, Shreveport; Chairman, Department of Otolaryngology–Head and Neck Surgery, Louisiana State University-Health, Shreveport, Shreveport, Louisiana

ANDREW J. NEMECHEK, MD, FACS Assistant Clinical Professor, Otolaryngology–Head and Neck Surgery, Department of Family Medicine, University of Colorado School of Medicine, Aurora, Colorado; Medical Director, Multidisciplinary, Head and Neck Tumor Program, Porter Adventist Hospital, Denver, Colorado

SHAWN D. NEWLANDS, MD, PhD, MBA, FACS Professor and Chair, Department of Otolaryngology, University of Rochester Medical Center; Chief, Department of Otolaryngology, Strong Memorial Hospital, Rochester, New York

JOHN P. NEY, MD, MPH Acting Instructor, Department of Neurology, University of Washington; Attending Neurologist, Department of Neurology, Puget Sound, VAMC, Seattle, Washington

BYRON K. NORRIS, MD ENT of Athens, Academic Institution, Athens, Georgia

MARK W. OCHS, DMD, MD Professor and Chair, Department of Oral and Maxillofacial Surgery, School of Dental Medicine, University of Pittsburgh; Associate Dean for Hospital Affairs, Department of Oral and Maxillofacial Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

PETER D. O'CONNOR, MD, OD Assistant Professor of Surgery, Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, Maryland; Chief, Sleep Surgery Division, Department of Surgery/ENT Service, San Antonio Military Medical Center, San Antonio, Texas

YOUNG S. OH, MD, FACS Assistant Clinical Professor, Department of Otolaryngology–Head and Neck Surgery, University of California, Irvine School of Medicine; Staff Surgeon, Department of Head and Neck Surgery, Southern California Permanente Medical Group, Kaiser Foundation Hospital–Orange County (CA), Irvine, California

OLUWAFUNMILOLA OKUYEMI, MD Post-Doctoral Research Scholar, Department of Otolaryngology, Washington University School of Medicine; Resident Physician, Department of Otolaryngology–Head and Neck Surgery, Barnes-Jewish Hospital, St Louis, Missouri

MIRIAM O'LEARY, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, Tufts University School of Medicine; Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, Tufts Medical Center, Boston, Massachusetts

ERIC R. OLIVER, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, Wake Forest School of Medicine, Medical Center Boulevard; Assistant Professor, Division of Surgical Science, Wake Forest Baptist Health, Medical Center Boulevard, Winston Salem, North Carolina

JAMES T. O'NEIL, MD Chief Resident, Department of Otolaryngology, Wake Forest School of Medicine; Chief Resident, Department of Otolaryngology, Wake Forest Baptist Hospital, Winston-Salem, North Carolina

JULINA ONGKASUWAN, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, Baylor College of Medicine; Assistant Professor, Department

of Otolaryngology–Head and Neck Surgery–Pediatric Otolaryngology, Baylor College of Medicine/Texas Children's Hospital, Houston, Texas

RICHARD R. ORLANDI, MD, FACS Professor, Department of Otolaryngology–Head and Neck Surgery, University of Utah; Professor, Department of Otolaryngology–Head and Neck Surgery, University of Utah Hospital and Clinics, Salt Lake City, Utah

DAVID M. OTTENWESS, Esq Managing Partner, Ottenwess, Allman & Taweel, PLC, Detroit, Michigan

STEPHANIE P. OTTENWESS, Esq Partner, Ottenwess, Allman & Taweel, PLC, Detroit, Michigan

TODD OTTESON, MD, MPH Associate Professor, Department of Otolaryngology, University of Pittsburgh School of Medicine; Pediatric Otolaryngologist, Division of Pediatric Otolaryngology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania

CATHERINE V. PALMER, PhD Associate Professor, Communication Science and Disorder, Department of Otolaryngology, University of Pittsburgh; Director, Audiology, Department of Otolaryngology, University of Pittsburgh Medical center, Pittsburgh, Pennsylvania

IRA D. PAPEL, MD Associate Professor, Department of Otolaryngology–Head and Neck Surgery, Johns Hopkins University, Baltimore, Maryland

STEPHEN S. PARK, MD Director, Division of Facial Plastic and Reconstructive Surgery, Department of Otolaryngology–Head and Neck Surgery, University of Virginia, Charlottesville, Virginia

ANDREW K. PATEL, MD Fellow, Department of Otolaryngology, Mayo Clinic Hospital, Phoenix, Arizona

KRISHNA G. PATEL, MD Director of Facial Plastic and Reconstructive Surgery, Medical University of South Carolina, Charleston, South Carolina

ZARA M. PATEL, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, Emory Health Care, Atlanta, Georgia

CHRIS PATRICOSKI, MD, FAAFP Clinical Director of Telemedicine, Health Information Technology, Alaska Native Tribal Health Consortium (ANTHC), Primary Care Physician, Anchorage, Alaska

STEPHEN W. PERKINS, MD, FACS Clinical Associate Professor, Department of Otolaryngology–Head and Neck Surgery, Indiana University School of Medicine; Private Practice, Meridian Plastic Surgery Center, Indianapolis, Indiana

MARK PERSKY, MD Professor of Clinical Otolaryngology, Departments of Otolaryngology, Albert Einstein College of Medicine, Bronx, New York; Chairman, Departments of Otolaryngology–Head and Neck Surgery, Beth Israel Medical Center, New York, New York

BRADLEY P. PICKETT, MD Assistant Professor, Department of Surgery, University of New Mexico; Division of Otology/Neurotology, Department of Surgery, University of New Mexico Health Sciences Center, Albuquerque, New Mexico

CARLOS D. PINHEIRO-NETO, MD, PhD Assistant Professor, Department of Otolaryngology and Neurology Surgery, Albany Medical College; Skull Base and Cranio-Maxillofacial Surgeon, Department of Otolaryngology, Albany Medical Center, Albany, New York

KAREN T. PITMAN, MD, FACS Professor, Department of Otolaryngology and Communicative Sciences, University of Mississippi Medical Center, Jackson, Mississippi

KEVIN L. POTTS, MD, FACS Assistant Professor, Division of Otolaryngology, Department of Surgery, University of Louisville; Department of Surgery, University of Louisville, Louisville, Kentucky

ANNA M. POU, MD, FACS Professor, Department of Otolaryngology–Head and Neck Surgery, Louisiana State University Health Sciences Center–New Orleans, New Orleans, Louisiana; Program Director, Department of Head and Neck Surgery, Our Lady of the Lake Regional Medical Center, Baton Rouge, Louisiana

JESS PRISCHMANN, MD Private Practice, Prischmann Facial Plastic Surgery, Edina, Minnesota

LIANA PUSCAS, MD, MHS Assistant Professor, Department of Surgery, Division of Otolaryngology–Head and Neck Surgery, Duke University; Attending Physician, Department of Surgery, Division of Otolaryngology–Head and Neck Surgery, Duke University Hospital, Durham, North Carolina

MURUGAPPAN RAMANATHAN JR., MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, Johns Hopkins University School of Medicine; Department of Otolaryngology–Head and Neck Surgery, The Johns Hopkins Hospital, Baltimore, Maryland

TANYA J. RATH, MD Assistant Professor, Director of Head and Neck Imaging, Department of Radiology, University of Pittsburgh School of Medicine; Assistant Professor, Department of Radiology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

YAEL RAZ, MD Assistant Professor, Department of Otolaryngology, University of Pittsburgh, Eye and Ear Institute, Pittsburgh, Pennsylvania

PETER C. REVENAUGH, MD Head and Neck Institute, Cleveland Clinic, Cleveland, Ohio

WILLIAM RUSSELL RIES, MD Professor, Carol and John S. Odess Chair in Facial and Plastic Reconstructive Surgery, Department of Otolaryngology, Vanderbilt University Medical Center, Nashville, Tennessee

CARLOS M. RIVERA-SERRANO, MD Resident, Department of Otolaryngology–Head and Neck Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

DAVID W. ROBERSON, MD Associate Professor in Otolaryngology, Harvard Medical School; Associate in Otolaryngology, Boston Children's Hospital, Boston, Massachusetts

JACOB G. ROBISON, MD, PhD Fellow, Departments of Otolaryngology, University of Pittsburgh, Eye and Ear Institute; Fellow, Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania

RACHEL E. RODITI, MD Resident, Otolaryngology, Department of Otolaryngology–Head and Neck Surgery, University of Rochester–School of Medicine and Dentistry; Resident, Otolaryngology, Department of Otolaryngology–Head and Neck Surgery, Strong Memorial Hospital, Rochester, New York

KENNETH D. RODRIGUEZ, MD Chief Resident, Department of Otolaryngology, University of Pittsburgh, Pittsburgh, Pennsylvania

PAMELA C. ROEHM, MD, PhD Assistant Professor, Department of Otolaryngology, New York University School of Medicine, New York, New York

HENRY H. ROENIGK JR, MD, FACP Professor Emeritus, Department of Dermatology, Northwestern University Medical School, Chicago, Illinois

EMILY ROGERS, MD Resident, Department of Surgery, University of Mississippi Medical Center, Jackson, Mississippi

PETER S. ROLAND, MD Professor and Chairman, Department of Otolaryngology–Head and Neck Surgery, University of Texas Southwestern Medical Center, Dallas, Texas

CLARK A. ROSEN, MD Professor, Department of Otolaryngology, University of Pittsburgh Medical Center; Director, University of Pittsburgh Voice Center; Professor, Department of Communication Sciences Disorders, University of Pittsburgh, Pittsburgh, Pennsylvania

RICHARD M. ROSENFELD, MD, MPH Professor and Chairman, Department of Otolaryngology, SUNY Downstate Medical Center; Chairman, Department of Otolaryngology, University Hospital of Brooklyn at LICH, Brooklyn, New York

MICHAEL J. RUCKENSTEIN, MD, FSc, FACS Professor, Vice Chairman, Department of Otorhinolaryngology–Head and Neck Surgery, University of Pennsylvania Health System, Philadelphia, Pennsylvania

LUKE RUDMIK, MD, FRCSC Clinical Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, University of Calgary; Clinical Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, Foothills Medical Centre, Calgary, Alberta, Canada

FRANCIS P. RUGGIERO, MD ENT–Head and Neck Surgery of Lancaster, Lancaster, Pennsylvania

MATTHEW S. RUSSELL, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, University of California, San Francisco; Otolaryngology Hospitalist, Department of Otolaryngology–Head and Neck Surgery, University of California, San Francisco Medical Center, San Francisco, California

MICHAEL J. RUTTER, MD Professor, Department of Otolaryngology–Head and Neck Surgery, University of Cincinnati; Attending/Faculty, Department of Otolaryngology–Head and Neck Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

MATTHEW W. RYAN, MD Assistant Professor, Department of Otolaryngology, University of Texas Southwestern Medical Center, Dallas, Texas

DIANE L. SABO, PhD Associate Professor, Department of Communication Science and Disorders, University of Pittsburgh; Director, Department of Audiology and Speech-Language Pathology, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania

BARRY M. SCHAITKIN, MD Professor, Department of Otolaryngology–Head and Neck Surgery, University of Pittsburgh; Chief, Division of Otolaryngology, UPMC Shadyside Hospital, Pittsburgh, Pennsylvania

RODNEY J. SCHLOSSER, MD Professor and Director of Rhinology, Department of Otolaryngology–Head and Neck Surgery, Medical University of South Carolina; Staff Surgeon, Department of Surgery (Otolaryngology), Ralph H. Johnson VA Medical Center, Charleston, South Carolina

NATHAN TODD NELSON SCHREIBER, MD Staff Physician, Department of Otolaryngology, Sequoia Hospital, San Mateo, California

JOHN M. SCHWEINFURTH, MD Professor, Department of Otolaryngology, University of Mississippi; Professor, Department of Otolaryngology, University of Mississippi Medical Center, Jackson, Mississippi

SCOTT SHADFAR, MD Chief Resident, Department of Otolaryngology–Head and Neck Surgery, University of North Carolina, Chapel Hill, North Carolina

MANISH D. SHAH, MD, MPhil, FRCS(C) Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, University of Toronto; Attending Physician, Department of Otolaryngology–Head and Neck Surgery, North York General Hospital, Toronto, Ontario, Canada

RAHUL K. SHAH, MD, FACS, FAAP Associate Professor, Department of Otolaryngology and Pediatrics, The George Washington University School of Medicine and Health Sciences; Associate Surgeon-in-Chief, Joseph E. Robert Jr. Center for Surgical Care, Children's National Medical Center, Washington, District of Columbia

FRED F. SHAHAN, MD Staff Physician, Department of Dermatology, Alvarado Hospital Medical Center, San Diego, California

NEIL T. SHEPARD, PhD Professor of Audiology, Department of Otolaryngology, Mayo Medical School; Chair of Audiology, Mayo Clinic, Rochester, Minnesota

MAISIE L. SHINDO, MD, FACS Professor of Otolaryngology, Director of Thyroid and Parathyroid Center, Department of Otolaryngology, Oregon Health and Science University, Portland, Oregon

WILLIAM W. SHOCKLEY, MD, FACS W. Paul Biggers Distinguished Professor of Otolaryngology/Head and Neck Surgery, Chief, Division of Facial Plastic and Reconstructive Surgery, Department of Otolaryngology–Head and Neck Surgery, University of North Carolina, Chapel Hill, North Carolina

SALLY R. SHOTT, MD Professor, Department of Otolaryngology–Head and Neck Surgery, University of Cincinnati; Professor, Department of Pediatric Otolaryngology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

JON D. SIMMONS, MD Assistant Professor, Department of Surgery, University of South Alabama School of Medicine; Assistant Professor, Department of Surgery, University of South Alabama Medical Center, Mobile, Alabama

JEFFREY P. SIMONS, MD Assistant Professor, Department of Otolaryngology, University of Pittsburgh School of Medicine; Assistant Professor, Staff Otolaryngologist, Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania

C. BLAKE SIMPSON, MD Professor, Department of Otolaryngology–Head and Neck Surgery, University of Texas Health Science Centre at San Antonio, San Antonio, Texas

PARUL SINHA, MBBS, MS Research Fellow, Department of Otolaryngology–Head and Neck Surgery, Washington University School of Medicine, St Louis, Missouri

DAVID F. SMITH, MD, PhD House Staff, Department of Otolaryngology–Head and Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland

JESSE E. SMITH, MD Assistant Clinical Professor, Department of Otolaryngology, University of Texas Southwestern Medical Center, Dallas, Texas; Facial Plastic Reconstructive Surgeon, Department of Surgery, John Peter Smith Hospital, Fort Worth, Texas

LIBBY J. SMITH, DO, FAOCO Associate Professor, Department of Otolaryngology, University of Pittsburgh; Laryngologist/Surgeon, UPMC Voice Center, UPMC Mercy Academic Institution, Pittsburgh, Pennsylvania

TIMOTHY L. SMITH, MD, MPH, FACS Professor, Department of Otolaryngology–Head and Neck Surgery, Oregon Health and Science University; Director, Oregon Sinus Center, Department of Otolaryngology–Head and Neck Surgery, Oregon Health and Science University, Portland, Oregon

JOHN C. SOK, MD, PhD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, Loma Linda University School of Medicine; Director, Loma Linda University Voice and Swallow Center, Department of Otolaryngology–Head and Neck Surgery, Loma Linda University Medical Center, Loma Linda, California

RYAN J. SOOSE, MD Assistant Professor, Department of Otolaryngology, University of Pittsburgh School of Medicine; Director, Division of Sleep Surgery, Department of Otolaryngology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

NICHOLAS C. SORREL, MD Physician in Training, Department of Otorhinolaryngology and Head and Neck Surgery, University of Texas at Houston; Physician in Training, Department of Otorhinolaryngology and Head and Neck Surgery, Memorial Herman Hospital, Houston, Texas

SHAUM S. SRIDHARAN, MD Resident, Department of Otolaryngology–Head and Neck Surgery, New York University; Chief Resident, Department of Otolaryngology–Head and Neck Surgery, New York University, New York, New York

BRENDAN C. STACK JR, MD, FACS, FACE Professor, Department of Otolaryngology–Head and Neck Surgery, University of Arkansas; Professor, Department of Otolaryngology–Head and Neck Surgery, University Hospital of Arkansas, Little Rock, Arkansas

MICHAEL E. STADLER, MD Assistant Professor, Division of Head and Neck Surgical Oncology and Reconstructive Surgery, Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin, Milwaukee, Wisconsin

CHRISTIAN L. STALLWORTH, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, University of Texas Health Science Center at San Antonio; Staff Otolaryngology, Department of Otolaryngology–Head and Neck Surgery, University Hospital System, San Antonio, Texas

JAMES A. STANKIEWICZ, MD Professor, Department of Otolaryngology–Head and Neck Surgery, Loyola University School of Medicine; Chairman, Department of Otolaryngology–Head and Neck Surgery, Loyola University/Trinity Health Care Center, Maywood, Illinois

MELISSA M. STATHAM, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, Emory University School of Medicine; Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, Emory Voice Center, Emory University Hospital–Midtown, Atlanta, Georgia

SHAWN M. STEVENS, MD Resident Physician, Department of Otolaryngology, Medical University of South Carolina, Charleston, South Carolina

MICHAEL G. STEWART, MD Professor and Chairman, Department of Otolaryngology–Head and Neck Surgery, Vice Dean of the Medical College, Weill Cornell Medical College; Chief of Service, Department of Otolaryngology–Head and Neck Surgery, New York–Presbyterian Hospital/Weill Cornell Medical Center, New York, New York

SCOTT P. STRINGER, MD, MS Professor and Chairman, Department of Otolaryngology and Communicative Sciences, University of Mississippi Medical Center, Jackson, Mississippi

PATRICK J. STROLLO JR, MD, FCCP, FAASM Professor of Medicine and Clinical and Translational Science, Department of Medicine, University of Pittsburgh School of Medicine, UPMC Montefiore; Medical Director, UPMC Sleep Medicine Center, Montefiore University Hospital, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

E. BRADLEY STRONG, MD Professor, Department of Otolaryngology, University of California, Davis; Vice Chairman, Department of Otolaryngology, University of California, Davis, School of Medicine, Sacramento, California

CHESTER L. STRUNK JR, MD Clinical Assistant Professor, Department of Otolaryngology, The University of Texas Medical Branch at Galveston, Galveston, Texas; Bay Area Ear, Nose and Throat Specialists, Pearland, Texas

JEFFREY D. SUH, MD Assistant Professor, Department of Head and Neck Surgery, University of California, Los Angeles, Los Angeles, California

LUCIAN SULICA, MD Associate Professor and Director, Laryngology/Voice Disorders, Department of Otolaryngology–Head and Neck Surgery, Weill Cornell Medical College; Attending Otolaryngologist, Department of Otolaryngology–Head and Neck Surgery, New York-Presbyterian Hospital, New York, New York

KURT F. SUMMERSGILL, DDS, PhD Associate Professor, Diagnostic Sciences, University of Pittsburgh–School of Dental

Medicine; Consultant, Department of Oral and Maxillofacial Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

JONATHAN M. SYKES, MD, FACS Professor of Otolaryngology, Director, Facial Plastic and Reconstructive Surgery, Department of Otolaryngology–Head and Neck Surgery, University of California, Davis Medical Center, Sacramento, California

CARL H. SNYDERMAN, MD, MBA, FACS Professor, Department of Otolaryngology and Neurology Surgery, University of Pittsburgh School of Medicine; Co-Director, Center for Cranial Base Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

NEELIMA TAMMAREDDI, MD Resident, Department of Otolaryngology, Louisiana State University Health Sciences Center–New Orleans, New Orleans, Louisiana

ANDREW B. TASSLER, MD Assistant Professor, Department of Otorhinolaryngology–Head and Neck Surgery, Albert Einstein College of Medicine; Assistant Professor, Department of Otorhinolaryngology–Head and Neck Surgery, Montefiore Medical Center, Bronx, New York

SHERARD A. TATUM, MD Professor, Department of Otolaryngology, SUNY Upstate Medical University, Syracuse, New York

MARCIE C. TAUZIN, MD Attending Staff, Touro Infirmary, New Orleans, Louisiana

ROBERT M. TAYLOR, MD Associate Professor, Departments of Neurology and Internal Medicine, The Ohio State University College of Medicine; Associate Professor, Division of Palliative Medicine, Department of Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio

TED L. TEWFIK, MD Professor and Director of CME, Department of Otolaryngology–Head and Neck Surgery; Professor of Pediatric Surgery, McGill University, Montreal, QC, Canada

DEAN M. TORIUMI, MD Professor, Head of Division of Facial Plastic and Reconstructive Surgery, Department of Otolaryngology–Head and Neck Surgery, University of Illinois at Chicago, Chicago, Illinois

BETTY S. TSAI, MD Assistant Professor, Department of Otorhinolaryngology, The University of Oklahoma Health Sciences Center; Attending Physician, Department of Otorhinolaryngology, OU Physicians, Oklahoma City, Oklahoma

JAY B. TUCHMAN, MD, FAAP Assistant Professor, Department of Anesthesiology, University of Pittsburgh School of Medicine; Assistant Professor, Department of Pediatric Anesthesiology, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania

ALEC VAEZI, MD Assistant Professor, Department of Otolaryngology, University of Massachusetts Medical School, Department of Otolaryngology, University of Massachusetts Memorial Medical Center, Worcester, Massachusetts

PAUL G. VAN DER SLOOT, MD, MS Assistant Professor, Otolaryngology–Head and Neck Surgery, University of Rochester Medical Center, Rochester, New York

NILESH R. VASAN, MD, FRACS Assistant Professor, Department of Otorhinolaryngology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

CRAIG R. VILLARI, MD Resident Physician, PGY-4, Department of Otolaryngology–Head and Neck Surgery, Emory University School of Medicine, Atlanta, Georgia

COURTNEY C. J. VOELKER, MD, PHD Clinical Fellow, House Ear Clinic; Clinical Fellow, St. Vincent's Medical Center, Los Angeles, California

JEFFREY T. VRABEC, MD Associate Professor, Bobby R Alford Department of Otolaryngology–Head and Neck Surgery, Baylor College of Medicine, Houston, Texas

WILLIAM E. WALSH, MD Assistant Professor, Facial Plastic and Reconstructive Surgeon, Otolaryngologist, Department of Otolaryngology–Head and Neck Surgery, University of Minnesota Medical Center, Fairview, Minneapolis, Minnesota

ROHAN R. WALVEKAR, MD Associate Professor, Department of Otolaryngology–Head and Neck Surgery, Louisiana State University Health Sciences Center, New Orleans, Louisiana

PELL ANN WARDROP, MD Assistant Professor, Department of Otolaryngology, University of Kentucky; Medical Director, Sleep Disorder Center, St Joseph Hospital, Lexington, Kentucky

MICHAEL JOHN WAREING, BSC, MBBS, FRCS (ORL-HNS) Lead Clinician, Department of Otolaryngology–Head and Neck Surgery, Barts and The London NHS Trust; Consultant Surgeon, ENT, The London Clinic, London, United Kingdom

MARK K. WAX, MD FACS FRCS(C) Professor Otolaryngology–Head and Neck Surgery, Professor Oral Maxillo Facial Surgery; Program Director, Chief Microvascular and Reconstructive Surgery, Department of Otolaryngology–Head and Neck Surgery, Oregon Health and Sciences University, Portland, Oregon

EDWARD M. WEAVER, MD, MPH Professor, Chief of Sleep Surgery, Department of Department of Otolaryngology–Head and Neck Surgery, University of Washington; Co-Director, UW Medicine Sleep Center, Harborview Medical Center, Seattle, Washington

PETER C. WEBER, MD, MBA Professor, Department of Otolaryngology, Rocky Mountain Ear Institute/Swedish Hospital, Englewood, Colorado

RANDAL S. WEBER, MD Professor and Chairman, Department of Head and Neck Surgery, University of Texas, MD Anderson Cancer Center, Houston, Texas

WILLIAM IGNACE WEI, MD Honorary Clinical Professor, Department of Surgery, The University of Hong Kong; Director of Li Shu Pui ENT Head and Neck Surgery Centre, Head, Department of Surgery, Department of Surgery, Hong Kong Sanatorium and Hospital, Hong Kong SAR

RICHARD O. WEIN, MD, FACS Associate Professor, Tufts University School of Medicine, Associate Professor, Department of Otolaryngology–Head and Neck Surgery, Tufts Medical Center, Boston, Massachusetts

PHILIP A. WEISSBROD, MD Assistant Professor, Division of Otolaryngology–Head and Neck Surgery, University of

California, San Diego, San Diego, California; Director, Center for Voice and Swallowing, Division of Otolaryngology–Head and Neck Surgery, UC San Diego Health System, La Jolla, California

ERIK KENT WEITZEL, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, SAUSHEC Joint Base San Antonio; Chief of Rhinology, Department of Otolaryngology–Head and Neck Surgery, San Antonio Military Medical Center, San Antonio, Texas

KEVIN C. WELCH, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, Loyola University School of Medicine, Maywood, Illinois

MATTHEW K. WHITLEY, MD Attending Physician, Department of Otolaryngology–Head and Neck Surgery, Pediatric Ear Nose and Throat of Atlanta, Atlanta, Georgia

SUSAN L. WHITNEY, PT, DPT, PhD, NCS, ATC, FAPTA Professor, Department of Physical Therapy and Otolaryngology, University of Pittsburgh; Program Director, Centers for Rehab Services, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

CHRISTA L. WHITNEY-MILLER, MD Assistant Professor, Department of Pathology and Laboratory Medicine, University of Rochester–School of Medicine and Dentistry; Staff Surgical Pathologist, Department of Pathology and Laboratory Medicine, Strong Memorial Hospital, Rochester, New York

EDWIN FRANCIS WILLIAMS, MD Medical Director, Williams Center Plastic Surgery Specialists, Latham, New York

MEGHAN N. WILSON, MD Resident, Department of Otolaryngology, Louisiana State University Health Sciences Center–New Orleans; Resident, Department of Otolaryngology, Louisiana State University Health Sciences Center–New Orleans, New Orleans, Louisiana

ANDREW WINKLER, MD Assistant Professor, Department of Otolaryngology, University of Colorado Denver; Director-Facial Plastic and Reconstructive Surgery, Department of Otolaryngology, University of Colorado Hospital, Aurora, Colorado

SARAH K. WISE, MD, MSCR Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, Emory University; Staff Physician, Department of Otolaryngology–Head and Neck Surgery, Emory University Hospital, Atlanta, Georgia

WILLIAM ANTHONY WOOD, MD, FACS, FAAOA Staff Otolaryngologist, Brattleboro Memorial Hospital, Brattleboro, Vermont

GAYLE E. WOODSON, MD Professor and Chair, Division of Otolaryngology, Head and Neck Surgery, Department of Surgery, SIU School of Medicine; Otolaryngology, Head and Neck Surgery, St. John's Hospital, Springfield, Illinois

TUCKER WOODSON, MD Professor and Chief Division Sleep Medicine, Department of Otolaryngology, Medical College of Wisconsin; Staff, Department of Otolaryngology, Froedtert Hospital, Milwaukee, Wisconsin

CHRISTOPHER T. WOOTTEN, MD, FACS Assistant Professor, Department of Otolaryngology, Vanderbilt University; Surgical Director, Complex Aerodigestive Evaluation Team, Department of Pediatric Otolaryngology, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee

PETER-JOHN WORMALD, MD, FRACS, FCS(SA), FRCS(Ed), MBChB Professor and Chairman, Department of Otolaryngology–Head and Neck Surgery, The University of Adelaide; Chairman, Department of Otolaryngology–Head and Neck Surgery, The Queen Elizabeth Hospital, Woodville South, South Australia, Australia

JUSTIN M. WUDEL, MD Resident, Department of Otolaryngology–Head and Neck Surgery, University of Colorado School of Medicine; Resident, Department of Otolaryngology–Head and Neck Surgery, University of Colorado Hospital, Aurora, Colorado

MIKE YAO, MD Clinical Associate Professor, Department of Otolaryngology, New York Medical College, Valhalla, New York

KATHLEEN L. YAREMCHUK, MD, MSA Chair, Department of Otolaryngology–Head and Neck Surgery, Henry Ford Hospital, Detroit, Michigan

ROBERT F. YELLON, MD Professor, Department of Otolaryngology, University of Pittsburgh School of Medicine; Co-Director, Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania

VyVy N. YOUNG, MD Assistant Professor, Department of Otolaryngology, University of Pittsburgh; Assistant Professor, Department of Otolaryngology, University of Pittsburgh Medical Center, UPMC Mercy, Pittsburgh, Pennsylvania

WARREN K. YUNKER, BSc, MD, PhD, FRCS(C) Assistant Professor, Department of Surgery, Foothills Medical Centre, University of Calgary; Assistant Professor, Department of Surgery, Alberta Children's Hospital, Calgary, Alberta, Canada

MARK A. ZACHAREK, MD, FACS, FAAOA Clinical Associate Professor, Department of Otolaryngology–Head and Neck Surgery, University of Michigan Health System, Associate Professor and Associate Program Director; Director Michigan Sinus Center, Department of Otorhinolaryngology, University of Michigan Health Systems, Ann Arbor, Michigan

ADAM M. ZANATION, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, University of North Carolina at Chapel Hill; Physician, Department of Otolaryngology–Head and Neck Surgery, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

IRENE ZHANG, MD Fellow, Head and Neck Surgery, Department of Otolaryngology, University of Pittsburgh Medical Center; Fellow, Head and Neck Surgery, Department of Otolaryngology, Eye and Ear Institute, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

LEE A. ZIMMER, MD, PhD Associate Professor, Department of Otolaryngology–Head and Neck Surgery, University of Cincinnati; Associate Professor, Department of Otolaryngology–Head and Neck Surgery, UC Health, Cincinnati, Ohio

JOHN A. ZITELLI, MD, PC Clinical Associate Professor, Department of Dermatology and Otolaryngology, University of Pittsburgh Medical Center; Staff Doctor, Zitelli & Brodland, PC, Skin Cancer Center, Mohs Surgery and Surgical Dermatology, Pittsburgh, Pennsylvania

DAVID A. ZOPF, MD Resident Surgeon, Department of Otolaryngology–Head and Neck Surgery, University of Michigan, Ann Arbor, Michigan

RICHARD A. ZOUMALAN, MD Clinical Professor, Department of Otolaryngology–Head and Neck Surgery, University of California, Los Angeles; Attending Surgeon, Department of Otolaryngology–Head and Neck Surgery, Cedars Sinai Medical Center, Beverly Hills, California

KAREN B. ZUR, MD Assistant Professor, Department of Otolaryngology–Head and Neck Surgery, Perelman School of Medicine, University of Pennsylvania; Director, Pediatric Voice Program; Associate Director, The Center for Pediatric Airway Disorders, Department of Otolaryngology–Head and Neck Surgery, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

FOREWORD

The editorial team of this fifth edition of *Head and Neck Surgery—Otolaryngology* is pleased to present you with the newest and most up-to-date version of the foremost textbook in *Head and Neck Surgery—Otolaryngology*. The fifth edition features a revised and more comprehensive table of contents authored by the thought leaders in our field focusing upon the modern practice of medicine.

This text is intended for use by students and practitioners at every level. The pace of the development of new material and information in the world of biomedical science has made information management a contemporary challenge. There is an increasing demand for the practice of evidence-based medicine. Clinical proficiency and mastery of the information are presented in a concise and clear manner in this text and will serve the practitioner in his/her preparation for the future.

The editorial team remains grateful for this opportunity to continue their pioneering efforts of Byron J. Bailey, MD, and the many section editors and authors who have contributed so much to making this the preeminent text of our field. Special thanks also goes to Jackie Lynch for her editorial assistance and a special acknowledgment of the detailed, meticulous artwork of Anthony Pazo.

Clark A. Rosen, MD
Jonas T. Johnson, MD

PREFACE

"More than a textbook—it's a learning system." That has been our challenging goal since the first edition of "*Head and Neck Surgery—Otolaryngology*" went to the printer 20 years ago. Once again, we began the planning of this fifth edition with the recruiting of experienced and expert authors capable of providing our readers with the most current and useful evidence-based information available for residents and practicing physicians intent on mastering the practice of our specialty.

Comprehensive, concise, and practical content that is presented in the format designed to increase the understanding, retention, and application of knowledge is the end result of the efforts of our outstanding team of Section Editors led by Jonas Johnson and Clark Rosen. Useful illustrations, helpful summary tables, and supplemental video segments enhance the effort of the learner to retain and apply the information contained in these volumes. A new and valuable study guide companion, *Bailey's Head and Neck Surgery: Otolaryngology Review*, will be published separately to assist with benchmarks of the progress that the reader has made.

And now, with sincere thanks to the authors and editors who have made this learning system possible, we have arrived once again at the point where vision becomes reality.

Many months of hard work have been transformed into a product with the potential to move clinical care to a higher level, and that is always the foundation of our striving.

We welcome our new readers and we applaud your decision to join us in this quest for greater understanding for ourselves and improved care for our patients.

Byron J. Bailey, MD, FACS
Chairman Emeritus, Department of Otolaryngology
The University of Texas Medical Branch
Galveston, Texas

I

Basic Science/General Medicine

Shawn D. Newlands *Karen T. Pitman*

Surgical Anatomy of the Head and Neck

1

Michael D. Maves

Anatomy is the basic science of all surgery. Surgery in the region of the head and neck cannot be considered safe unless the surgeon thoroughly understands the anatomy of this area and its important variations. Although anatomic structures and the relations between them do not change, our knowledge of anatomy must be continually updated to meet the challenge of new surgical techniques and approaches. This chapter is an overview of the surgical anatomy of the head and neck with a focus on the major regions. It is not a substitute for thorough anatomic knowledge, which can be gained only through intensive study in a cadaver laboratory and an operating room.

THE CRANIUM

Scalp

The cranium is covered by the hair-bearing scalp, which is divided into layers of skin and subcutaneous tissue, galea aponeurotica, loose connective tissue, and periosteum or pericranium covering the calvarial vault. The blood supply of the scalp comes from the paired supraorbital and supratrochlear arteries anteriorly, the terminal branches of the superficial temporal arteries laterally, and the occipital vessels posteriorly. This rich vascularity provides a network on which small scalp flaps can be based and rotated, as in the management of male pattern baldness. Sensation to the scalp is provided by branches of cranial and spinal nerves.

Calvaria

The bony vault of the cranium, the calvaria, consists of the unpaired frontal bone, the paired parietal bones, and the unpaired occipital bone (Fig. 1.1). In the lateral aspect, the greater wing of the sphenoid bone and the temporal bone complete the cranium. There is a rich layer of diploic bone between the inner and outer tables of the calvaria. This is a source for split-thickness calvarial bone grafts, which often are used in head and neck reconstruction. The calvarium is thickest at the external occipital protuberance and in the parietal region. It is thinnest over the temporal region. This allows ready access for neurotologic operations on the middle fossa. The venous circulation of the calvaria is provided by diploic veins, which drain to the veins of the scalp or into the dural venous sinuses. In some instances, the diploic veins are connected to each other, and this communication allows osteomyelitis that originates in the frontal sinus to involve the frontal bone, scalp, and dura.

CRANIAL FOSSAE

The intracranial cavity is roughly divided into three fossae. The anterior or frontal cranial fossa contains the paired frontal lobes and provides access to the nasal cavity for the olfactory nerves through the cribriform plate. The crista galli provides superior midline extension of the nasal septum. The middle cranial fossa contains the temporal lobes. In this important junction of the cranial cavity, the middle meningeal artery arises from the foramen spinosum, and the trigeminal nerve enters through the superior orbital fissure (V1), the foramen rotundum (V2), and the foramen ovale (V3). Cranial nerves II, III, IV, and VI, which traverse the cavernous sinus and enter the orbit, also course through the middle cranial fossa. The internal carotid artery is in its place in the carotid siphon as it traverses the cavernous sinus in this region. The posterior cranial fossa contains the paired cerebellar hemispheres and the brainstem. In this location, the internal auditory meatus is associated with the seventh and eighth cranial nerve complex. The jugular foramen, transverse sinus, and foramen magnum are the major landmarks of the posterior cranial fossa.

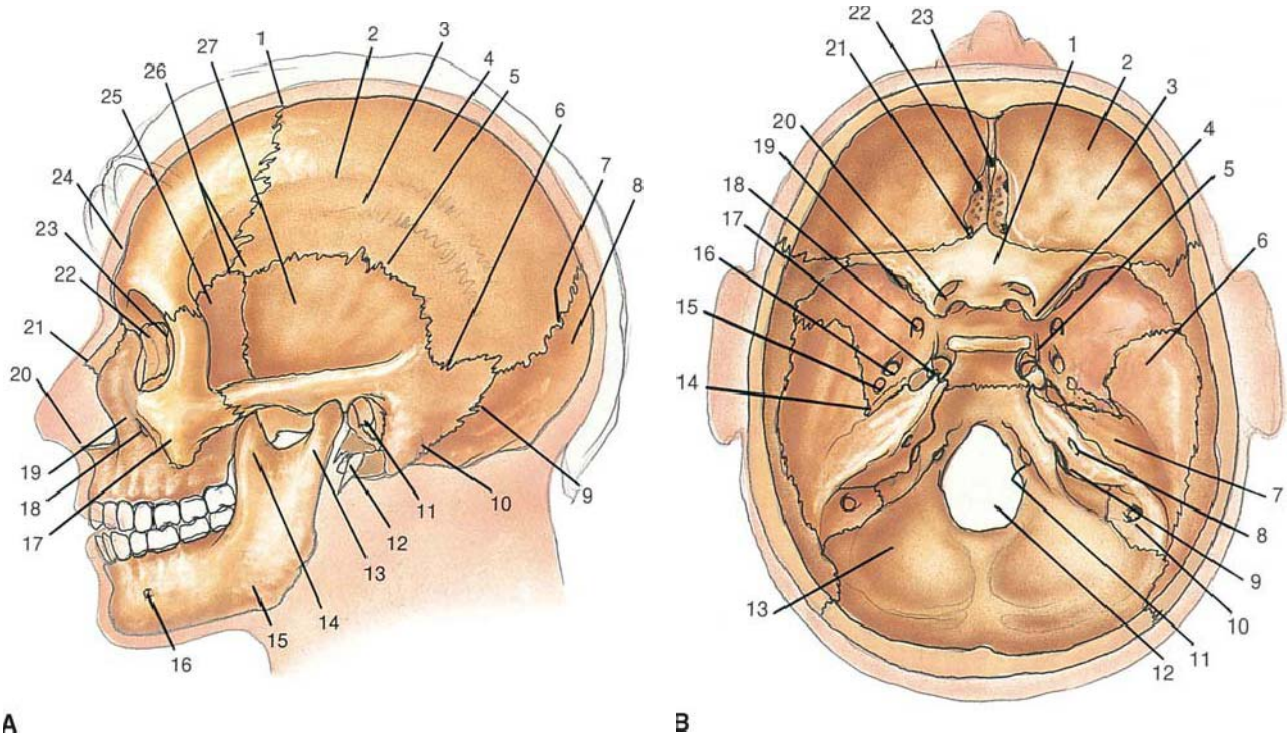


Figure 1.1 Scalp, cranium, and intracranial cavity. **A**: *1*, Coronal suture; *2*, superior temporal line; *3*, inferior temporal line; *4*, os parietale; *5*, squamous suture; *6*, parietomastoid suture; *7*, lambdoid suture; *8*, occipital bone; *9*, occipitomastoid suture; *10*, mastoid process; *11*, external acoustic meatus; *12*, styloid process; *13*, condyle of mandible; *14*, coronoid process of mandible; *15*, body of mandible; *16*, mental foramen; *17*, zygomatic bone; *18*, infraorbital foramen; *19*, frontal process (maxilla); *20*, anterior nasal spine; *21*, nasal bone; *22*, lacrimal bone; *23*, orbital lamina of ethmoid bone; *24*, glabella; *25*, sphenoid bone; *26*, pterion; *27*, temporal bone. **B**: *1*, Sphenoid bone; *2*, frontal bone; *3*, anterior cranial fossa; *4*, anterior clinoid process; *5*, carotid sulcus; *6*, middle cranial fossa; *7*, petrous portion of temporal bone; *8*, internal acoustic meatus; *9*, jugular foramen; *10*, mastoid foramen; *11*, hypoglossal canal; *12*, foramen magnum; *13*, posterior cranial fossa; *14*, sulcus for greater and lesser petrosal nerves; *15*, foramen spinosum; *16*, foramen ovale; *17*, foramen lacerum; *18*, foramen rotundum; *19*, superior orbital fissure; *20*, optic canal; *21*, anterior ethmoidal foramen; *22*, anterior ethmoidal foramen; *23*, foramen cecum.

EYELID, ORBIT, AND EYE

Eyelids

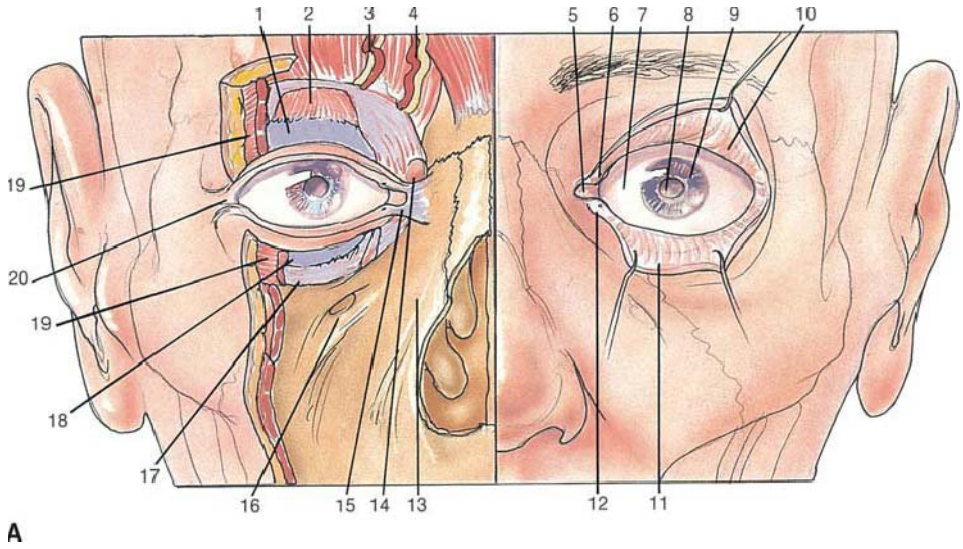
The upper and lower eyelids are similar in structure, although the upper eyelid is more mobile and has features not found in the lower eyelid. The space between the eyelids is known as the palpebral fissure, which is limited medially and laterally by the canthi. At the medial canthus is the lacrimal caruncle, where there is a small lake of tears and the tiny papillae of the lacrimal duct system. The conjunctiva is a thin mucous membrane layer that covers the inner aspects of the eyelids and extends onto the surface of the globe.

Tarsus

The upper tarsal plate provides rigidity to the upper eyelid and is larger than the lower tarsus (Fig. 1.2). Each eyelid consists (from without inward) of skin, subcutaneous tissue, voluntary muscle of the orbicularis oculi, orbital septum, tarsus, smooth muscle, and conjunctiva. The more freely mobile upper lid receives the insertion of the levator palpebrae superioris muscle. The orbicularis oculi is the sphincteric muscle of the upper and lower eyelids. It attaches at a medial palpebral ligament and spreads in an arc laterally and inferiorly to provide a sphincteric muscle to the eye. It receives innervation from the temporal and zygomatic branches of the facial nerve. This muscle interdigitates with the frontalis muscle and the corrugator supercilii.

Blood Supply

The arterial supply of the eyelids is provided by the angular branch of the facial artery, which forms an anastomotic network with the supraorbital and supratrochlear artery and shares a small contribution from the superficial temporal vessels. The veins of the eyelids are larger and more numerous than the arteries and drain into the ophthalmic and angular veins medially and the superficial temporal vein laterally. Accompanying the peripheral arterial arcade of the upper eyelid, the veins of the small venous plexus drain into the ophthalmic vein, which drains posteriorly to the cavernous sinus. The veins in this region of the face do



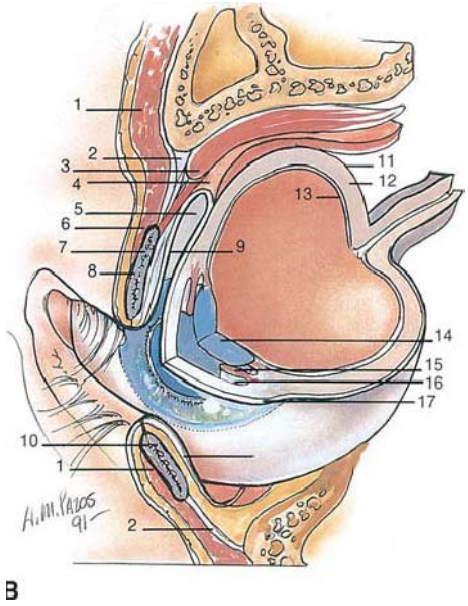


Figure 1.2 Eyelids and external adnexa. **A**: *1*, Superior tarsus; *2*, levator palpebrae superioris muscle; *3*, supraorbital artery and nerve; *4*, supratrochlear artery and nerve; *5*, lacrimal caruncle; *6*, superior lacrimal papilla and puncta; *7*, bulbar conjunctiva over sclera; *8*, pupil; *9*, cornea; *10*, superior palpebral conjunctiva; *11*, inferior palpebral conjunctiva; *12*, inferior lacrimal papilla and puncta; *13*, maxilla; *14*, lacrimal sac; *15*, medial palpebral ligament; *16*, infraorbital foramen; *17*, orbital septum; *18*, inferior tarsus; *19*, orbicularis oculi muscle (cut); *20*, lateral palpebral ligament. **B**: *1*, Orbicularis oculi muscle; *2*, orbital septum; *3*, levator palpebrae superioris muscle; *4*, superior tarsal muscle (Müller muscle); *5*, superior conjunctival fornix; *6*, orbicularis oculi muscle (palpebral portion); *7*, superior tarsus; *8*, tarsal glands; *9*, palpebral conjunctiva; *10*, inferior tarsus; *11*, sclera; *12*, choroid; *13*, retina; *14*, lens; *15*, iris; *16*, anterior chamber; *17*, cornea.

not have valves and may propagate septic emboli posteriorly. This is a particularly dangerous situation for patients who have infections in the areas of the eyelids or periorbital abscess. These patients are at risk of cavernous sinus thrombosis.

Lacrimal System

The lacrimal apparatus consists of a secretory portion, the lacrimal gland, its ducts, the drainage apparatus, the lacrimal canaliculi and sac, and the nasolacrimal duct (Fig. 1.3). The lacrimal gland is partially divided into two portions by the lateral horn of the aponeurosis of the levator palpebrae. The larger orbital portion of the gland lies in a shallow fossa on the frontal bone and is in contact anteriorly with the orbital septum. The excretory ductules of the lacrimal gland run through the orbital part of the gland, run through or close to the posterior part of the palpebral portion, and are joined by ducts from this portion.

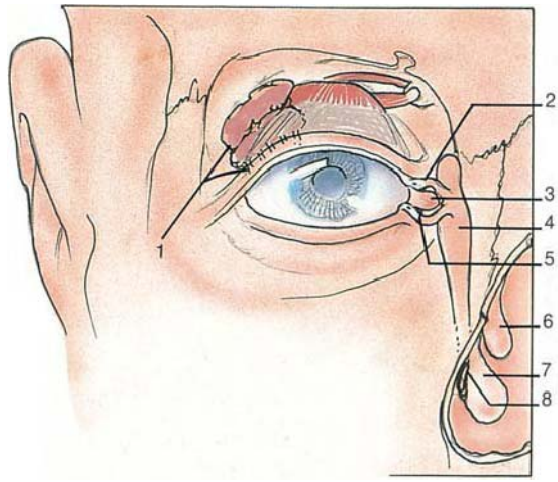


Figure 1.3 Lacrimal apparatus and drainage system. *1*, Lacrimal gland and ducts; *2*, superior lacrimal papilla and puncta; *3*, lacrimal caruncle; *4*, lacrimal sac; *5*, inferior lacrimal papilla and puncta; *6*, middle nasal concha; *7*, inferior nasal concha; *8*, opening of nasolacrimal duct.

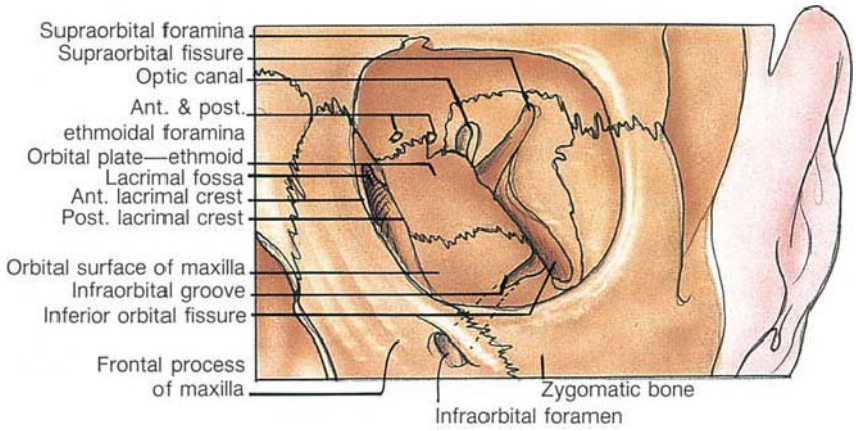


Figure 1.4 Bony orbit.

Removal of the palpebral portion can destroy the drainage of the entire gland.

Movement of the eyelid distributes tears over the surface of the eye, and any excess tends to accumulate in the lacrimal lake. This structure drains into the paired superior and inferior canaliculi and from there into the lacrimal sac. The lacrimal sac is housed in the bony lacrimal fossa of the medial orbital wall. This drains into the nasal lacrimal duct and eventually into the inferior meatus of the nose.

Orbit

The bony orbit consists of the medial wall occupied largely by the ethmoid bone, lacrimal bone, and a portion of the nasal process of the maxilla (Fig. 1.4). The floor of the orbit consists of the roof of the maxilla. The inferior orbital fissure is at its lateral extent. The zygomatic bone and greater wing of the sphenoid form the lateral orbital wall and join the frontal bone superiorly to complete the pyramidal bony orbit. On its medial aspect are the paired ethmoidal foramina, which provide a route to the orbit for the anterior and posterior ethmoidal arteries. The optic canal posteriorly transmits the optic nerve and ophthalmic artery. The superior orbital fissure transmits cranial nerves III, IV, V, and VI and provides an aperture for the ophthalmic vein.

Eye

The eye consists of the cornea and sclera in the anterior aspect. The anterior chamber protrudes as a second sphere on the structure of the orbit. The lens and iris form the posterior portion of the anterior chamber. Contained within the substance of the eye is the vitreous. The retina rests on the choroid. The fovea centralis is the focal point of the eye. Asymmetric to the structure of the orbit is the insertion of the optic nerve and ciliary arteries.

The seven voluntary muscles of the orbit are the levator palpebrae superioris; the superior, inferior, medial, and lateral rectus muscles; and the superior and inferior oblique muscles (Fig. 1.5). The smooth muscles of the orbit are the orbitalis muscle, the superior and inferior tarsal muscles, and ciliary and iridial muscles within the eye. The superior oblique is supplied by cranial nerve IV, the lateral rectus

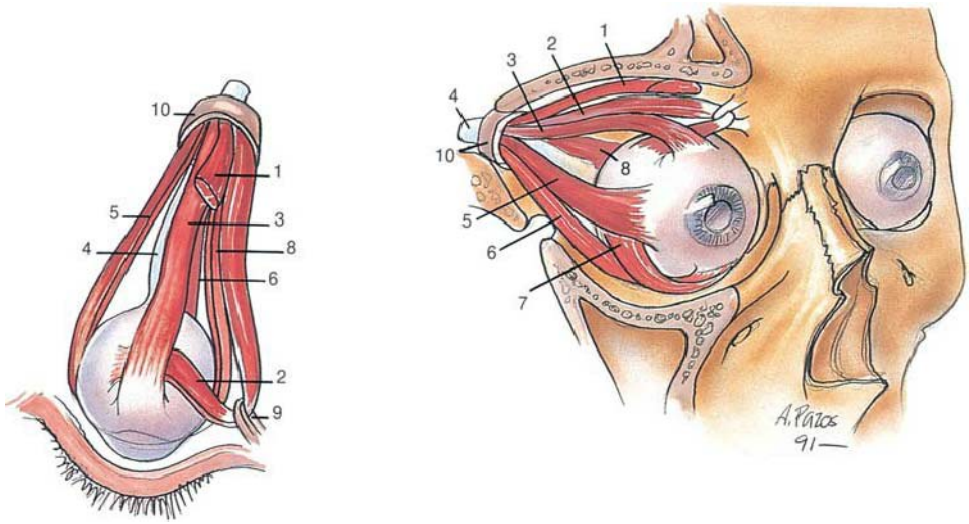


Figure 1.5 Eye muscles. *1*, Levator palpebrae superioris muscle; *2*, superior oblique muscle; *3*, superior rectus muscle; *4*, optic nerve; *5*, lateral rectus muscle; *6*, inferior rectus muscle; *7*, inferior oblique muscle; *8*, medial rectus muscle; *9*, trochlea; *10*, annular tendon.

is supplied by cranial nerve VI, and the other voluntary muscles of the orbit are supplied by cranial nerve III. The tarsal and orbital muscles (of Müller) are supplied by sympathetic fibers derived from the carotid plexus and from the superior cervical ganglion. The dilator pupillae, the sphincter pupillae, and the ciliary muscle are supplied by parasympathetic fibers through the oculomotor nerve (III).

The primary blood supply to the orbit is through the ophthalmic artery. The primary drainage is through the ophthalmic vein, which drains directly into the cavernous sinus. An additional anastomotic network is present on the anterior aspect of the face in the form of an arcade of vessels around the eyelids and through the pterygoid plexus.

THE EAR

The development and the anatomic and physiologic features of the ear are discussed in Chapters 140 and 141.

NOSE AND PARANASAL SINUSES

External Nose

The external part of the nose is a roughly pyramidal shape. The skeleton of the external nose is partly bony and partly cartilaginous and membranous. The nasal bones, which are usually narrow and thicker above, wider and thinner below, articulate firmly above with the nasal part of the frontal bone and with each other laterally with the nasal process of the maxilla (Fig. 1.6). Attached to the inferior aspect of the nasal bones are the upper lateral cartilages. These are continuous with the cartilaginous septum. In the inferior aspect, the lobule of the nose is formed mostly by the lower lateral cartilages, which consist of a medial and lateral crus. There are several small cartilages within the nasal ala. The chief arterial supply of the nose is from the facial artery through the angular artery and superior labial arteries. Venous drainage is similar, with a component gaining access to the ophthalmic vein through draining vessels from the trochlear and angular veins.

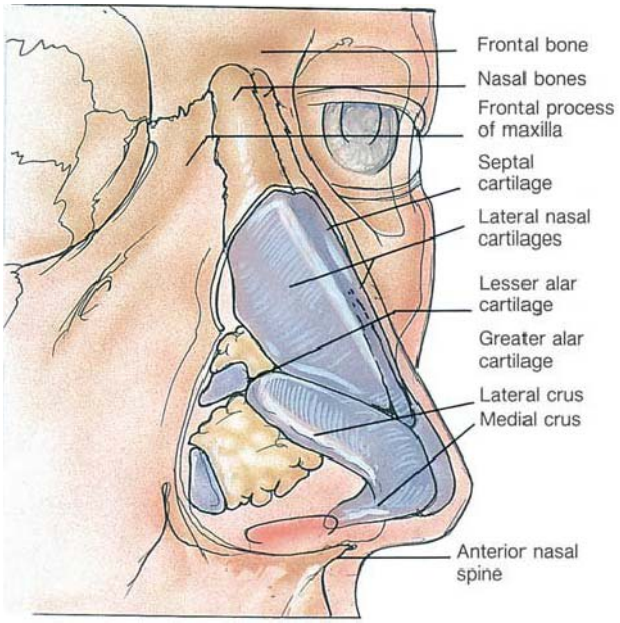


Figure 1.6 Bony and cartilaginous anatomic configuration of the external nose.

Nasal Cavity

The nasal cavities are also known as the *nasal fossae*. The nasal septum consists of the nasal septal cartilage, the nasal crest of the maxilla, the nasal crest of the palatine bone, the vomer, and the perpendicular plate of the ethmoid bone. The lateral nasal wall is formed by the prominent nasal turbinates. The meatus are situated below the corresponding turbinates (Fig. 1.7). The inferior meatus provides drainage

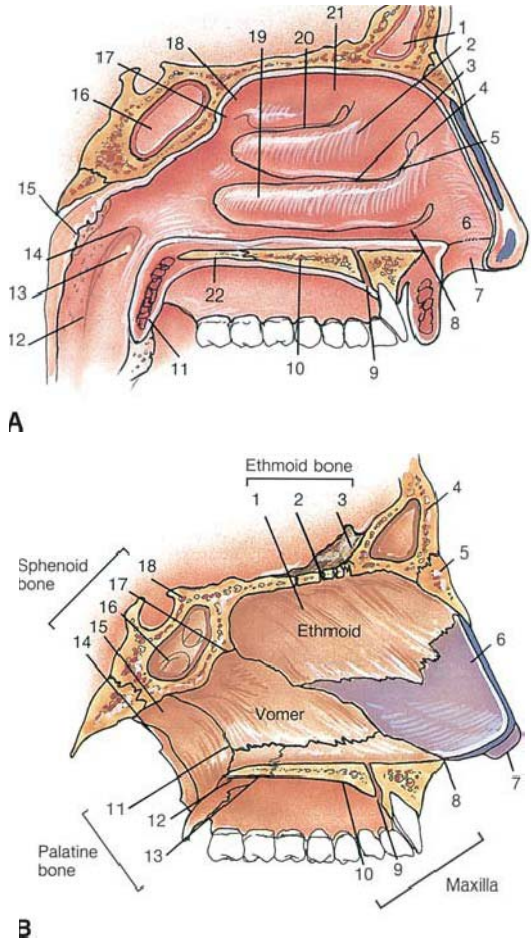


Figure 1.7 **A:** Lateral nasal wall. *1*, Frontal sinus; *2*, middle nasal concha; *3*, middle nasal meatus; *4*, agger nasi; *5*, atrium of middle nasal concha; *6*, limen; *7*, vestibule; *8*, inferior nasal meatus; *9*, incisive canal; *10*, palatine process of maxilla; *11*, soft palate; *12*, pharyngeal recess; *13*, eustachian tube orifice; *14*, torus tubarius; *15*, adenoid; *16*, sphenoid sinus; *17*, sphenoid sinus opening; *18*, sphenoethmoidal recess; *19*, inferior nasal concha; *20*, superior nasal meatus; *21*, superior nasal concha; *22*, palatine bone. **B:** Nasal septum. *1*, Perpendicular plate; *2*, cribriform plate; *3*, crista galli; *4*, frontal bone; *5*, nasal bone; *6*, septal cartilage; *7*, medial crus; *8*, anterior nasal spine; *9*, incisive canal; *10*, palatine process; *11*, perpendicular plate; *12*, postnasal spine; *13*, horizontal plate; *14*, lateral pterygoid plate; *15*, medial pterygoid plate; *16*, sphenoid sinus; *17*, crest; *18*, body.

for the nasolacrimal duct. The middle meatus provides drainage for the anterior nasal sinuses, namely the frontal sinus, anterior ethmoid sinuses, and the maxillary sinus. The superior meatus provides drainage for the posterior sinuses, namely the posterior ethmoid and sphenoid sinuses.

The arterial supply of this region is from internal carotid sources through the anterior and posterior ethmoid arteries and from an external carotid source through the sphenopalatine artery. Contributions also may exist from the greater palatine vessels and the septal branch of the superior labial artery. These form an important anastomotic network in the anterior septum known as the *Kiesselbach plexus*, which accounts for most nosebleeds.

Sinuses

The paranasal sinuses consist of the paired frontal, ethmoid, maxillary, and sphenoid sinuses (Fig. 1.8). The frontal sinus develops as one of several outgrowths from the region of the frontal recess. Two, three, or even more frontal sinuses on a side have been reported, and some persons have no frontal sinus. The degree of pneumatization of the frontal sinuses varies. Pneumatization may extend into the roof of the orbit and laterally into the frontal bone as far as the sphenoid wing. The frontal sinuses drain into the anterior aspect of the middle meatus.

Ethmoid Sinuses

The ethmoid sinuses consist of a variable number of separate cavities that honeycomb the ethmoid bone between the upper part of the lateral nasal wall and the medial wall of the orbit. The anterior ethmoid cells are divided into frontal recess cells, which open into the frontal recess of the middle meatus; infundibular cells, which open into the ethmoid infundibulum; and bullar or middle ethmoid cells, which open directly into the middle meatus on or above the ethmoid bulla. There may be one to seven posterior ethmoid cells. The bullae and posterior ethmoid cells may encroach on each other and overlap, the bullar cells spreading backward or the posterior cells spreading forward. The posterior ethmoid cells drain into the superior meatus.

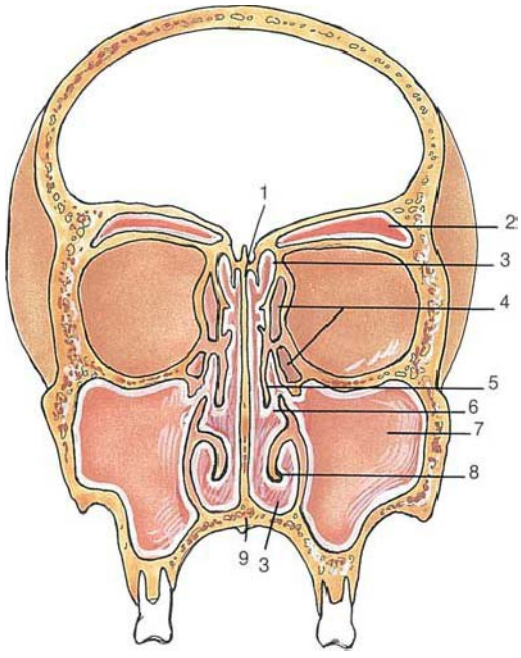


Figure 1.8 Paranasal sinuses. *1*, Nasal septum; *2*, frontal sinus; *3*, nasal cavities; *4*, ethmoidal cells; *5*, middle nasal concha; *6*, middle nasal meatus; *7*, maxillary sinus; *8*, inferior nasal concha; *9*, hard palate.

Sphenoid Sinus

The sphenoid sinus usually opens into the sphenoethmoidal recess above and behind the superior nasal concha. The ostium usually is in the posterior wall of the recess, but sometimes it is on its lateral wall. The degree of pneumatization of the sphenoid sinus varies. This variation is an important factor in surgical approaches to the pituitary gland. The relations of the sphenoid sinus are important because of the surrounding anatomic structures. The optic nerves are superior to the sinus, and the internal carotid artery is lateral to the sinus within the cavernous sinus. The maxillary nerve lies in the inferior lateral portion of the sinus in the anterior aspect. The hypophysis lies within the posterior superior portion of the sphenoid sinus and can be approached through transsphenoidal hypophysectomy.

Maxillary Sinus

The maxillary sinus usually is the largest of the paranasal sinuses and is situated in the body of the maxilla. Its anterior wall is the facial surface of this bone, and its posterior wall is the infratemporal surface. Its medial wall is that of the nasal cavity. The roof of the maxillary sinus is also the floor of the orbit, and it also may be affected in blow-out fractures of the orbit. The maxillary sinus drains into the middle meatus of the nasal cavity. The roots of the posterior molar teeth may extend into the sinus. The maxillary sinus is bounded posteriorly by the pterygomaxillary fossa, through which course the terminal branches of the internal maxillary artery. These vessels can be approached through the maxillary sinus for relief of epistaxis.

THE FACE

Facial Bones and Muscles

The bones of the face include the frontal and nasal bones and the facial bones proper—maxilla, mandible, zygomatic, and palatine bones. The facial and mimetic muscles are divided into five chief groups concerned with the mouth, nose, orbit, ear, and scalp (Fig. 1.9). The platysma muscle in the neck also belongs to the facial group. The chief action of these muscles is on skin into which they insert. All these muscles are innervated by the facial nerve.

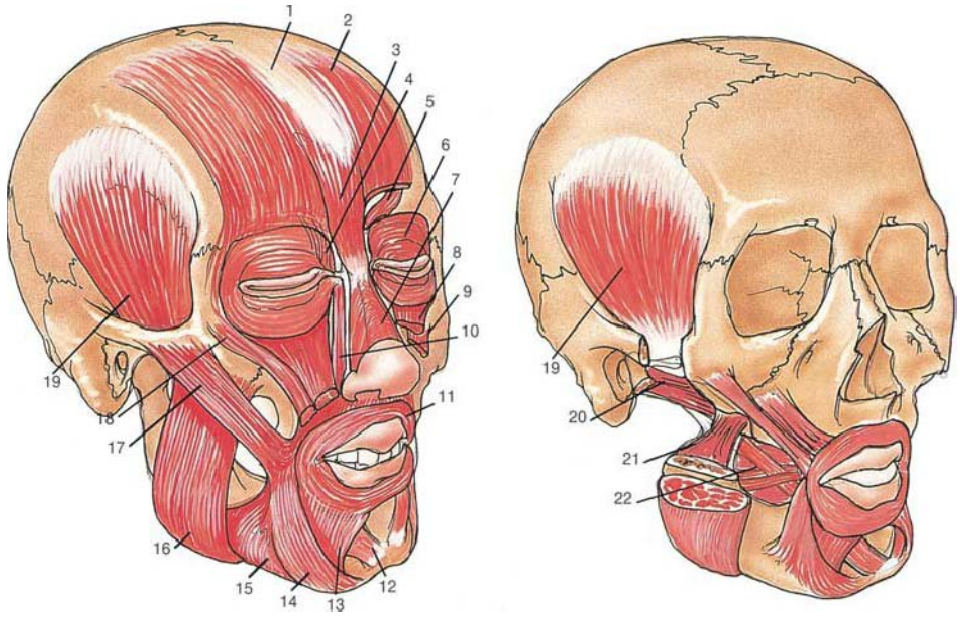


Figure 1.9 Facial muscles. *1*, Galea aponeurotica; *2*, frontalis; *3*, procerus; *4*, depressor supercilii; *5*, corrugator supercilii; *6*, orbicularis oculi; *7*, nasalis; *8*, levator labii superioris; *9*, levator anguli oris; *10*, levator labii superioris alaeque nasi; *11*, orbicularis oris; *12*, mentalis; *13*, depressor labii inferioris; *14*, depressor anguli oris; *15*, platysma; *16*, masseter; *17*, zygomaticus major; *18*, zygomaticus minor; *19*, temporalis; *20*, lateral pterygoid; *21*, medial pterygoid; *22*, buccinator.

Parotid Gland

The parotid gland, which is anterior to and below the lower part of the ear, extends subcutaneously backward over the anterior portion of the sternocleidomastoid muscle, forward over the masseter muscle, and deeply behind the ramus of the mandible to lie between the mandible and the external acoustic meatus and mastoid process (Fig. 1.10). The gland is roughly divided into a lateral and medial portion by the course of the facial nerve. Related to the parotid gland are several periparotid and intraparotid lymph nodes, which may swell. The parotid gland drains through the parotid duct. It is innervated by the auriculotemporal nerve from the otic ganglion.

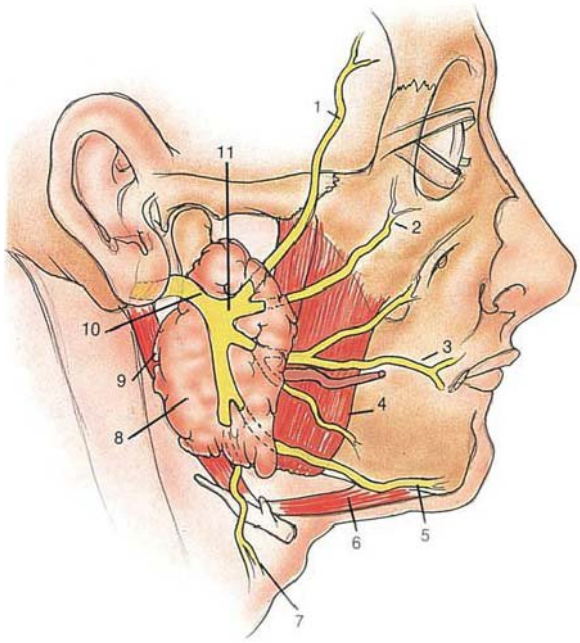


Figure 1.10 Parotid gland and facial nerve. *1*, Temporal branch; *2*, zygomatic branch; *3*, buccal branch; *4*, masseter muscle; *5*, marginal mandibular branch; *6*, anterior digastric muscle; *7*, cervical branch; *8*, parotid gland; *9*, posterior digastric muscle; *10*, seventh cranial or facial nerve; *11*, pes anserinus.

Facial Nerve

The anatomic characteristics of the facial nerve vary in the extracranial portion of the nerve. Identification of the nerve depends on marking the position of the posterior belly of the digastric muscle, the external meatal cartilage, the tympanomastoid suture line, and the styloid process.

ORAL STRUCTURES

Maxilla

The maxilla is the chief component of the upper jaw (Fig. 1.11). In addition to housing the dental apparatus and the maxillary sinus, it is related posteriorly to the medial and lateral pterygoid plates. The hard palate unites the paired maxilla and forms the bony roof of the oral cavity. Sensation to the upper teeth is provided by the maxillary nerve through the posterior superior and anterior superior alveolar nerves. The infraorbital nerve, another branch of V2, provides sensation over the face of the maxilla and soft tissues.

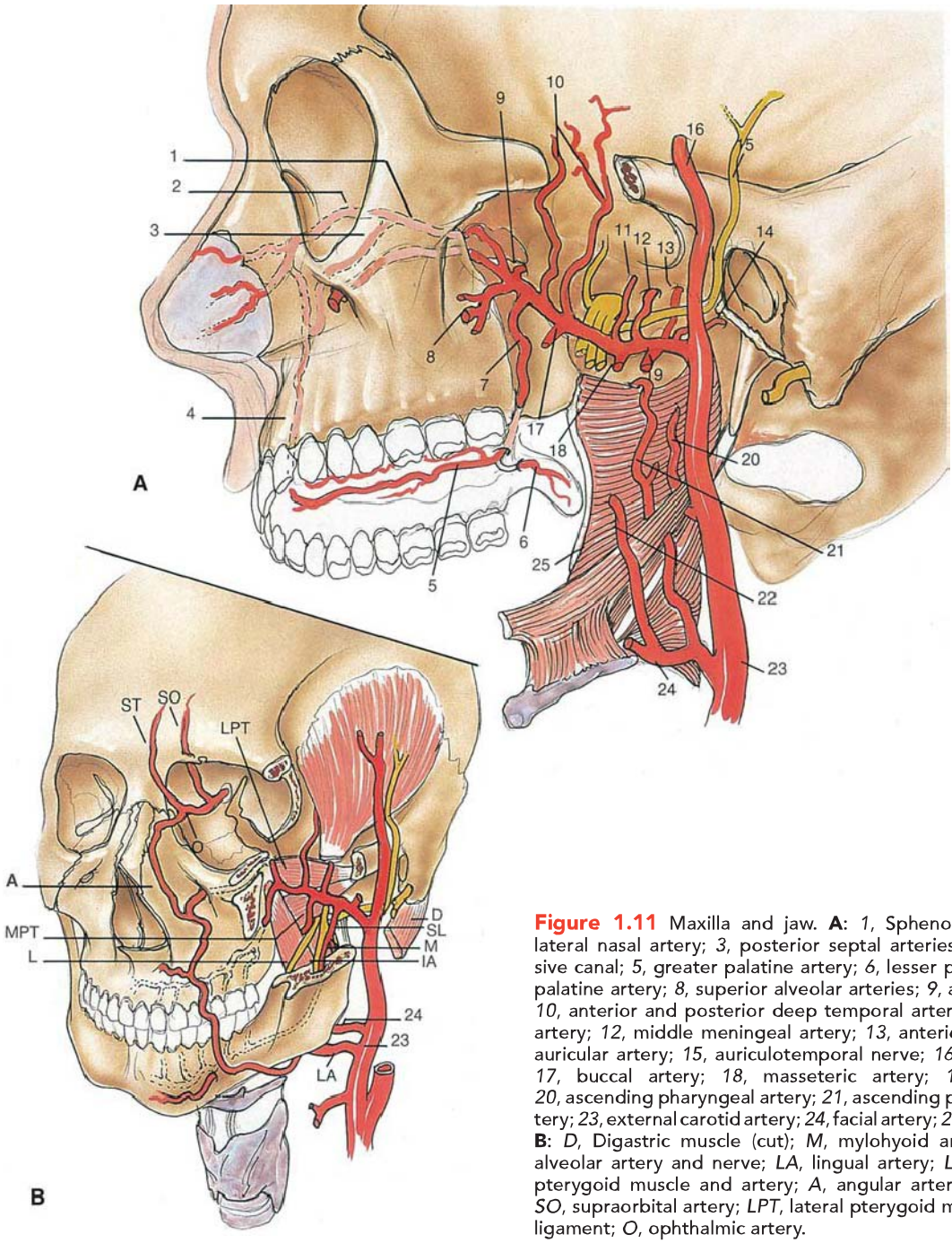


Figure 1.11 Maxilla and jaw. **A**: *1*, Sphenopalatine artery; *2*, posterior lateral nasal artery; *3*, posterior septal arteries; *4*, anastomosis in the incisive canal; *5*, greater palatine artery; *6*, lesser palatine artery; *7*, descending palatine artery; *8*, superior alveolar arteries; *9*, artery of the pterygoid canal; *10*, anterior and posterior deep temporal arteries; *11*, accessory meningeal artery; *12*, middle meningeal artery; *13*, anterior tympanic artery; *14*, deep auricular artery; *15*, auriculotemporal nerve; *16*, superficial temporal artery; *17*, buccal artery; *18*, masseteric artery; *19*, inferior alveolar artery; *20*, ascending pharyngeal artery; *21*, ascending palatine artery; *22*, tonsillar artery; *23*, external carotid artery; *24*, facial artery; *25*, superior constrictor muscle. **B**: *D*, Digastric muscle (cut); *M*, mylohyoid artery and nerve; *IA*, inferior alveolar artery and nerve; *LA*, lingual artery; *L*, lingual nerve; *MPT*, medial pterygoid muscle and artery; *A*, angular artery; *ST*, supratrochlear artery; *SO*, supraorbital artery; *LPT*, lateral pterygoid muscle; *SL*, sphenomandibular ligament; *O*, ophthalmic artery.

Palate

The palate intervenes between the nasal and oral cavities (Fig. 1.12). It consists of the maxilla, the horizontal process of the palatine bone, and the pterygoid plates. Soft tissues covering this area form the hard and soft palates of the roof of the mouth. The skeletal core of the soft palate is the palatine aponeurosis. The most superficial muscle fibers on the pharyngeal surface of the soft palate are those of the palatopharyngeus muscle. The levator veli palatini, tensor veli palatini, and uvular muscle complete the structures of the soft palate.

Mandible

The mandible, or lower jaw, consists of the tooth-bearing body and the ramus that extends upward from the angle of the mandible. The ramus, including the angle, is covered externally by the masseter muscle, which is crossed by the facial nerve and parotid duct. Between the ramus and the medial pterygoid muscle are the inferior alveolar and lingual nerves. Overlapping the posterior border of the ramus is the parotid gland, and within and paralleling this border is the upper portion of the external carotid artery. The superficial branch of this artery emerges from

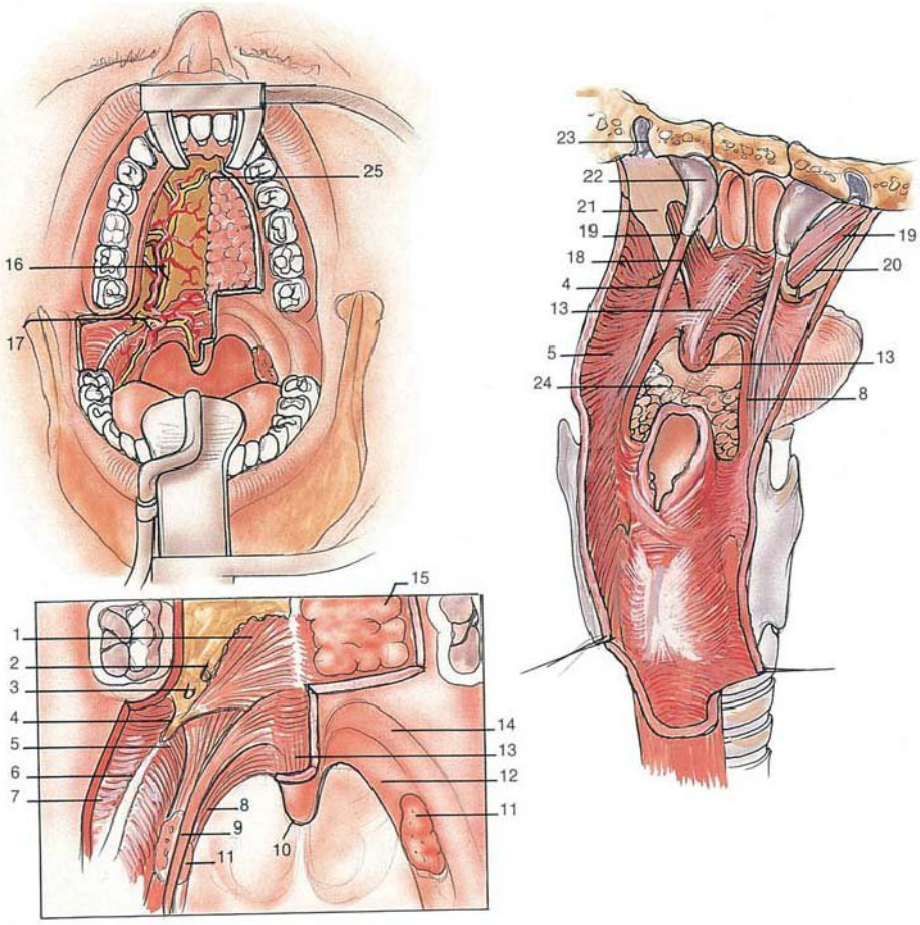


Figure 1.12 Palate. *1*, Veli palati muscles; *2*, greater palatine foramina; *3*, lesser palatine foramina; *4*, pterygoid hamulus; *5*, superior pharyngeal constrictor muscle; *6*, pterygomandibular raphe; *7*, buccinator muscle; *8*, palatopharyngeus muscle; *9*, palatoglossus muscle; *10*, uvula; *11*, palatine tonsil; *12*, palatopharyngeal arch; *13*, uvular muscle; *14*, palatoglossal arch; *15*, palatine glands; *16*, greater palatine artery and nerve; *17*, lesser palatine artery and nerve; *18*, salpingopharyngeus muscle; *19*, levator veli palatini muscle; *20*, tensor veli palati muscle; *21*, pharyngobasilar fascia; *22*, cartilaginous auditory tube; *23*, carotid canal; *24*, vallate papillae; *25*, incisive foramen.

the parotid gland behind the temporomandibular joint, and its internal maxillary branch runs transversely deep to the ramus. Inferiorly and medially, the angle and posterior part of the body of the mandible are related to the submandibular gland, and medially, the anterior part of the mandible is adjacent to the sublingual glands. The musculature most intimately concerned with the mandible and its movements consists of the masseter, temporal, and two pterygoid muscles (Fig. 1.9). These muscles govern mastication and are innervated by the third division of the trigeminal nerve.

Hyoid Bone and Tongue

The hyoid bone, to which are attached infrahyoid and suprahyoid muscles, effectively separates the anterior suprahyoid and infrahyoid fascial compartments. The suprahyoid muscles are the digastric and stylohyoid

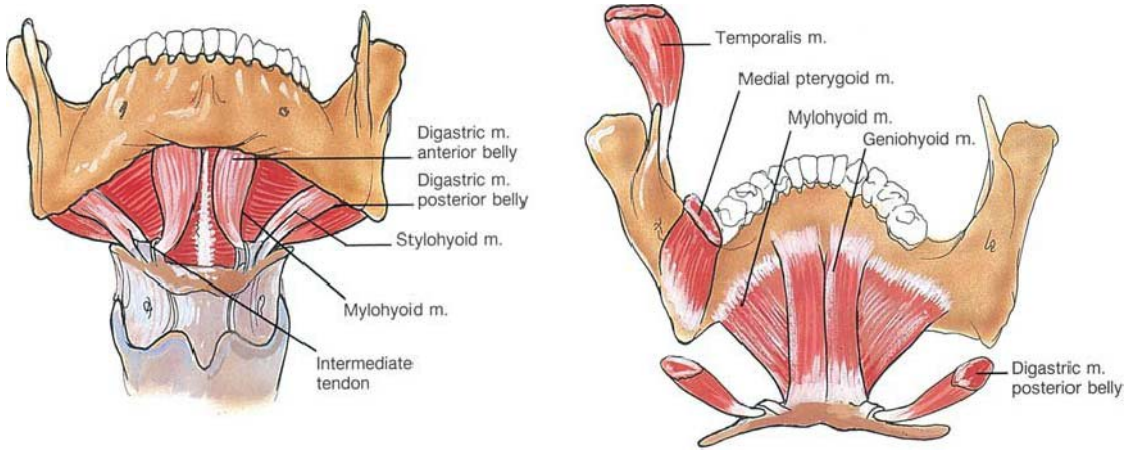


Figure 1.13 Suprahyoid muscles.

muscles, the mylohyoid and the geniohyoid muscles, and the muscles of the tongue (Fig. 1.13). The extrinsic muscles of the tongue are the genioglossus, the hyoglossus, and the styloglossus. The intrinsic muscles of the tongue are complicated bundles of interlacing fibers, among which are connective tissue septa. The midline septum lies between and effectively separates the muscles, nerves, and vessels of the two sides. It is an almost bloodless midline plane.

Submandibular Gland

The submandibular gland occupies most of the submandibular triangle and expands beyond this area over the superficial structures of the anterior and posterior bellies of the digastric muscle (Fig. 1.14). Its posterior border is close to the lower part of the parotid gland at the angle of the jaw, where it is separated from this gland by the stylomandibular ligament. The submandibular gland is crossed superficially by the facial vein and sometimes by the ramus mandibularis branch of the facial nerve. The larger submandibular lymph nodes lie along the superficial upper border of the gland, between it and the mandible. The anterior portion of the submandibular gland lies directly against the mylohyoid muscle and the mylohyoid nerve. Medial to the mandible and above the level of the submandibular gland is the lingual nerve in its course toward the tongue. When the submandibular gland is removed, the facial vein is sacrificed, but the ramus mandibularis branch of the facial nerve is preserved to avoid disruption of the corner of the mouth. The facial artery passes across the upper surface of the gland, usually grooving it deeply before rounding the lower border of the mandible, and must be sacrificed in removal of the gland. The submandibular and sublingual glands are innervated from the submaxillary ganglion fibers that accompany the sensory fibers of the lingual nerve. These fibers originate in the chorda tympani and pass into the submandibular ganglion.

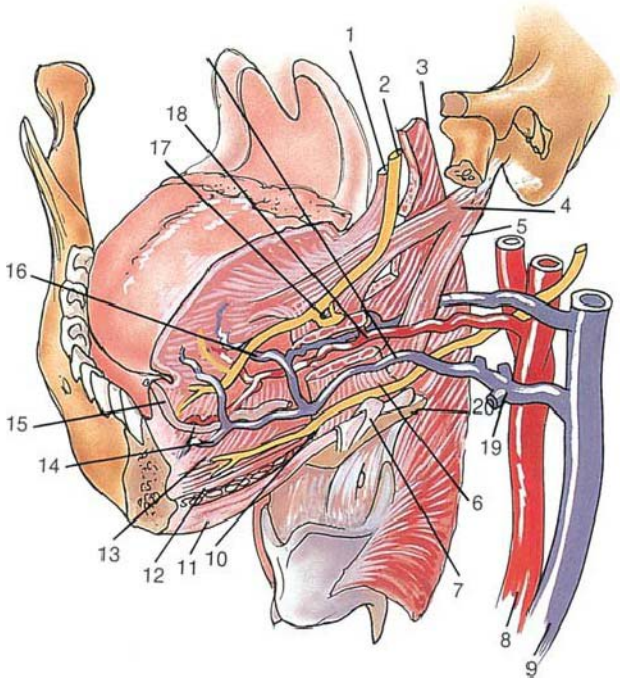


Figure 1.14 Submandibular triangle. *1*, Palatoglossus muscle; *2*, lingual nerve; *3*, superior constrictor muscle; *4*, styloglossus muscle; *5*, stylopharyngeus muscle; *6*, hyoglossus muscle (cut); *7*, stylohyoid muscle (cut); *8*, external carotid artery; *9*, internal jugular vein; *10*, hypoglossal nerve; *11*, digastric muscle, anterior belly; *12*, geniohyoid muscle; *13*, genioglossus muscle; *14*, sublingual artery and vein; *15*, submandibular duct; *16*, deep lingual artery and vein; *17*, submandibular ganglion; *18*, deep lingual artery; *19*, common facial vein; *20*, hyoid bone.

PHARYNX AND LARYNX

The wall of the pharynx consists of mucosa and voluntary muscle. The mucosal structure of the pharynx varies. That of the nasal part is ciliated and resembles the mucosa of the nose. In the rest of the pharynx, the epithelium is stratified

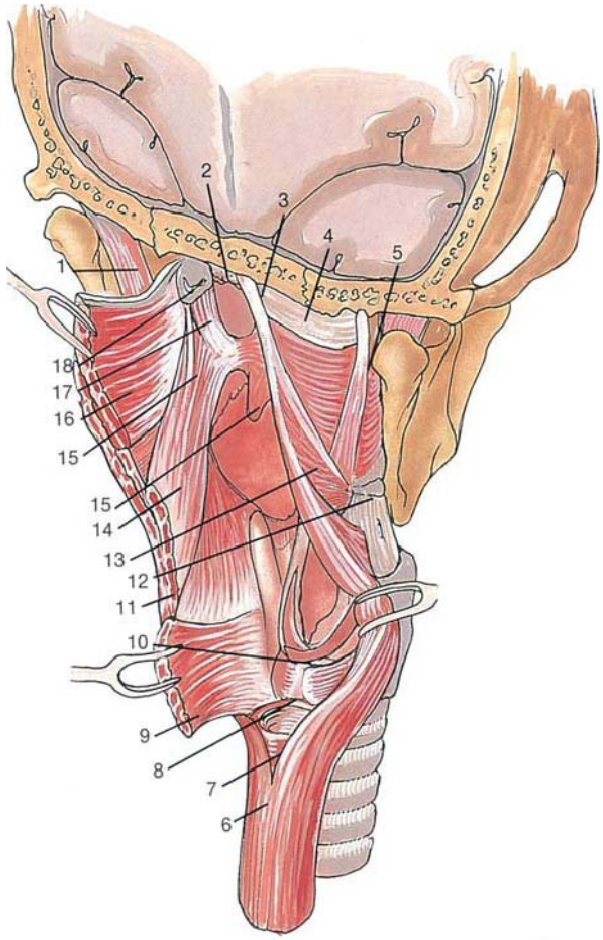


Figure 1.15 Pharynx. *1*, Digastric muscle, posterior belly; *2*, adenoid; *3*, pharyngeal raphe; *4*, pharyngobasilar fascia; *5*, stylopharyngeus muscle; *6*, longitudinal esophageal muscle; *7*, circular esophageal muscle; *8*, posterior cricoarytenoid muscle; *9*, cricopharyngeus muscle; *10*, transverse and oblique interarytenoid muscle; *11*, inferior constrictor muscle; *12*, hyoid bone; *13*, middle constrictor muscle; *14*, palatopharyngeus muscle; *15*, uvula; *16*, superior constrictor muscle; *17*, levator veli palati muscle; *18*, cartilaginous auditory tube. Please note that the posterior belly of the digastric muscle arises from the mastoid notch on the medial side of the base of the mastoid process.

squamous tissue. The muscular wall of the pharynx with its thin covering of buccal pharyngeal or visceral fascia is separated from the prevertebral fascia by an area of loose connective tissue that constitutes the retropharyngeal space.

Nasopharynx

The nasal part of the pharynx, the nasopharynx, is continuous anteriorly through the choanae with the nasal cavities (Fig. 1.15). The floor is the upper surface of the soft palate. The fornix or roof, the mucosa of which is attached close to the base of the skull, slopes downward and backward to become continuous with the posterior wall. The eustachian tubes are prominent on the lateral aspect of the nasal pharynx. There may be adenoid tissue in the superior recess of the nasopharynx.

Oropharynx

The oropharynx is continuous anteriorly through the fauces, or oral pharyngeal isthmus, with the oral cavity. The boundaries of the fauces are the posterior border of the soft palate above, the palatine arches laterally, and the dorsum of the tongue. Below the fauces, the anterior wall of the pharynx is the posterior or pharyngeal dorsum of the tongue. On the posterior parts of the dorsum of the tongue lie irregular nodules of tissue known as the lingual tonsils. The lateral wall of the passageway of the fauces houses the large palatine tonsils. The lingual tonsils in the anterior aspect, the palatine tonsils in the lateral aspect, and the pharyngeal tonsils or adenoids in the posterior and superior aspects form a ring of lymphoid tissue known as the Waldeyer ring.

Hypopharynx

The laryngeal part of the pharynx, or hypopharynx, extends from just above the level of the hyoid bone superiorly to the lower border of the cricoid cartilage inferiorly, narrowing rapidly to become continuous with the esophagus. The anterior wall is formed laterally by mucosa on the medial surface of the thyroid cartilage and centrally or medially by the larynx and its appendages. Above are the epiglottis and the aditus of the larynx. Below the aditus, the anterior wall of the pharynx is also the posterior wall of the larynx. Lateral to the epiglottis are the lateral glossoepiglottic folds that form the anterolateral boundary between the oral and laryngeal parts of the pharynx. Below these folds, the hypopharynx extends forward around the sides of the larynx between this area and the thyroid cartilage. These bilateral expansions are the piriform recesses or sinuses.

The intrinsic portion of the larynx consists of the epiglottis, false vocal folds, laryngeal ventricles, paired true vocal folds, and arytenoid cartilages in the posterior aspect. Contained within the aryepiglottic folds are the paired corniculate and cuneiform cartilages. The space between the two vocal folds is the glottis.

The muscles of the pharynx are the superior, middle, and inferior constrictors. These muscles look like ice cream cones inserted into one another. They gradually merge to form the cricopharyngeus muscle at its inferior extent and then the esophagus. Each constrictor inserts with the corresponding muscle of the opposite side and the midline into a posterior midline raphe. These muscles are innervated by cranial nerve X through the pharyngeal plexus. Dehiscence in the pharyngeal constrictors may give rise to Zenker diverticula. Immediately lateral to the pharyngeal muscles are the great vessels of the neck and cranial nerve X.

Larynx

The major structural elements of the larynx are the shield-shaped thyroid cartilage and cricoid cartilages (Fig. 1.16). They join through the cricothyroid joint. The superior cornua of the thyroid ala articulate through several small cartilages with the hyoid bone. Overlying the structure of this skeletal framework are the infrahyoid muscles, which include the paired sternohyoid, sternothyroid, omohyoid, and thyrohyoid muscles.

The epiglottis is formed of fibroelastic cartilage and has multiple perforations that allow free access of lymphatic drainage or tumor to the preepiglottic space. The preepiglottic space is a C-shaped space bounded superiorly by the median glossoepiglottic ligament, inferiorly by the thyroid cartilage, anteriorly by the thyrohyoid membrane, and posterolaterally by the epiglottis and aryepiglottic folds. Free dissemination of tumor can occur within the preepiglottic space. The paired arytenoid cartilages provide an attachment for the vocal ligament and movement of the vocal folds. The intrinsic muscles of the larynx are innervated by the recurrent laryngeal nerve. The exception is the cricothyroid muscle, which is innervated by the superior laryngeal nerve. The recurrent laryngeal nerve enters inferiorly and laterally to the cricothyroid articulation through the Killian-Jamieson area. The recurrent laryngeal nerve on the left originates over the aortic arch and ascends in the neck to innervate the larynx. On the right, this structure goes around the subclavian artery.

THE NECK

Cervical Triangles

The prominent landmarks of the neck are the hyoid bone, the thyroid cartilage, the trachea, and the sternocleidomastoid muscles (Fig. 1.17). The sternocleidomastoid muscles divide each side of the neck into two major triangles, anterior and posterior. The anterior triangle of the neck may be further delimited by the strap muscles into the superior and inferior carotid triangles. The posterior triangles or lateral triangles of the neck are formed by the posterior border of the sternocleidomastoid muscle anteriorly, the clavicle inferiorly, and the anterior border of the trapezius muscle

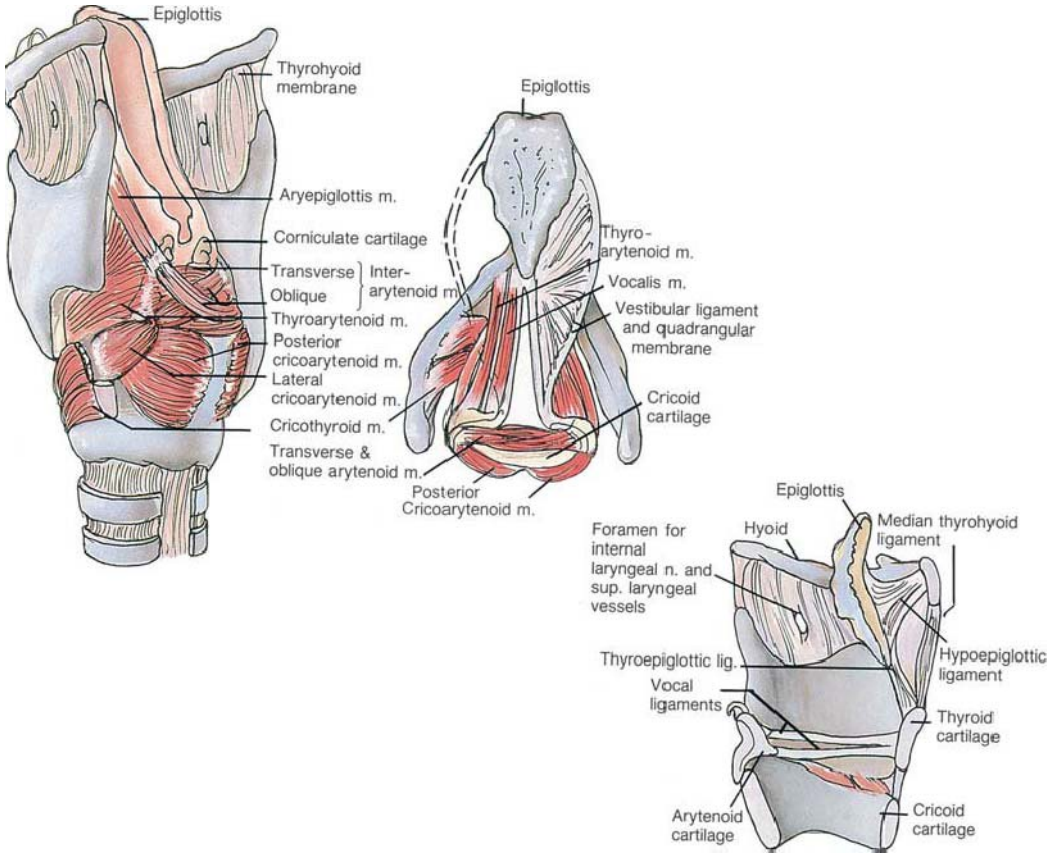


Figure 1.16 Larynx.

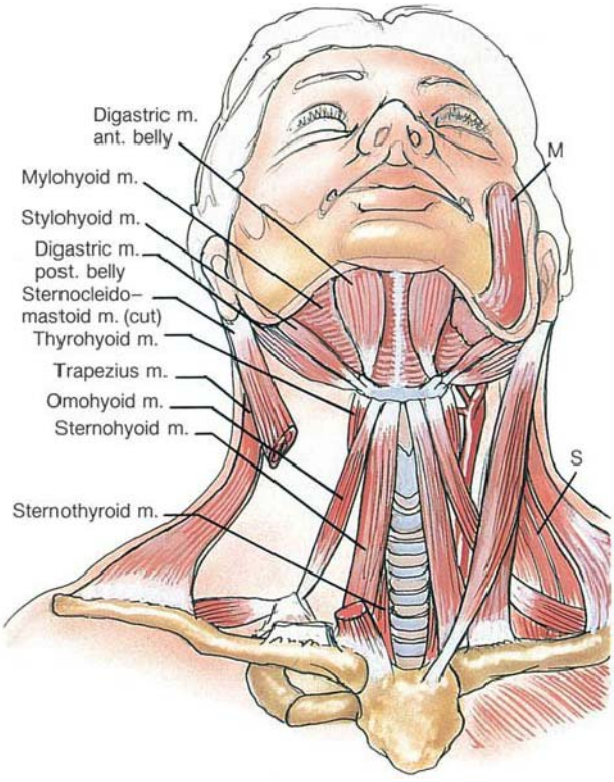


Figure 1.17 Muscles and triangles of the neck. *S*, scalene muscle; *M*, masseter.

posteriorly. The omohyoid muscle divides this triangle of the neck into a small inferior subclavian triangle and a larger posterior occipital triangle. Deep to these muscles are the scalenes, which form much of the muscle mass of the posterior and lateral portions of the neck. The brachial plexus and subclavian artery course between the anterior and middle scalene muscles. The subclavian vein courses anteriorly to the anterior scalene muscle.

Inferior Portion of the Neck

In the inferior root of the neck and closely associated with the brachial plexus are the paired phrenic nerves that course medially to innervate the diaphragm (Fig. 1.18). These nerves originate in the ventral rami of the cervical plexus of the third, fourth, and fifth cervical nerve rootlets. The subclavian artery gives rise to the thyrocervical trunk. The transverse cervical and suprascapular arteries usually course laterally over the surface of the phrenic nerve. This relation allows identification of these structures. The vagus nerve lies further medially and is contained within the carotid sheath. It shares the sheath with the common, internal, and external carotid arteries and jugular vein. Posterior to the carotid sheath lies the cervical sympathetic nerve. On the surface of the carotid sheath lie the ansa hypoglossi nerves.

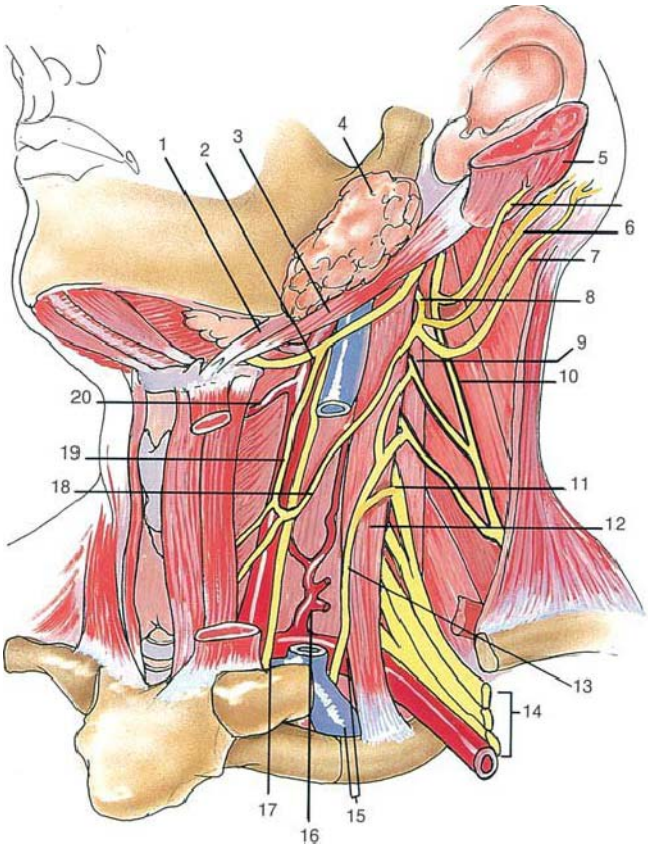


Figure 1.18 Root of neck. *1*, Stylohyoid muscle; *2*, hypoglossal nerve (cranial nerve XII); *3*, digastric muscle; *4*, parotid gland; *5*, sternocleidomastoid muscle; *6*, greater auricular nerve; *7*, lesser occipital nerve; *8*, ventral ramus (C2); *9*, ventral ramus (C3); *10*, accessory nerve (cranial nerve XI); *11*, ventral ramus (C5); *12*, anterior scalene muscle; *13*, phrenic nerve; *14*, brachial plexus; *15*, subclavian artery and vein; *16*, thyrocervical trunk; *17*, vagus nerve; *18*, inferior root ansa cervicalis; *19*, superior root ansa cervicalis; *20*, superior thyroid artery.

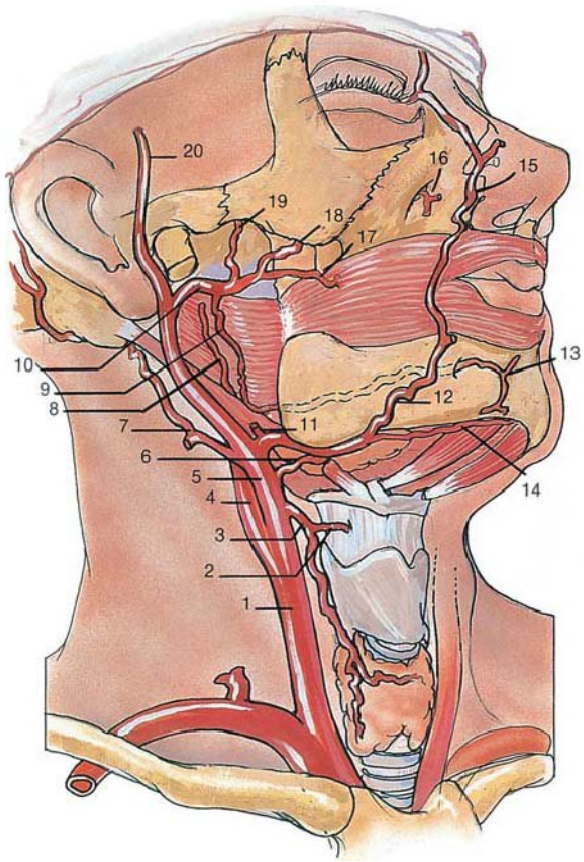


Figure 1.19 Arterial supply of the neck. *1*, Common carotid artery; *2*, superior laryngeal artery; *3*, superior thyroid artery; *4*, internal carotid artery; *5*, external carotid artery; *6*, lingual artery; *7*, occipital artery; *8*, ascending pharyngeal artery; *9*, inferior alveolar artery; *10*, maxillary artery; *11*, ascending palatine artery; *12*, facial artery; *13*, mental artery; *14*, submental artery; *15*, angular artery; *16*, infraorbital artery; *17*, buccal artery; *18*, sphenopalatine artery; *19*, middle meningeal artery; *20*, superficial temporal artery.

Lateral Portion of the Neck

The dominant structure of the lateral cervical triangle is the spinal accessory nerve. It emanates from the posterior border of the sternocleidomastoid muscle in close association with the splay of nerves of the cervical sensory plexus. It innervates the trapezius muscle on its inferior aspect in close association with the transverse cervical artery or suprascapular artery, which variably supplies the trapezius muscle.

Arterial Supply

The two common carotid arteries differ in length because the right carotid usually arises from the brachycephalic artery behind the sternoclavicular joint and the left arises from the arch of the aorta (Fig. 1.19). Both arteries end by bifurcating into the internal and external carotid arteries. Over the lateral aspect of these arteries course the paired hypoglossal nerves. The internal carotid artery is situated more posteriorly and has no branches. The external carotid artery has branches and lies slightly anteriorly. This information can be crucial in differentiating the two vessels for ligation. From its origin, the internal carotid artery ascends directly toward the carotid canal and is crossed laterally, in ascending order, by the hypoglossal nerve, occipital artery, posterior belly of the digastric and associated stylohyoid muscle, and the posterior auricular artery. Still higher and close to the base of the skull, the external carotid artery is anterolateral to the internal carotid artery, and the stylopharyngeus muscle and associated glossopharyngeal nerve, the pharyngeal branch of the vagus, and the stylohyoid ligament all pass laterally to the internal carotid, between it and the external carotid artery.

After its origin in the carotid triangle, the external carotid artery passes upward, deep to the posterior belly of the digastric and stylohyoid muscles, and crosses the styloglossus and the stylopharyngeus muscles on their lateral aspects; then, parallel to the ramus of the mandible, it passes into the deeper portion of the parotid gland. The external carotid artery has branches to the superior thyroid, lingual, facial, ascending pharyngeal, occipital, posterior auricular, maxillary, transverse facial, and superficial temporal arteries.

Venous Supply

The veins of the neck vary considerably in their connections with each other and in their relative sizes (Fig. 1.20). Those conducting blood downward from the head and face include the external jugular, anterior jugular, internal jugular, and vertebral veins. At the base of the neck are the suprascapular and transverse cervical veins and the subclavian vein, which unites with the internal jugular vein to form the brachycephalic or innominate vein. The subcutaneous veins and the external and anterior jugular veins are especially variable in size and course.

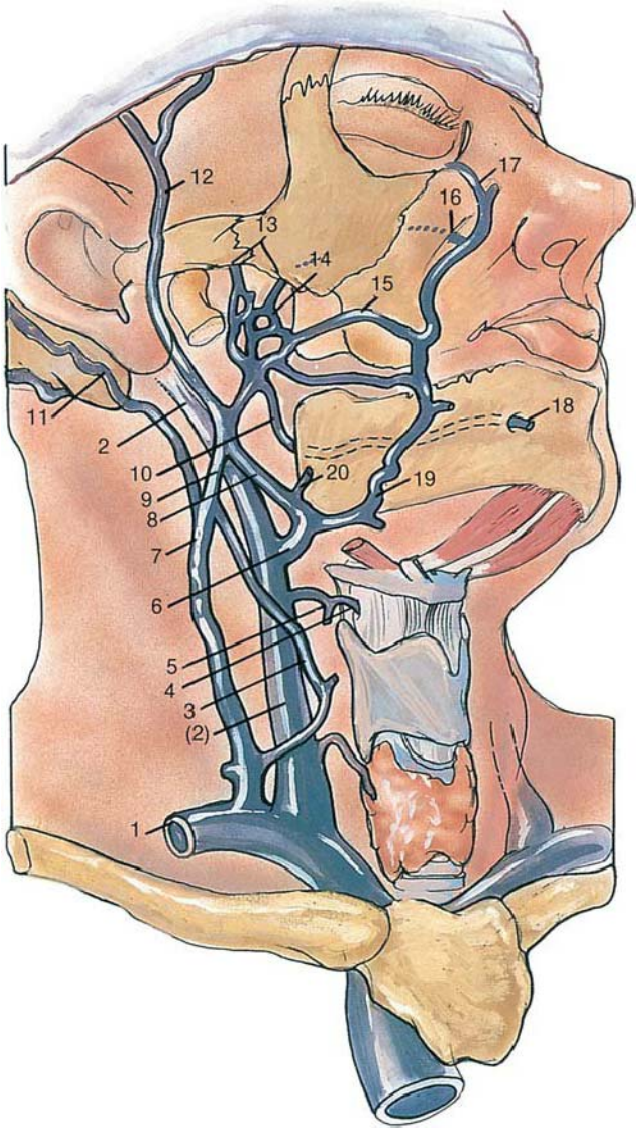


Figure 1.20 Venous supply of the neck. *1*, Subclavian vein; *2*, internal jugular vein; *3*, anterior external jugular vein; *4*, superior laryngeal vein; *5*, superior thyroid vein; *6*, common facial vein; *7*, posterior external jugular vein; *8*, retromandibular vein, anterior division; *9*, retromandibular vein, posterior division; *10*, inferior alveolar vein; *11*, posterior auricular vein; *12*, superficial temporal vein; *13*, deep temporal vein; *14*, pterygoid plexus; *15*, deep facial vein; *16*, infraorbital vein; *17*, angular vein; *18*, mental vein; *19*, facial vein; *20*, external palatine vein.

Lymphatic Vessels

The lymphatic system of the neck consists of numerous lymph nodes intimately connected with each other by lymphatic channels and the terminations of the thoracic and right lymphatic ducts. The deep cervical lymph nodes are numerous and prominent, and many of them are large. They form a chain embedded in the connective tissue of the carotid sheath. Most are in that portion of the sheath around the internal jugular vein. They extend from the base of the skull to the base of the neck. Two nodes that deserve particular attention are the superior jugulodigastric node at the junction of the internal jugular vein and the posterior belly of the digastric and the inferior juguloomohyoid node at the junction of that muscle and the internal jugular vein. Block resection of the neck in a standard radical or modified manner relies on reproducible and consistent lymphatic drainage pathways for success.

Viscera

The visceral structures of the neck include the thyroid and parathyroid glands, a portion of the pharynx, the larynx, the trachea, the esophagus, and sometimes portions of the thymus (Fig. 1.21). The thyroid gland lies below and on the side of the thyroid cartilage, covered anteriorly by the infrahyoid muscles. A pyramidal lobe of the thyroid may extend superiorly from the isthmus that connects the two lobes of the thyroid gland. On the posterior surface of the thyroid gland lie the paired parathyroid glands. Successful parathyroid exploration and thyroidectomy depend on accurate identification and preservation of the recurrent laryngeal nerves and identification of the parathyroid glands. Landmarks that are used successfully to locate these

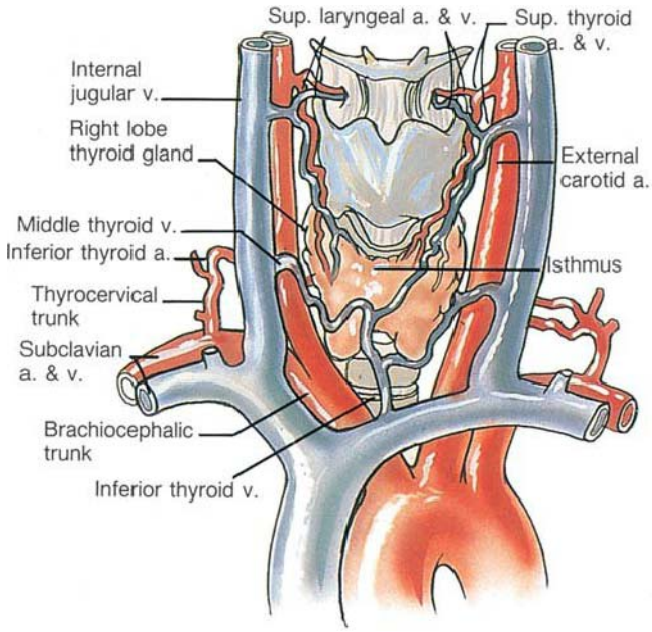


Figure 1.21 Thyroid and parathyroid glands.

structures include the trachea, common carotid artery, and inferior thyroid artery, which form a triangle within which the surgeon usually finds the recurrent laryngeal nerve. Lymphatic drainage occurs along the peritracheal nodes. Venous drainage similarly is directed inferiorly along the inferior thyroid veins.

The four or more parathyroid glands develop from the dorsal extremities of the third and fourth pharyngeal pouches. As the thyroid and thymus and their associated parathyroid glands move caudally from the region in which they originate, the thymus normally descends beyond the level at which the thyroid halts. The parathyroids from the fourth pouches (superior parathyroid glands) usually are situated more craniad than the thyroid gland, and those derived from the third pouches (inferior parathyroid glands) are usually freed from the thymus and become associated with the thyroid gland at its lower pole. Both sets of parathyroid glands usually are situated on the posterior aspect of the lateral lobes of the thyroid gland, but there are many exceptions. Because of the manner in which they arise and migrate into the neck, the glands often are displaced and may be situated in other portions of the thyroid gland or lie above or below it.

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2 Basic Surgical Principles

A. Bradley Boland *Emily Rogers*

PREOPERATIVE ASSESSMENT AND EVALUATION

Frequently overlooked by surgeons, the preoperative assessment is one of the most important components to planning a successful operation. The preoperative evaluation begins in the office with a detailed history and physical. All medications, including herbal supplements and dosages, must be recorded. It is also prudent to discuss illicit drug use, alcohol consumption, and tobacco use with the patient as these social habits can affect anesthesia and postoperative outcomes. Functional capacity can be assessed with questions about activities of daily living. Patients who can climb one flight of stairs or walk several blocks expend four or more metabolic equivalents (METs) and typically require no further cardiac workup (Table 2.1) (1). However, patients who can do little more than dress themselves will need further cardiac assessment prior to surgery (2). Based on the information gathered at this initial visit, the patient's overall health status can be judged and further assessment completed as necessary.

The goal of preoperative assessment is to identify patients who are at risk of perioperative complications and work to limit their risk prior to surgery. The most important component is the cardiac assessment. The American College of Cardiology (ACC) and American Heart Association (AHA) created a task force in 1997 to develop perioperative guidelines to better direct the preoperative workup. These guidelines were updated in 2007 and provide tools to evaluate cardiac status prior to noncardiac surgery (1). The guidelines are summarized in algorithm format (Fig. 2.1) (1). The primary decisions are limited to two essential questions—should the patient undergo additional cardiac evaluation prior to surgery, and is a perioperative beta-blocker indicated to reduce the risk of cardiac complications?

While the algorithm appears complex at first glance, it is actually a very simple tool to quickly answer these questions. The first step is to identify the urgency of the procedure, as emergent or more urgent procedures cannot wait for thorough cardiac evaluation and possible revascularization. The next step is determining the risk of the procedure being performed. For most otolaryngology cases, the risk will be low to intermediate as the high-risk category is generally reserved for vascular operations. Once these steps are completed, the patient's current functional status and symptoms as well as past medical history are utilized to determine the need for further preoperative cardiac assessment, such as stress testing and potential referral for formal cardiology evaluation.

The algorithm utilizes five clinical risk factors—history of ischemic heart disease, prior or compensated heart failure, diabetes mellitus, chronic kidney disease, and cerebral vascular disease—to identify and stratify a patient's risk for cardiac complications. In addition, any symptoms of active myocardial ischemia, heart arrhythmia, valvular heart disease, or decompensated heart failure should prompt a formal cardiology referral. Per the ACC/AHA guidelines, an ECG should be obtained in all patients with a history of coronary artery disease, peripheral vascular disease, or congestive heart failure who are undergoing head and neck surgery. Currently, there is no consensus on minimum age at which an ECG should be routinely obtained. If an abnormality is identified on ECG, then this would also prompt referral to a cardiology subspecialist for further evaluation.

Perioperative beta-blockade has been shown to reduce the incidence of perioperative cardiac risk in patients with any of the five clinical risk factors listed in the prior paragraph. Beta-blockade should be considered in these higher risk patients even in emergent operations. Usually patients with chronic medical conditions that predispose them to heart disease will have a primary internal medicine

TABLE 2.1 ESTIMATED ENERGY REQUIREMENTS FOR VARIOUS ACTIVITIES

1 MET	Can you … Take care of yourself? Eat, dress, or use the toilet? Walk indoors around the house? Walk a block or 2 on level ground at 2–3 mph (3.2–4.8 kph)?	4 METs	Can you… Climb a flight of stairs or walk up a hill? Walk on level ground at 4 mph (6.4 kph)? Run a short distance? Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?
4 METs			Do light work around the house like dusting or washing dishes?
		>10 METs	Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football? Participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?

Modified from Hlatky, et al. A brief self administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol* 1989;64:651–654, copyright 1989, with permission from Elsevier, and adapted from Fleisher LA, et al. *Circulation* 2007;116(17):e418–e419, with permission. Ref. (28).
kph, kilometers per hour; MET, metabolic equivalent; mph, miles per hour.

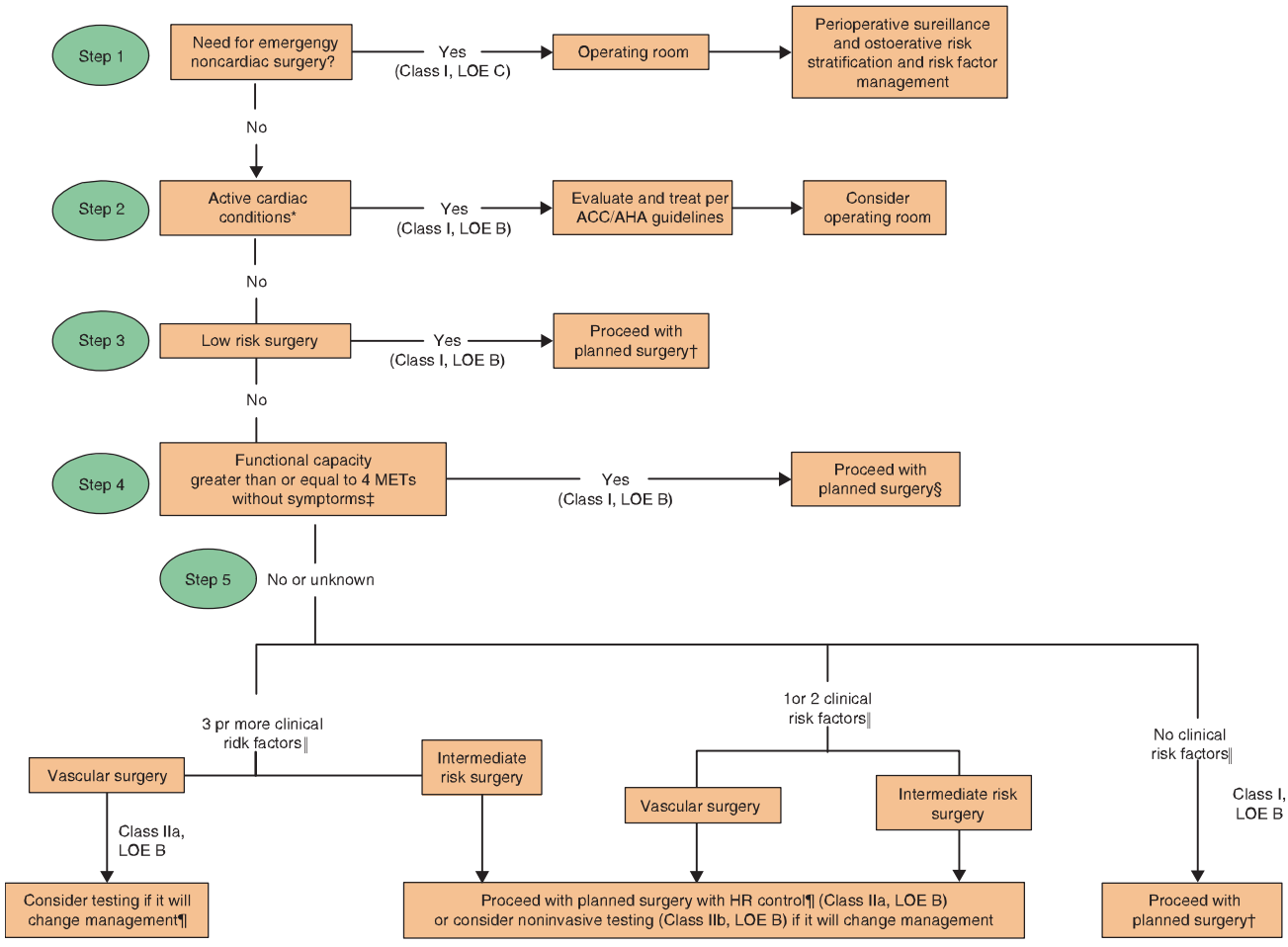


Figure 2.1 Cardiac evaluation and care algorithm for noncardiac surgery based on active clinical conditions, known cardiovascular disease, or cardiac risk factors for patients 50 years of age or greater. From Fleisher LA, et al. *Circulation* 2007;116(17):e418–e419, with permission.

physician who can assist in the decision-making process when the operation is done on an elective basis.

After the cardiac assessment, the next most important factor in preoperative management is pulmonary evaluation. Patients with a history of restrictive or obstructive pulmonary disease, long-term smokers, oxygen-dependent patients, and/or a recent history of upper respiratory infection need further pulmonary workup. Pulmonary studies including a chest x-ray, arterial blood gas, or pulmonary function testing are examples of routine tests required for preoperative risk assessment and management. Often patients with chronic lung disease will need detailed evaluation and recommendations for perioperative management from a pulmonary subspecialist (3).

Renal and hepatic function also affect perioperative patient management and risk. The clearance of medications from the body is nearly always affected by either renal or hepatic function. Therefore, both should be assessed with careful history and laboratory assessment as indicated to appropriately choose and dose perioperative medications including antibiotics, beta-blockers, sedatives, and analgesics. Patients with asymptomatic elevations in liver-associated enzymes often can proceed to surgery without delay. However, patients with active hepatitis or cirrhosis do have an increased risk of postoperative complications and mortality, which may require postponement of surgery and/or aggressive preoperative planning for risk reduction (4). Hepatic dysfunction alone can be an independent risk factor for perioperative morbidity and mortality, especially in patients undergoing high-risk operations. Bleeding complications are increased due to the propensity for coagulopathy from decreased liver synthetic function and thrombocytopenia from splenic sequestration associated with severe liver disease. Head and neck operations are considered low to intermediate risk, and the studies that have defined perioperative risk include few head and neck operations (5). One study limited to the evaluation of perioperative risk in otolaryngology cases found a history of hepatitis was associated with complications, but only five patients with hepatitis or a history of hepatitis were included in the analysis (6). Another recent study found no statistically significant increase in overall flap complications in patients with hepatic dysfunction although there was an increase in incidence of postoperative flap hematoma (7).

Perioperative medication management is essential even in the absence of renal or hepatic impairment. A complete medication review including over-the-counter and herbal supplements is important not only to assess a patient's known comorbidities but also to prevent intra- and postoperative complications. In general, most chronic medications can be taken with a glass of water the morning of the operation. Common exceptions to this rule include oral hypoglycemic medications, chronic anticoagulation, diuretics, and nonstatin hypolipidemics. However, the risk and benefit for continuing each individual medication should be addressed preoperatively. Type I and II diabetic patients on chronic insulin therapy will need to develop a perioperative plan with their primary physicians or endocrinologists especially for longer, more complex operations.

Anticoagulation and antiplatelet therapy alone can involve significant preoperative planning and execution. The indication for anticoagulation is important for devising a plan for perioperative management. For instance, if a patient is taking anticoagulation for the treatment of acute venous thromboembolic (VTE) disease or has a mechanical heart valve, it is much more important to maintain therapeutic anticoagulation throughout the perioperative period than if a patient is taking anticoagulation for prevention of VTE, in patients with a remote history of cerebrovascular accident, or in patients with atrial fibrillation. Antiplatelet therapy planning is likewise dependent on the reason for use. In most cases, antiplatelet therapy will be discontinued due to operative bleeding risk. Exceptions are when bleeding risk is minimal or discontinuation will cause a life-threatening complication, that is, coronary artery stent thrombosis.

INFORMED CONSENT

Consent is the process of obtaining permission to perform a surgical procedure after thoroughly informing the patient about all aspects of the procedure. Consent is typically obtained from the patient on whom the procedure will be performed; however, should the patient in need of surgery be unable to provide consent, the next of kin or legal guardian can provide consent. Examples of the types of patients who are unable to personally give consent are not limited to the following: patients under the age of 18, patients who are intubated and/or sedated, and patients with mental health problems or mental handicaps. Patients giving consent must have decision-making capabilities.

The consent must state in layman's terms the procedure that is to be performed as well as the risks, benefits, and alternatives. Risks of the surgical procedure, including possible complications, should be discussed with the patient. Benefits of the procedure should also be made clear to the patient. Alternatives to the procedure should be reviewed and it should be clarified that the alternative to refuse surgery is the patient's ultimate choice. In acquiring consent, the patient must understand his or her disease process, the goals of the procedure, and possible outcomes.

UNIVERSAL PRECAUTIONS

In 1987, the Centers for Disease Control (CDC) published a report on the prevention of blood-borne pathogen transmission in the world of health care. This document, in comparison to a similar report by the CDC in 1983, made recommendations for health care workers, which would eventually become known as "Universal Precautions." This

new report highlighted the importance of consistent use of body fluid precautions regardless of the patient's bloodborne infection status. It was wisely felt that the patients' accurate infection status was often unknown and therefore safest to implement universal precautions.

The CDC recommends the use of gloves, barrier gowns, and mucous membrane barriers, including eye protection and masks, when there is contact with body fluids or blood. Gloves are to be worn by the health care worker any time there is contact with blood or body fluids and must be changed after contact with each patient. Gowns should be donned any time a splash of blood or body fluids is expected, especially during procedures. Mucous membrane barriers, masks and eye protection, should also be worn if a splash is expected in order to prevent exposure to the eyes, nose, or mouth.

STERILE TECHNIQUE

The idea of sterile technique has evolved over the last 150 years. Joseph Lister is regarded as the father of aseptic surgical technique. In the late 1860s, Lister adopted carbolic acid for use in the operating theater in the attempt to decrease surgical wound infections and the development of gangrene. At the time, carbolic acid was being used to treat sewage odors with great success. Lister's surgical team washed their hands with carbolic acid, soaked bandages in carbolic acid, and cleaned the surgical site and instruments with carbolic acid. Lister found a dramatic decrease in surgical wound infections with the use of carbolic acid; however, carbolic acid was toxic to those who used it chronically (8). In time, the use of iodine- and alcohol-based skin preparations for both patients and surgeons evolved, and the use of surgical gloves became standard practice after being introduced by William Halsted. This section discusses aspects of sterile technique in the operating room in the hopes that surgical site infection rates can continue to improve.

Surgical Hand Scrub

The surgical hand scrub is the first step to aseptic technique and must be understood and mastered. The scrub includes the hands, forearms, and fingernails to remove debris and reduce the microbial load on the skin. Fingernails should be kept short and all jewelry removed.

The two most common types of antiseptic skin agents are povidone–iodine and chlorhexidine gluconate. Each agent has advantages and disadvantages and all surgeons should have a working knowledge of these different agents attributes. Both povidone–iodine and chlorhexidine gluconate are fast acting and effective against gram-positive organisms, gram-negative organisms, fungi, enveloped viruses, and *Mycobacterium tuberculosis*. The povidone–iodine scrub is inactivated when in contact with blood or sputum and has the potential for obvious cloth and skin staining. It should also be noted that chronic use of povidone–iodine while pregnant can lead to fetal hypothyroidism (9).

Chlorhexidine gluconate when combined with alcohol provides a quick scrub and is not affected by contact with blood or sputum. It is also effective for a longer period of time, which provides more coverage during a surgical procedure and even following the operation. Chlorhexidine should be avoided in the middle and inner ear as it can cause ototoxicity (10).

Surgical Site Preparation

After arrival to the surgery center or hospital, the patient's street clothes should be exchanged for a hospital gown. When considering hair removal, if possible it is best not to remove any hair as all forms of preoperative hair removal result in an increase in wound infection rates. Nonetheless, sometimes hair in the operative field must be removed and should be removed by clipping only. Shaving should always be avoided as it can cause skin nicks that can then harbor bacteria and cause wound infections.

The CDC and Surgical Care Improvement Project (SCIP) both advise clipping hair just prior to surgery if hair removal is required. Patients need to be instructed not to shave the operative site before surgery. In a prospective study completed by Cruse and Foord, surgical site infections were found to be highest in those shaved with a rate of 2.3%. Patients who underwent hair clipping had an infection rate of 1.7%, and those who had no form of hair removal had an infection rate of 0.9% (11).

The goal of surgical site preparation is to clean the skin and reduce the microbial load before incision. In the past, povidone–iodine or chlorhexidine–alcohol solutions were used interchangeably. Today, new studies show that chlorhexidine–alcohol is superior and should be used preferably. In a study comparing the two, 849 patients undergoing surgery were assigned either povidone–iodine or chlorhexidine–alcohol for preoperative skin antisepsis. The povidone–iodine group had a surgical site infection rate of 16% compared to 9.5% in the chlorhexidine–alcohol group (12).

INSTRUMENTS AND SUTURE MATERIAL

There are hundreds of different types of surgical instruments available to the surgeon, and with time most surgeons learn these different instruments; however, most surgeons operate with only a handful of trade standards. We review the most commonly used instruments within the operating room in this section.

Instruments

Scalpels

Scalpels are composed of two parts—the handle and the blade. Scalpel handles and blades are made of either carbon

steel or stainless steel—carbon steel blades are generally sharper and stainless steel blades last longer. Bard-Parker and Beaver are the two major types of scalpel handles. The Bard-Parker is the most widely used scalpel handle—it has a wide, flat handle and easily holds the Bard Parker no. 10, no. 11, and no. 15 blades. The Beaver handle is typically round and fits with a no. 67 or no. 64 blade and is useful for delicate, more defined procedures.

Scalpel blades come in all shapes and sizes, but the most commonly used blades are the no. 10, no. 11, and no. 15. The no. 10 blade is wide with a convex belly and is ideal for large incisions—it is not appropriate for small, meticulous incisions. The no. 11 blade tapers to a sharp point, making it very good for punctate, stab-like incisions or for incision/drainage incisions. The no. 15 blade is the most extensively used blade because it is small and great for precise incisions.

Scissors

Scissors are one of the main components in the surgeon's instrument armamentarium. There are several different types of surgical scissors and each has a specific purpose in the operating theater and should be used appropriately. The most commonly used scissors are the suture cutting scissors. These can be either curved or straight, but should only be used to cut suture. Using fine cutting scissors to cut sutures will lead quickly to very dull blades.

Scissors can be short or long, blunt or sharp tipped, or curved or straight. Metzenbaum scissors are specifically for sharp meticulous dissection and come in several different sizes. Mayo scissors are heavier for blunt dissection work. Iris scissors are typically short, sharp, and ideal for head and neck surgeries. Gradle scissors are similar to Iris scissors but tend to have a shaper tip for more delicate dissection.

Forceps

The most common forceps used within the operating suite are the Adson, Debakey, and Bishop-Harmon forceps. Forceps can be smooth, toothed, or serrated. It is important to not use serrated forceps on the skin as this can lead to a crush injury. Adson forceps are either smooth or toothed and are used for picking up skin edges. Debakey forceps are used within wounds for grasping delicate structures—they should never be used on skin. Bishop-Harmon forceps are small and lightweight and ideal for fine skin work.

Suture Material

Suture material is broken down into two major types—absorbable and nonabsorbable. Absorbable suture is enzymatically digested and loses tensile strength around 60 days. The most commonly used absorbable sutures are surgical gut, polyglactin (Vicryl), polydioxanone (PDS II), glycolic acid (Maxon), and poliglecaprone 25 (Monocryl). Nonabsorbable suture material is not hydrolyzed and maintains tensile strength. The most commonly used nonabsorbable sutures are silk, nylon, polypropylene (Prolene), and polyester (Dacron, Ethibond). It should be noted, however, that while silk is referred to as a "nonabsorbable" suture material, it is a naturally produced fiber and is absorbed by the body after a prolonged period of time.

Suture material is further divided into monofilament and braided classes. Monofilament suture is composed of one single strand of material and pulls through tissue easily with less trauma. Braided suture is made up of several strands of material and is easy to handle. One drawback of using braided suture is the possibility of organisms to reside between the strands and thus lead to a higher rate of wound infections (13).

Size of suture is important when closing different types of wounds. The size of suture is calculated by the diameter of the suture to handle a specific tensile strength. Suture size is described using zeros—the higher number of zeros equals a fine, small suture. For example, 2-0 Vicryl is much thicker and stronger than 4-0 Vicryl and the same is true for all types of suture material.

Other important factors to consider when choosing suture material are the memory, elasticity, and tissue reactivity of different types of material. Memory is the ability of a suture material to return to its original configuration. Sutures with increased memory are more difficult to handle and require more knots. Sutures with high memory are glycolic acid (Maxon), polypropylene (Prolene), and polydioxanone (PDS II). Elasticity of a suture material refers to the suture's ability to stretch and then return to its original length. Elasticity is important when dealing with wounds that are prone to postoperative swelling. Tissue reactivity is the amount of inflammation produced in response to the suture material. Studies show that synthetic and monofilament sutures have the least amount of tissue reactivity (14).

BODY POSITIONING AND EXPOSURE

One of the most important and often overlooked principles in surgery is achieving adequate exposure of the surgical site. Excellent exposure is obtained with careful preoperative planning and continuous attention to detail. In order to gain adequate exposure, the patient must be positioned appropriately. For example, when preparing for a thyroidectomy the neck must be extended to expose the operative field. This specific exposure can be aided with the placement of an axillary roll to further extend the neck. Attention to patient positioning preoperatively allows for an easier experience intraoperatively.

ANTIBIOTIC SELECTION

Preoperative antibiotics are administered to prevent surgical site infections. Wounds are classified into clean,

TABLE 2.2 WOUND CLASSIFICATION (15)

Class	Definition
Clean	No breaks in sterile technique, No inflammation, Noncontaminated skin
Clean–contaminated	Small break in sterile technique, Entry into GI, respiratory, or GU tracts with no gross spillage
Contaminated	Major break in sterile technique, Major contamination from GI, GU, or respiratory tracts
Dirty	Infected wound with purulent material

clean–contaminated, contaminated, and dirty depending on the anatomical site of the procedure (Table 2.2). Most clean cases do not require prophylaxis; however, this is controversial and is usually at the surgeon's discretion. All cases involving the gastrointestinal tract, including the oropharynx, should receive prophylactic antibiotic coverage.

Prophylactic antibiotics must be given within 1 hour of incision. Studies show that antibiotic concentration within tissues is optimal when given just prior to skin incision (16). The SCIP Guidelines, which were developed to reduce surgical site infection rates, also require that prophylactic antibiotics be given within 1 hour before incision. Should the operation exceed 6 hours or one to two half-lives of the antibiotic, then repeating the antibiotic intraoperatively should be considered. If prophylactic antibiotics are continued postoperatively, they should not be administered more than 24 hours after surgery end time. Studies indicate that the continuation of prophylactic antibiotics past 24 hours provides no benefit in preventing surgical site infections (17). Another potential drawback of prolonged antibiotic administration is the development of drug-resistant bacteria.

Preoperative antibiotic selection is determined by the anatomical location of the procedure and any patient allergies to specific antibiotics. The antibiotic selected should have bactericidal coverage for organisms that are most likely present in that particular anatomical location. If antibiotics are to be administered in a clean operation, then cefazolin and cefuroxime are the recommended antibiotics. Most wound infections following clean cases are secondary to *Staph* or *Strep* species and therefore, first- or second-generation cephalosporins provide adequate coverage. In patients who have a known drug allergy to cephalosporins, vancomycin or clindamycin can be used. For procedures involving the oral cavity, oropharynx, laryngopharynx or esophagus, antibiotics should cover aerobic and anaerobic bacteria and oral flora. Ampicillin/sulbactum, amoxicillin/clavulanate, or clindamycin provides adequate coverage. Major head and neck surgical cases that involve skin and oral or pharyngeal incisions are high risk for mixed infections. Coverage with clindamycin plus either gentamicin, tobramycin, ceftazidime or aztreonam provide coverage.

POSTOPERATIVE CARE

Postoperative care following head and neck surgery varies according to the complexity of the procedure; however, many will remained hospitalized for a minimum of 1 day. Postoperative complications, such as deep vein thrombosis and upper respiratory infections or pneumonia, should be avoided with methodical prophylaxis. Postoperative care is a responsibility of not only the physician, but also the nursing staff and patient. Expectations should be discussed with the patient, his/her family, and the nursing staff.

Dressings, wounds, and incision sites should be checked postoperatively for the development of a hematoma, evidence of bleeding, or early wound infection. Rapid development of a hematoma postoperatively, especially in the neck, can require a return to the operating room for evacuation. Early signs of wound infection such as erythema or drainage from the wound may necessitate removal of sutures and packing of the wound.

Postoperative glucose control is imperative. Diabetics need close glucose monitoring both pre- and postoperatively. In a study by Latham in 2001, it was shown that in patients undergoing coronary artery bypass grafting who had glucose values greater than 200 postoperatively had a twofold increase in surgical site infections (18). More recently, studies have emerged from the cardiothoracic literature that argue moderate glucose control [129–179] rather than tight glucose control [<126] results in better patient outcomes. Bhamidipati et al. (19), reporting from the University of Virginia in 2011 in a cohort of 4,658 cardiac bypass patients, found that patients with moderate glucose control had a lower mortality (2.0%) and complication rate (11.1%) than those patients with tight glucose control (2.9%, 19.4%, respectively). Consequently, diabetics must be followed closely and judicious use of sliding scale insulin should be implemented as needed.

VENOUS THROMBOEMBOLISM PROPHYLAXIS

Complications related to VTE are common in patients undergoing surgical procedures. The incidence of symptomatic deep venous thrombosis (DVT) and pulmonary embolism (PE) varies among surgical specialties (20,21).

In general, surgical specialties with high risk for such complications include orthopedics, neurosurgery, general surgery (especially major abdominal surgery); while specialties with low risk for such complications include urology, gynecology, and otolaryngology (22).

Venous prophylactic measures have been shown to reduce the incidence of perioperative VTE complications. These include mechanical measures (e.g., pneumatic

compression devices) and pharmacological measures (e.g., unfractionated heparin/low molecular weight heparin). As a result, attempts have been made to tailor prophylactic therapy to patients based on differential risk profiles (Table 2.3) (22).

One such approach, by the American College of Chest Physicians (20), relies on grouping patients by surgical specialty, then risk stratifying individual patients within each group. In risk stratifying individual patients, the age of the patient, the presence/absence of malignancy, the type of procedure (major/minor surgery), and a previous history of VTE are all factors that are considered.

While specific guidelines regarding prophylaxis have been formalized for patients undergoing orthopedic surgery, general surgery, and neurosurgery, this is not the case with otolaryngologic procedures. A first step in this process is to attempt to quantify the incidence of VTE complications in patients undergoing otolaryngologic procedures. Several retrospective reviews have addressed this question.

Moreano et al. (23) from the University of Iowa reporting in 1998 found the incidence of DVT and PE in their cohort of 12,805 patients to be 0.3% and 0.2%, respectively. This being more common in patients undergoing head and neck surgery (0.6%, 0.4%) and less common in patients with head and neck trauma (0.1%, 0.1%) and general otolaryngology (0.01%, 0.04%). They found patient age and the presence or absence of pneumatic compression to be independent risk factors.

Lee et al. (24) from the University of Toronto reporting in 2008 on their cohort of approximately 9,835 patients reported an overall incidence of DVT and PE to be 0.1% and 0.05%, respectively. They also noted highest incidence in patients undergoing major head and neck surgery. Chen et al. (25) from Memoral Sloan Kettering Cancer Center in their cohort of 6,759 procedures reported results similar to those noted by Lee et al. (24).

Innis and Anderson (21) from the Lahey Clinic in Boston reported that in their cohort of 6,122 patients that the overall incidence of DVT and PE was 0.1% and 0.02%, respectively. The incidence of DVT in patients treated for malignancy was 0.6% and without malignancy 0.01%. Innis and Anderson compared their results with those obtained by Moreano, and speculated that the reduced incidence of VTE in their group might be due to the use of pneumatic compression and subcutaneous heparin in all admitted patients. They further concluded that patients undergoing otolaryngologic procedures are a low risk for VTE complications. This conclusion is supported by a recent report regarding the incidence of VTE after thyroid and parathyroid surgery of 0.16% without prophylaxis, but with a serious bleeding complication rate of 1.58% in those given pharmacoprophylaxis (26).

Innis and Anderson recommend the following: (a) Early mobilization with or without the use of pneumatic compression in low-risk patients. (b) Pneumatic compression or pharmacologic prophylaxis for moderate-risk patients. (c) Both pneumatic compression and pharmacologic prophylaxis for high-risk patients. A similar algorithm was developed by Davidson et al. (27) for patients undergoing plastic surgical procedures.

It should be stressed, however, that decisions regarding prophylactic measures to prevent VTE should be based

TABLE 2.3 LEVELS OF THROMBOEMBOLISM RISK AND RECOMMENDED THROMBOPROPHYLAXIS IN HOSPITAL PATIENTS FROM THE AMERICAN COLLEGE OF CHEST PHYSICIANS (2008) (20)

Levels of Risk	Approximate DVT Risk without Thromboprophylaxis, %[a]	Suggested Thromboprophylaxis Options[b]
Low risk		
Minor surgery in mobile patients	<10	No specific thromboprophylaxis
Medical patients who are fully mobile		Early and "aggressive" ambulation
Moderate risk		
Most general, open gynecologic or urologic surgery patients	10–40	LMWH (at recommended doses), LDUH bid or tid, fondaparinux
Medical patients, bed rest or sick		
Moderate VTE risk plus high bleeding risk		
High risk		
Hip or knee arthroplasty, HFS	40–80	LMWH (at recommended doses), fondaparinux, oral vitamin K antagonist (INR 2–3)
Major trauma, SCI		
High VTE risk plus high bleeding risk		Mechanical thromboprophylaxis[c]

Note: The descriptive terms are purposely left undefined to allow individual clinician interpretation.
[a]Rates based on objective diagnostic screening for asymptomatic DVT in patients not receiving thromboprophylaxis.
[b]See relevant section in this chapter for specific recommendations.
[c]Mechanical thromboprophylaxis includes IPC or VFP and/or GCS; consider switch to anticoagulant thromboprophylaxis when high bleeding risk decreases.

on an individual patient basis after full evaluation of the surgical procedure, its likely impact on the patient, and patient risk factors.

HIGHLIGHTS

- Five clinical risk factors are used to stratify a patient's risk for cardiac complications prior to surgery. They are history of ischemic heart disease, prior or compensated heart failure, diabetes mellitus, chronic kidney disease, and cerebral vascular disease.
- Fetal hypothyroidism can occur with chronic povidone–iodine use while pregnant. Chlorhexidine in the inner ear can cause ototoxicity.
- Hair removal should be avoided if possible. If hair removal is required, hair should be removed by clipping just before surgery rather than shaving.
- Prophylactic antibiotics continued after surgery should not be administered for more than 24 hours after surgery.
- The decision to start VTE prophylactic measures should be based on an individual patient basis.

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3 Perioperative Management Issues

David M. Barrs

This chapter presents selected aspects of medical management in the perioperative period, which is defined as the time just before, during, and after the operative procedure.

PREOPERATIVE EVALUATION

History and physical examination remain the cornerstones of the preoperative evaluation, with particular attention to specific conditions such as diabetes, bleeding disorders, and insufficiency of cardiac, pulmonary, and renal systems. In an era of cost containment, laboratory tests, radiographic examination, and specialty consultation are performed on an outpatient basis and are tailored to finding information that could modify or delay surgery (1–7). The incidence of abnormal laboratory results is extremely low in the asymptomatic patient and, in general, routine laboratory tests are not ordered in patients younger than 50 years. Healthy pediatric patients undergoing minor procedures such as pressure-equalizing tube placement should need no laboratory or radiographic evaluation. Pregnancy testing should be obtained for any woman of childbearing age because it may be in the best interest of the mother and fetus to consider a delay of elective surgery. Patients with specific medical conditions need more extensive examinations tailored to their problems. Current American College of Surgeons and American Society of Anesthesiology recommendations for preoperative testing are mentioned in the appropriate sections (4–7).

PREOPERATIVE MALNUTRITION

Protein–calorie malnutrition is associated with immunosuppression, poor wound healing, decreased basal metabolic rate, longer and more expensive hospital stays, and a higher mortality rate. Most otolaryngology patients are well nourished, but this is not the case with many head and neck cancer patients who have difficulty maintaining adequate oral intake to prevent weight loss. In the surgical patient, mild to moderate malnutrition is defined as an unintentional weight loss of 6% to 12% of the usual body weight in the preceding 3 to 6 months or 80% to 85% of ideal body weight. Severe malnutrition is suggested with weight loss greater than 12%, serum albumin less than 2.5 g/dL, serum prealbumin less than 5 mg/dL, serum transferrin less than 200 mg/dL, and decreased immune function manifested as total lymphocyte count less than 900 mm^3 (8–12).

Patients with mild to moderate malnutrition may undergo most otolaryngology surgeries, with attention given to nutrition in the postoperative period; however, severe malnutrition should be treated with 7 to 10 days of nutritional replacement before elective surgery. The daily caloric requirement for most hospitalized adults is 25 to 35 kcal/kg of body weight. Protein is usually required at 0.5 to 1.0 g/kg/day, but the critically ill patient may need an increase to 1.5 to 2.0 g/kg/day. Daily caloric requirements (basal energy expenditure) can be estimated by formulas such as the Harris-Benedict scale, available in standard nutrition textbooks, although the values may have to be increased 1.25 to 1.5 times due to the stress of surgery. Because poor oral intake is presumed to have caused the malnutrition, most replacement therapy should be in the form of total parenteral nutritional (TPN) therapy or enteral feedings. Enteral feedings are preferable to TPN for several reasons, including providing more nutrients, less likelihood of hyperglycemia, promotion of immune function, elimination of a central catheter, buffering of gastric acid, and less expense (10,11). Enteral feedings can be either a blenderized normal diet or a nutritionally complete commercial formula with an energy supply of 1 to 2 kcal/mL or higher. For nasogastric tubes, gravity bolus feedings are usually given at an initial rate of 50 to 100 mL every 4 hours, increasing to 240 to 360 mL every 4 hours. Continuous feedings may be preferable to bolus

since they constantly buffer gastric acid, reduce aspiration risk, and have smaller residual volumes. They can be started at 25 to 30 mL/h and increased after 24 hours by 25 mL/h until the target intake is reached. The limiting factors in the volume of tube feedings include vomiting, cramping, abdominal distention, and diarrhea. Because regurgitation or aspiration is a risk of tube feedings, residual gastric volume should be checked every 4 hours and before each tube feeding. A gastric residual volume of 300 to 400 mL may signal intolerance for gastric tube feedings. In patients with long-term nutritional needs, a percutaneous endoscopic gastrostomy or surgically placed jejunostomy tube often is required. Jejunal tubes require continuous peristaltic pump infusion at a slower rate and with isotonic solutions. In severely malnourished patients, caution must be used because of the "refeeding syndrome," caused by a reactive hyperinsulinemia secondary to the sudden intake of glucose. Particular attention is paid to fluid overload and congestive heart failure, cardiac dysrhythmias, glucose intolerance, and electrolyte abnormalities such as hypophosphatemia, hypokalemia, and hypomagnesemia.

For patients who are unable to take nutrition by the gastrointestinal tract, replacement should be with TPN delivered through a central venous line. Consultation with the appropriate dietary service is essential. A common TPN solution has at least 1 kcal/mL and contains 500 mL each of 50% dextrose and 500 mL of 10% amino acids, with added vitamins, electrolytes, and trace elements. Fat emulsion composed of soybean or safflower oil as a 10% to 20% solution, 250 to 500 mL, can be given as little as weekly to supply essential fatty acids. The three components with additives can also be mixed in a 3-L bag, termed "3-in-1 solution," and given over a 24-hour period and is often used to simplify administration. In general, the infusion is started with 1,000 mL in the first 24 hours and increased as tolerated to 2,000 mL/day. Two liters of solution provides at least 2,000 to 2,500 cal/day and essential nutrients. It is important in both enteral nutrition and TPN to provide enough water to prevent azotemia and hypernatremia. Some formulas now contain substances previously thought to be "nonessential" such as arginine, glutamine, and omega-3 fatty acids. These "immunonutrition" solutions have been found to decrease the incidence of infections.

The safety of TPN requires frequent monitoring. Vital signs and glucose should be monitored every 6 hours initially. When the patient is on a stable regimen, glucose, weight, caloric and protein intake, serum electrolytes, and blood urea nitrogen (BUN) can be checked twice weekly. Liver-function studies, serum magnesium, total protein, albumin, transferrin, triglycerides, complete blood count (CBC), prothrombin time (PT), and iron levels are measured weekly. Meticulous care of the central catheter is required to prevent catheter-site infection.

Tube feedings are withheld on the day of surgery. TPN is tapered before surgery and should not be given intraoperatively because of the risk of hyperglycemia. In the postoperative period, feeding as early as possible, either by mouth or tube feeding, is encouraged, and postoperative TPN should be used only if enteral feedings cannot be accomplished within 5 to 7 days after surgery. For tube feedings, water may be provided within hours of the termination of surgery, whereas full-strength formula at a rate of 30 mL/h can be started on the first postoperative day for most patients.

HEMATOLOGIC ABNORMALITIES

Blood Components and Transfusion

Specific indications for preoperative transfusion are discussed in the following sections (13–16). Rapid correction of hematologic deficiencies usually depends on blood transfusions. Whole blood is rarely used; it is separated into its components for safety and efficiency (Table 3.1). The broadest coverage for urgent surgery in patients with coagulation abnormalities is fresh frozen plasma (FFP), which contains all the clotting factors, although no platelets are present, and the fibrinogen level is low. Fibrinogen transfusion is no longer used because of the high risk of viral transmission; cryoprecipitate is used to treat low fibrinogen levels.

Serious complications to transfusions include immune-mediated hemolytic reactions, anaphylactic reactions, and transmission of viral or bacterial disease. More recently, the immunosuppressive effect of the antigenic components of blood, termed immunomodulation, has been recognized (15). Far more common are mild hypersensitivity and nonhemolytic febrile reactions. Pretreatment with an antihistamine (diphenhydramine, 50 mg) and acetaminophen usually minimizes such reactions and permits completion of the transfusion. Of specific concern is the patient who has undergone massive transfusion. Volume overload may be minimized by using packed red blood cells. Hyperkalemia, hypokalemia, hyperammonemia, and

TABLE 3.1 BLOOD COMPONENTS

Fraction	Indication
Packed red blood cells	Acute hemorrhage, symptomatic anemia
FFP	Replace multiple coagulation deficits, specific coagulation deficits if factor concentrates unavailable
Platelets	Quantitative and qualitative platelet disorders
Cryoprecipitate	Low fibrinogen, factor VIII, von Willebrand's factor XIII
Factor concentrates	Specific factor deficits, especially VIII, IX, V
Plasma derivatives	Immunoglobulin, high titer antibodies

acidosis require specific treatment. Massive transfusions may lead to significant thrombocytopenia and coagulation factor depletion. Clotting studies such as activated partial thromboplastin time (aPTT), PT or international normalized ratio (INR), which is PT corrected to an international standard, platelet counts, and fibrinogen levels should be monitored for any sign of coagulopathy. Hypothermia can be minimized by warming blood and crystalline replacement. Citrate toxicity can cause a decrease in ionized calcium. Replacement with calcium gluconate (10 mL, 10%, IV) is reserved for symptomatic hypocalcemia and is not given prophylactically.

Alternatives to transfusion should be considered preoperatively. For elective surgery, the patient can be an autologous donor with a maximum of 1 U donated every 72 hours, up to 72 hours before surgery, as long as the patient maintains a hematocrit of greater than 33%. Autologous donation, however, is not cost-effective unless significant blood loss is anticipated. Other methods include isovolemic hemodilution (removal of whole blood preoperatively, replacement with crystalloid, and reinfusion after acute blood loss), intraoperative autotransfusion (return of processed blood from the operative field), or use of erythropoietin for several weeks preoperatively to stimulate red blood cell production.

Erythrocyte Abnormalities

A preoperative hemoglobin level should be obtained on all female patients but is not necessary in asymptomatic male patients younger than 50 years who do not have a history of bleeding or anemia. Anemia is significant because of the decreased oxygen-carrying capacity available during anesthesia (13–17). The previous minimal acceptable hemoglobin level of 10 g/dL for surgery or transfusion has been lowered to 6 to 7 g/dL, which is adequate for tissue oxygen delivery if circulating volume is normal. Healthy patients or chronically anemic patients may undergo surgery safely at these levels if minimal blood loss is expected. Two situations may require transfusion: active bleeding and coronary artery disease. In the patient with coronary artery disease, the hemoglobin should be increased to 10 g/dL or hematocrit of 30% (15) before surgery.

Elevated hemoglobin and hematocrit levels, respectively, greater than 16.5 g/dL and 55% in males and 15.3 g/dL and 52% in females also requires evaluation to exclude polycythemia or erythrocytosis (17,18). The most common cause is a relative polycythemia caused by reduced plasma volume from conditions such as dehydration. Tests, such as an increased chromium 51 red cell mass and low erythropoietin levels, may point toward a diagnosis of Polycythemia vera, which is associated with a higher incidence of thrombotic and hemorrhagic perioperative complications. For elective surgery, the patient should ideally be stable for several months before surgery. A hematocrit of 45% can be obtained with phlebotomy by removing 125 to 200 mL of blood every other day in healthy individuals, and slower removal in older patients or patients with cardiac disease. Platelet counts should ideally also be reduced to less than 500,000. In the emergency situation, whole blood can be removed and replaced with crystalloid.

Two hemoglobinopathies are of concern. The first is sickle cell disease. Sickle cell trait is not associated with increased surgical risk. In patients with the homozygous condition, the level of hemoglobin S should be reduced to avoid sickling crisis or acute chest syndrome during anesthesia or during the postoperative period. The simplest method is to transfuse to a hemoglobin level of 10 g/dL before surgery. Hypoxia, hypernatremia, hypothermia, acidosis, and volume depletion should be avoided. Hypotonic fluids should be given to decrease blood viscosity (17,18). The second hemoglobinopathy is glucose-6-phosphate dehydrogenase deficiency, which causes oxidant damage to hemoglobin within erythrocytes and is almost exclusively seen in men. Preoperative screening for this deficiency should be performed if a family history of the deficiency or unexplained hemolysis exists. The condition is not a risk for surgery, but certain medications should be avoided in the postoperative period to minimize the risk of hemolysis.

Platelet Abnormalities

Thrombocytopenia is defined as a platelet count of less than 140,000/mL (13). For otolaryngologic surgery with minimal anticipated blood loss, a platelet count of 20,000/mL may be sufficient, but the platelet count should be 50,000/mL for more major surgery. Each unit of platelets for transfusion will increase the platelet count 5,000 to 10,000/mL, and the platelet half-life is usually 2 to 3 days, unless increased destruction occurs. Ideally, the platelet count should be maintained above 20,000/mL for 3 to 4 days postoperatively. Thrombocytopenia developing in the postoperative period is unusual unless massive transfusion has been necessary, but sepsis, disseminated intravascular coagulation (DIC), and drug-induced thrombocytopenia must be considered.

Qualitative platelet disorders with abnormalities in platelet function may exist even with a normal platelet count. Platelet dysfunction may be present if a patient has a history of uremia or dialysis, liver disease, von Willebrand disease (vWD), abnormal bleeding from previous surgery, or with a recent history of ingestion of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), or other medicine, such as penicillin, that may affect platelet function. Aspirin is the most potent of the cyclooxygenase (COX) inhibitors, and irreversibly inhibits platelets for 5 to 7 days. Other NSAIDs, such as ibuprofen, are competitive inhibitors, and the platelet dysfunction can be reversed with desmopressin acetate (DDAVP). The selective COX-2 inhibitors, such as celecoxib, in usual doses do not cause platelet dysfunction. Thienopyridine class agents, such as clopidogrel, and glycoprotein 2b/3a receptor inhibitors, such as abciximab,

prevent platelet aggregation, and are not reversible. Tests for qualitative platelet dysfunction can be considered. In the past, a bleeding time was performed, but this test is now considered a global screening test, is often inadequate to identify many causes of platelet dysfunction, and is not useful as a predictor of bleeding during surgery. Current evaluation includes tests for platelet aggregometry, membrane glycoproteins, capillary tube shear testing, and should include screening for deficiency in von Willebrand factor (vWF), necessary for platelet adhesiveness. DDAVP may reverse the action of some platelet inhibitors such as NSAIDs or elevated BUN, may increase vWF, and may partially reverse the platelet dysfunction. Platelet transfusions or administration of DDAVP should be performed if emergency surgery is necessary. In elective surgery, medications causing platelet dysfunction should be stopped between 4 and 10 days before surgery, except in certain conditions such as the recent insertion of drug eluting cardiac stents.

Disorders of Hemostasis

The yield of routine preoperative coagulation studies, such as PT, aPTT, and platelet counts, is quite low unless the patient's history indicates a bleeding problem. This history should be searched carefully for congenital or acquired abnormalities of bleeding (18,19) (Table 3.2).

The perioperative management of patients receiving anticoagulant therapy requires specific comment. Heparin augments the effects of antithrombin (previously termed antithrombin III), which inhibits clotting enzymes, specifically factor Xa and thrombin (20). Low-molecular-weight heparins (LMWHs), such as enoxaparin, are increasingly used for deep venous thrombosis (DVT) prevention andginactivate factor Xa more than thrombin. LMWH has several advantages over heparin, including less risk of heparin-induced thrombocytopenia, longer subcutaneous injection half-life, and less necessity for monitoring anticoagulant effect. Warfarin, the most common anticoagulant, is given orally and is a vitamin K antagonist that decreases production of vitamin K–dependent clotting factors. Direct thrombin inhibitors, such as bivalirudin, are irreversible, but may cause less bleeding than heparin, so are preferred during procedures such as percutaneous coronary angioplasty. The need for anticoagulation should be discussed with the patient's primary care physician, and the method of preoperative discontinuation of the anticoagulant should be based on the estimated risk of DVT, pulmonary embolism (PE), or stroke (19). Patients in a low-risk category may simply have warfarin discontinued 2 to 3 days before surgery and restart it after surgery. Low-risk patients include those with aortic valve prosthesis or a resolved cause of a previous DVT. High-risk patients, such as those with a history of emboli of cardiac origin, atrial fibrillation, or mitral valve disease or prosthesis, should have warfarin discontinued several days before surgery and replaced with heparin. Intravenous heparin should be used to increase the aPTT to 1.5 to 2 times normal levels. Twelve hours before surgery, heparin should be discontinued, and the PTT will return to normal by the time of surgery. The effect of warfarin may be counteracted with vitamin K administration, as indicated in Table 3.2.

If surgery is imminent in a patient after anticoagulation with a warfarin product, 2 to 4 U of FFP may be given to correct the coagulation-factor deficiencies immediately while vitamin K takes effect. Repeated PT or INR tests should be

TABLE 3.2 DISORDERS OF HEMOSTASIS

Disorder	Corrective Action
Inherited deficiency	
Hemophilia A (VIII)	Factor VIII concentrate or recombinate VIII, FFP, CP Minor defect: DDAVP
vWD (VIII, vWF)	DDAVP (except type 2B vWD) Intermediate purity factor VIII with high vWF CP
Hemophilia B (IX)	Factor IX or recombinate IX concentrate (preferred) FFP (note: CP does not contain IX)
Acquired deficiency	
Liver disease	Rapid reversal: vitamin K, 10 mg, SC or IV, q12h × 3 days
Vitamin K deficiency Warfarin administration	FFP 2–4 U Monitor dose with PT or INR
Heparin	Protamine, 1 mg neutralizes 100 U heparin (avoid overcorrection—monitor aPTT)
DIC	FFP, CP, platelets

FFP, fresh frozen plasma; CP, cryoprecipitate; aPTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; DIC, disseminated intravascular coagulation; vWD, von Willebrand's Disease.

performed to evaluate the results of therapy. If an emergency situation arises in the heparinized patient, either with unfractionated heparin or LMWH, protamine sulfate may be given to antagonize heparin immediately. Unlike heparin, however, LMWH is only partially reversed with the administration of protamine making it less safe in patients at high risk of bleeding (15,20,21). Caution, however, should be used in the administration of protamine because it can induce a hypercoagulable state. On the one hand, it is crucial to note that FFP will not correct the coagulation defect caused by heparin. On the other hand, reversal of direct thrombin inhibitors must be accomplished by infusion of FFP.

The timing for restarting anticoagulants postoperatively depends on patient risk factors for thrombosis and embolization and on the type of surgery and hemostasis obtained at surgery. In neurotologic surgery and possibly airway surgery in which bleeding would present a life-threatening problem, anticoagulation should be delayed at least 36 to 48 hours. Rapid anticoagulation then is accomplished with intravenous heparin, whereas slower anticoagulation is accomplished simultaneously by restarting oral warfarin.

Intraoperative and Postoperative Bleeding

When the cause of intraoperative or postoperative bleeding is not an unsecured vessel, a search must be made for a coagulation disorder (15–18). Screening tests include CBC (hemoglobin, hematocrit, platelet count, and morphology), PT (INR), aPTT, qualitative platelet tests as noted earlier, and fibrinogen. Further testing and treatment depend on the findings of these preliminary tests as follows (15):

1. Normal PT and aPTT: The most common abnormality is impaired platelet activity, either thrombocytopenia or platelet dysfunction. Treatment is with platelet transfusion or DDAVP, as previously discussed. Other causes include factor XIII or fibrinogen deficiency.
2. Normal PT, abnormal aPTT: Drug-induced effect (heparin), vWD, or clotting factor deficiency, such as hemophilia, should be suspected and treated as noted earlier.
3. Abnormal PT and normal aPTT: Present with liver disease or warfarin anticoagulation, treated with vitamin K and FFP administration.
4. Both PT and aPTT abnormal: The first step is to repeat aPTT and PT testing to exclude laboratory error. If this is not present, then severe reductions in multiple clotting factors are present, and severe malnutrition with depleted vitamin K–dependent clotting factors, DIC, severe hemodilution, or nephrotic syndrome may be present.

Hemodilution and nephrotic syndrome coagulopathy is caused by decreased concentration of clotting factors, whereas DIC is the result of consumption of clotting factors. Moderate DIC initiates intravascular microthrombi, which lodge in critical organs and can produce adult respiratory distress syndrome or renal and hepatic failure. Severe DIC occurs when the intravascular microthrombi trigger an overwhelming fibrinolytic response and resultant dissolution of previously formed clots, leading to bleeding. The bleeding in DIC is the result of a cycle of clot formation and fibrinolysis, leading to consumption of clotting factors. In addition to the routine coagulation tests, a search is made for the presence of fibrin split products and D-dimer, the latter produced when plasmin acts on crosslinked fibrin. A high D-dimer level, especially greater than 2,000 ng/mL, is presumptive evidence of DIC (21). Treatment of DIC in the past had included the use of heparin to stop the clotting and allow return of clotting factors to more normal levels. Current recommendations for treatment are to remove the clotting stimulus (e.g., dead tissue, abscess), correct hypothermia, and correct blood loss with packed red cells and clotting factors with FFP and platelets.

THROMBOEMBOLIC DISEASES

DVT and PE are significant postoperative problems (17,22,23). Major risk factors are immobilization, history of thromboembolic disease, varicose veins, oral contraceptives and estrogen compounds, age older than 40 years, malignancy, central venous catheters, antiphospholipid syndrome, and hypercoagulable states such as erythrocytosis, thrombocytosis, and inherited thrombophilic disorders such as Leiden factor V mutation, prothrombin 20210 mutation, and deficiencies of substances antithrombin III, protein C, and protein S, which results in decreased lysis of clots.

Preventive Measures

Mechanical preventive measures usually are used first in otolaryngology patients. Any method designed to increase lower-extremity blood return is helpful. Traditional measures include early mobilization, leg elevation, elastic stockings, and physical therapy. A newer innovation is the external pneumatic compression boot, which is applied to the calf and thigh. The boot is intermittently inflated, the pressure held, and then deflated to massage blood up from the lower extremity. They should be considered for any patient who may not be mobilized early or who is undergoing a neurotologic, neurosurgical, or airway procedure in which prophylactic anticoagulation may not be indicated. Caution is used in patients with severe peripheral arterial vascular disease because vascular supply to the lower extremity may be compromised.

The pharmacologic methods of prevention of thromboembolic complications, such as heparin or warfarin, are quite effective, but they require starting the patient on treatment before surgery, which increases the risk of bleeding during surgery. The traditional use of heparin, 5,000 U, twice daily, in the perioperative period has been replaced by different protocols: (a) an adjusted dose of unfractionated heparin IV or SC to increase the aPTT by 2 to 3 seconds; or (b) LMWH, such as enoxaparin, 1 mg/kg,

q12h; (c) a factor Xa inhibitor, such as fondaparinux, 2.5 to 5 mg daily for adults greater than 50 kg., or (d) warfarin to increase the INR to 2–3.

Diagnosis

The risk of embolization from calf vein thrombosis is usually small, but thrombosis propagation to the more proximal femoral and iliac veins markedly increases the chance of pulmonary embolization. Accurate diagnosis of postoperative DVT is difficult but important to prevent unnecessary anticoagulant therapy. A positive Homan sign, unexplained fever, pitting edema, and localized discomfort or discoloration over leg veins may indicate underlying DVT. These signs, however, are quite insensitive and may give little indication of a serious DVT. D-Dimer testing, normally useful in DVT diagnosis, is always positive in the postoperative or trauma patient (21,22). If a duplex ultrasonography shows a noncompressible clot, a DVT can be assumed. Ascending contrast venography, with contrast material injected into a foot vein, has been largely abandoned due to the technical difficulty. If these tests are positive, then anticoagulation is instituted with unfractionated or LMWH, followed by warfarin. A search for underlying factors, such as hypercoagulable state, may be undertaken.

Pulmonary Embolism

Despite preventive measures, DVT and subsequent PE may develop (22,23). The diagnosis is difficult, but PE should be suspected in patients with sudden onset of tachypnea, dyspnea, chest pain, hemoptysis, hypoxia, delirium, or dysrhythmias. For patients at risk for PE where no contraindication exists, anticoagulation should be started while testing is performed. If significant clinical suspicion exists, further studies can include contrast-enhanced spiral computed tomography (CT) scan combined with a CT venogram of the pelvis and leg, a ventilation–perfusion (VQ) scan, magnetic resonance angiography, or pulmonary angiography. If the pulmonary CT scan shows one or more luminal filling defects, especially bilateral, the diagnosis of PE is almost certain (21). Conversely, if the VQ scan is normal, there is little chance of a PE. Pulmonary angiography is performed in high-risk patients with equivocal test results.

Management

If no contraindication exists, anticoagulation is necessary in all patients with proximal DVT and PE (23). In neurotologic, skull base, or procedures in the airway, the risk of bleeding must be considered. In other cases, heparin should be given immediately and continued for a minimum of 5 days, with the aPTT maintained in a range of 1.5 to 2 times control, while oral warfarin anticoagulant therapy is initiated to therapeutic levels. If the PE is massive, streptokinase, urokinase, or recombinant tissue plasminogen activator should be considered as thrombolytic therapy. Inferior vena caval interruption is used when anticoagulation is contraindicated or recurrent emboli are found in adequately anticoagulated patients.

ENDOCRINE ABNORMALITIES

Diabetes Mellitus

Hyperglycemia is defined as a fasting blood glucose (BG) level greater than 126 mg/dL, a pre-meal BG greater than 140 mg/dL, a random BG greater than 180 mg/dL, or a 2-hour glucose tolerance test glucose greater than 200 mg/dL (24–25). Multiple studies, both medical and surgical, have shown substantial increases in complications and mortality of hyperglycemic hospitalized patients (24–29). Approximately half of intensive care unit (ICU) patients and one-third of all hospitalized patients will be hyperglycemic during their hospitalization. Tight diabetic control is a challenge even for patients undergoing minor otolaryngology procedures and is critical in major procedures with prolonged hospital recoveries. Surgery and anesthesia increase production of stress hormones and worsen hyperglycemia.

Bedside capillary point of care (POC) testing is now the preferred method of BG monitoring as opposed to laboratory BG testing. Use of sliding scale insulin administration, which is a set amount of insulin for a given BG, is no longer recommended. A measurement of HbA1c aids in assessing average blood levels of glucose over the preceding 1 to 2 months. Oral hypoglycemic and non-insulin injectable antidiabetic medications are discontinued on admission. Insulin is the preferred method to achieve glycemic control in hospitalized patients. Recent recommendations use the concept of basal intermediate or long acting insulin once or twice daily with bolus rapid-acting or regular insulin before meals and at bedtime based on POC glucose testing (See Table 3.3). Patients who are not eating or on enteric nutrition have bolus insulin based on POC glucose testing every four to six hours. Supplemental "corrective" short or rapid acting insulin is given for BG levels above the pre-meal target of 140 mg/dL or random BG of 180 mg/dL (24). In the perioperative period, all insulin-dependent diabetics receive basal/bolus treatment, while Type 2 non-insulin dependent diabetics can have insulin treatment initiated based on BG measurements. Type 1 diabetics require insulin, even if fasting, to prevent severe hyperglycemia and ketoacidosis. Insulin is given subcutaneously (sc) as opposed to an IV bolus in hospitalized patients. Similarly, in surgery, the trend is away from IV bolus to either sc or continuous insulin infusion pumps. Tighter control of glucose levels requires close observation to prevent hypoglycemia, defined as BG less than 70 mg/dL. It is important that diabetics receive 3 g/kg of body weight each day of

TABLE 3.3 MANAGEMENT OF SURGICAL PATIENTS WITH HYPERGLYCEMIA

Basal–Bolus Insulin Treatment

Total daily insulin dose: 0.5 units insulin/kg × weight in kg
  0.2–0.4 units/kg in renal insufficiency, elderly, and lean patients
Example: Weight = 72 kg
  72 kg × 0.5 = 36 units insulin
  Basal dose (long acting, e.g., glargine insulin) = 18 units
    Example: Given once daily in AM or split twice daily
  Bolus dose (short or rapid-acting insulin) = 18 units in 3 divided doses
    Example: 6 units given before each meal
  Corrective dose = Short or rapid-acting insulin given in addition to the bolus dose for BG above optimal levels
    Example: Initial 2–6 units while basal and bolus doses adjusted

carbohydrates to prevent protein catabolism and lipolysis. Dextrose 5% in water at 100 mL/h provides 5 g glucose per hour.

Long-term management of poorly controlled patients is complex and best managed by the endocrinologist and multispecialty diabetic team. The otolaryngologist should know, however, basic management of postoperative increases in glucose. The most severe postoperative exacerbation is diabetic ketoacidosis (DKA) and is a true medical emergency with marked dehydration secondary to osmotic diuresis, hyperventilation in reaction to metabolic acidosis, and decreased levels of consciousness. The patient should be managed in the ICU. Immediate laboratory tests should include glucose (fingerstick or blood); potassium; serum ketones; other electrolytes such as magnesium, calcium, and phosphate; and blood gases to document the level of acidosis. All are repeated every 1 to 2 hours until the patient is stable, glucose is less than 250 mg/dL, and ketones have resolved. Cardiac monitoring is accomplished to exclude ectopy. Normal saline is given empirically over 20 to 30 minutes for volume repletion while test results are pending. The treatment of DKA is to give rapid-acting IV insulin, 10 to 15 U or 0.1 to 0.15 U/kg followed by the same dose hourly or via infusion pump. It is crucial, however, that potassium levels be determined and potassium replacement started at 10 to 40 mEq/h concurrently or before insulin to avoid profound hypokalemia, which can result from insulin facilitation of intracellular movement of potassium. The goal is to reduce the glucose level 50 to 75 mg/dL/h until the glucose level is 250 mg/dL.

In the less emergent situation, regular insulin is given at a dose of 4 to 10 U subcutaneously every 4 to 6 hours. Alternatively, a constant regular insulin infusion can be administered with a loading dose of 0.1 to 0.2 U/kg, followed by an infusion rate of 0.1 U/kg/h in a 0.9% sodium chloride solution. Blood glucose levels are measured every 1 to 2 hours. The patient then may be monitored during surgery in the same way as the well-controlled diabetic. Hyperosmolar nonketotic syndrome, characterized by hyperglycemia and dehydration, primarily requires restoration of intravascular volume and lower doses of insulin (0.05 to 0.15 U/kg/h). Discharge insulin or oral hypoglycemic agent dose depends on glucose control at the end of the patient's hospitalization.

Thyroid and Parathyroid Disorders

Patients with mild to moderate hypothyroidism may undergo emergency surgery with little increase in morbidity. For elective surgery, gradual replacement of hormone is preferred because rapid repletion can lead to relative adrenal insufficiency and angina in patients with coronary insufficiency. Synthetic levothyroxine, with a usual daily dose of 0.1 to 0.2 mg (1.8 mcg/kg/day), is the preferred replacement medication and may be given orally or intravenously in the same dose (30). The patient with severe hypothyroidism may have low temperature, hypotension, hyponatremia, hypoventilation, and hypoglycemia. Severe hypothyroidism can have an initial presentation postoperatively, especially in the elderly. Whether present in the preoperative patient needing urgent surgery or developing in the postoperative period, severe hypothyroidism can be treated with IV thyroxin, 200 to 500 mcg. Hydrocortisone, 100 mg IV every 12 hours, also should be given because adrenocorticotropin pituitary responsiveness to stress may be decreased (31). Hydrocortisone is continued until serum cortisol can be evaluated and pituitary responsiveness checked. Although fluid volume must be restored, free water clearance is diminished. Care must be taken with hypotonic intravenous solutions to avoid hyponatremia and water intoxication.

Elective surgery in hyperthyroid patients should be delayed, if possible, until the patient is in a euthyroid state. If urgent surgery must be performed in the thyrotoxic patient, iodines, propranolol, and thionamide antithyroid drugs, such as propylthiouracil (PTU) or methimazole,

should be used to reduce the risk of thyrotoxic crisis (30–33). PTU blocks thyroid hormone production, inhibits the conversion of thyroxine (T4) to triiodothyronine (T3), and usually is given in an oral dose of 100 to 200 mg three times daily. Methimazole is given either as divided doses of 10 mg every 8 to 12 hours, or as a single 20- to 40-mg daily dose. In the routine treatment of thyrotoxicosis, methimazole is preferred to PTU because fewer adverse reactions occur, especially PTU-induced hepatitis, and compliance is potentially higher with a single daily dose. PTU is preferred in pregnancy and the treatment of thyroid storm, the latter due to PTU blockage of extrathyroidal deiodination of T4 to T3. Iodides induce a transitory inhibition of thyroid hormone production and release from the gland and decrease vascularity of the gland, which lasts 10 to 14 days. Iodides can be given as a saturated solution of potassium iodide at a dose of 5 drops orally every 6 hours or Lugol's solution, 10 drops, three times daily. Palpitations, tachycardia, and tremor can be controlled with a beta-blocker such as propranolol in an initial dose of 20 to 40 mg, taken orally four times daily or 1 to 2 mg, given intravenously every 4 to 6 hours. Hydrocortisone should be given to counter relative adrenal insufficiency. Replacement thyroxine should be given postoperatively, and a thyroid-stimulating hormone and T_4 checked 6 to 12 weeks after surgery.

Thyrotoxic crisis, or thyroid storm, manifests by severe exaggeration of the classic symptoms of thyrotoxicosis and may develop intraoperatively or in the immediate postoperative period (30–33). The patient may have a marked fever, sweating, tachycardia, vomiting, abdominal pain, and delirium. Large doses of the same medications are given (Table 3.4). In the treatment of thyrotoxic crisis, the order of medical therapy is important. Although iodide blocks release of thyroid hormone, it also is the precursor for oxidation to iodine. For this reason, PTU is given first to prevent this oxidation used in hormone production, and then, at least 30 minutes later, iodide is given to block hormone release. Supportive therapy includes temperature control with acetaminophen or a cooling blanket. Sedation and oxygen therapy may be needed, and the patient should receive adequate glucose-containing intravenous solutions because of the high metabolic rate. Aspirin is contraindicated since it binds to thyroid binding globulin and displaces T4, increasing the available hormone.

TABLE 3.4 MEDICAL CONTROL OF THYROTOXIC CRISIS

1. Propylthiouracil, 200 mg, q4h or methimazole, 30 mg, q6h
2. Sodium iodide, 500 mg, IV, twice daily
3. Propranolol, 1–2 mg/min (total 10 mg) or 40–80 mg, PO, q6h, prn pulse >100
4. Dexamethasone, 4 mg, q6h, or hydrocortisone, 100 mg, IV, q6h
5. Replacement of volume deficit
6. Treatment of infections

Hypocalcemia, defined as a serum level less than 9 mg/dL if albumin is normal, may develop in any person undergoing parathyroid or bilateral thyroid surgery (32). After surgery, serum calcium and phosphate levels should be determined every 6 to 8 hours for the first several days, followed by daily levels thereafter. Serum ionized calcium alone is the optimal single measure if albumin levels are uncertain (31). If the calcium level decreases to less than 7.0 mg/dL, signs or symptoms of latent tetany should be sought. A positive Chvostek or Trousseau sign, hyperreflexia, numbness or tingling in the extremities, or circumoral paresthesias are indications to begin calcium replacement. Oral replacement can be accomplished with calcium carbonate, 250 to 500 mg, orally, four times daily, and vitamin D_3, 0.25 to 2.00 mg, orally, daily.

Laryngeal stridor, overt tetany, or seizures are medical emergencies and require IV calcium replacement. Calcium gluconate (10%) is less irritating than calcium chloride and is given as one to two ampules (10 to 20 mL) diluted in 50 to 100 mL of dextrose solution infused over a 10-minute period. Each ampule contains 1 g of calcium gluconate and 93 mg of elemental calcium. This emergency infusion of calcium gluconate can be repeated every 15 to 20 minutes, followed by a continuous infusion. The infusion can be prepared with six ampules of 10% calcium gluconate (540 mg elemental calcium) in 500 mL of D5W given at 1 mL/kg/h, giving approximately 1 mg/kg/h of elemental calcium (34). Deficiencies in magnesium, sodium, and albumin must be corrected. Overly rapid replacement of calcium can potentiate digitalis toxicity in cardiac patients. Hyperventilation in an anxious patient will cause a respiratory alkalosis with resultant worsening of the hypocalcemia. Patients with prolonged hypocalcemia may require oral calcium carbonate or calcium citrate replacement with 1.5 to 3 g each day of elemental calcium and vitamin D.

Adrenal Glucocorticoids

Adrenal insufficiency in otolaryngology patients is usually due to prior long-term steroid use with suppression of the hypothalamic–pituitary–adrenal axis (34–36). The normal oral daily maintenance dose of hydrocortisone is 20 mg in the morning and 10 mg in the afternoon. Prednisone is 4, methylprednisolone is 5, and dexamethasone is 25 times more powerful than hydrocortisone. Patients who have been taking as low a dose as prednisone 5 mg for 2 weeks in the preceding year are assumed to have suppressed endogenous production of cortisol and should be treated with supplemental steroids for surgery (34,37). Patients who are currently taking steroids, those with known adrenal insufficiencies, and even patients with Cushing syndrome also should be covered with supplemental steroids in the perioperative period. Large quantities of cortisol, in the range of 300 mg daily, are released from the adrenal gland during stresses such as surgery. The dose of administered steroids is designed to be in this same range (Table 3.5). Failure to

TABLE 3.5 REPLACEMENT IV HYDROCORTISONE FOR ADRENAL SUPPRESSION

Minor surgical procedures:
Usual daily corticosteroid dose
Additional 100 mg before surgery

Major surgical procedures:
100 mg the night before surgery
100 mg before surgery and every 8 h during surgery
100 mg, every 8 h, postoperatively for 24 h
50 mg, every 8 h, of the second postoperative day
Taper to maintenance over 3–5 d
Maintain 200–400 mg daily if ongoing stress or complication

provide replacement glucocorticoids can result in loss of vascular tone, with hypotension that is refractory to fluids or pressor agents. Other research, however, suggests that ongoing daily prednisone doses less than 10 mg or treatment with any dose completed more than 3 months previously does not suppress endogenous cortisone secretion and does not require supplemental therapy (25). If this approach is taken, the clinician should be ready to supply replacement corticosteroids if symptoms suggestive of adrenal insufficiency appear.

Primary adrenal insufficiency is rare but may first appear perioperatively as acute adrenal crisis. The symptoms are not specific and can include hypotension, weakness, dizziness, fever, nausea, vomiting, and abdominal pain. In the face of unexplained hypotension, adrenal insufficiency must be considered and treated empirically if hypotension is refractory. Blood should be drawn for measurement of serum levels of cortisol, adrenocorticotropic hormone (ACTH), electrolytes, glucose, BUN, and creatinine. After blood work is drawn, an immediate bolus of dexamethasone, 4 to 8 mg, or 100 to 200 mg of hydrocortisone is given intravenously, followed by fluids containing glucose and saline to correct volume deficiencies. Maintenance hydrocortisone is started, 100 mg IV, every 6 hours, until the condition stabilizes. The cortisol and ACTH levels should be sufficient to differentiate between pituitary or adrenal causes, but if not, a rapid 250-mcg ACTH stimulation test is performed to check peak cortisol response (should exceed 20 mcg/dL) (35). Mineralocorticoid replacement should not be necessary while the patient is receiving IV fluids. Both hydrocortisone and prednisone have mineralocorticoid effects, but dexamethasone does not.

Pituitary

The otolaryngologist often is involved in the removal of pituitary adenomas and other skull-base surgery. If a complete hormonal evaluation has not been performed, the surgeon should be aware of possible adrenal and thyroid insufficiency. More common, however, are perioperative diabetes insipidus (DI) and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion (38,39).

Central DI is caused by a decreased level of antidiuretic hormone (ADH), which impairs kidney free-water reabsorption, leading to increased thirst and large volumes of dilute urine in the face of inappropriate hypernatremia and hyperosmolarity of the serum. In effect, the patient has a free-water deficit. Other conditions may mimic central DI, including nephrogenic resistance to ADH. The stress of surgery normally increases ADH secretion and free-water retention, resulting later in a water diuresis that may be mistaken for DI. Excessive intravenous fluid replacement also may result in a large urinary volume secondary to the input. Mannitol given during neurologic and skull-base surgery may produce an osmotic diuresis. A diagnosis of DI should be restricted to patients with urinary outputs greater than 200 mL/h with associated hypernatremia, increased serum osmolarity, and low urinary osmolality usually less than 300 mOsm. The diagnosis rests on measuring the urine osmolality response to administered ADH in the dehydrated patient. In DI patients, the urine osmolality increases at least 50% and often 200% to 400%. The patient should be monitored with frequent intake and output, body weights, urine osmolality, and serum sodium.

In mild cases, simple oral intake of water to satisfy thirst may provide adequate free water. In more severe cases or in the patient not taking water orally, IV 5% dextrose in water with only enough sodium to cover obligate sodium requirements is given. The volume should equal the urinary loss plus insensible losses. For high urinary volumes (i.e., 3 to 4 L daily), pharmacologic replacement should be considered as follows.

Treatment may be initiated with DDAVP, a long-acting vasopressin analogue given intranasally at a dose of 10 to 40 mcg daily or orally 0.1 to 1.2 mg daily, both in two to three divided doses. The parenteral preparation is 10 times the strength, given SC or IV, 2 to 4 mcg daily in two divided doses. An alternative is aqueous pitressin, which has the drawbacks of short duration of action and a vasoconstrictor effect, which may precipitate angina. The dose is 5 to 10 U two to four times daily. Only half the calculated free-water deficit should be supplied in the first 24 hours. In the postoperative patient, the condition will usually resolve over a 3- to 5-day period with conservative treatment of water replacement and judicious use of ADH compounds.

The SIADH secretion is characterized by "inappropriate" conservation of water, and manifest as euvolemic, hypoosmotic hyponatremia with a urine osmolality that is abnormally concentrated (greater than 100 mOSM) compared with serum osmolality (38,39). Because surgery and trauma cause ADH release, excessive administration of hypotonic IV solutions should be avoided. Treatment usually is accomplished by fluid restriction to 1,000 mL/day and use of 3% hypertonic saline if serum sodium is less than 110 mEq/L or seizures are present. Demeclocycline, which inhibits the renal effects of ADH, is used for prolonged treatment. A parenteral preparation, conivaptan,

blocks the effect of vasopressin on the V2 receptors in the kidney and produces an increase in water excretion (39). The dose is 20 mg given over 30 minutes, and then followed by 20 mg continuously over 24 hours for 1 to 3 days. Rapid correction should be avoided, especially in neurosurgical cases, to lessen the chance of cerebral overhydration and edema and permanent demyelinating neurologic damage from central myelinolysis. Correction of the hyponatremia should not exceed 10 to 12 mEq/L for 24 hours.

CARDIOVASCULAR DISORDERS

Current American College of Cardiology and American Heart Association guidelines for perioperative cardiovascular evaluation list four conditions that require evaluation before noncardiac surgery: (a) unstable coronary syndromes such as unstable or severe angina and recent myocardial infarction less than 1-month old; (b) decompensated heart failure; (c) significant arrhythmias such as high grade or Mobitz II atrioventricular block or supraventricular arrhythmias with uncontrolled ventricular rate, and (d) significant valvular disease such as aortic stenosis (40). Other risk factors for postoperative cardiovascular morbidity include (a) age older than 70 years; (b) peripheral vascular disease; (c) insulin-dependent diabetes; (d) creatinine greater than 2.0; (e) history of cerebrovascular disease (transient ischemic attack or stroke); and (f) poor functional capacity, less than 4 METS on the Duke Activity Status Index, which is the equivalent of climbing one flight of stairs (29). Head-and-neck surgery is classified as an "intermediate risk" surgery. In asymptomatic patients, a routine electrocardiogram (ECG) is recommended for patients older than 50 years and compared with any available prior ECGs. Noninvasive cardiac testing for patients with risk factors includes exercise stress test, myocardial perfusion imaging with tracers such as Thalium-201 in conjunction with exercise or pharmacologic stress, and dobutamine stress echocardiography. Invasive testing, such as coronary angiography, is reserved for patients at high risk or with positive noninvasive tests. If the patient is taking cardiac medications (e.g., digitalis), serum levels should be obtained to ensure optimal levels before surgery. Electrolytes like potassium, magnesium, and calcium should be measured to attempt to decrease the likelihood of perioperative dysrhythmias. Further preoperative considerations include cardiac consultation to set pacemakers to the uninhibited mode and to turn off internal defibrillators.

Recommendations for the use of beta-blocking medication in noncardiac surgery continues to evolve. The 2007 ACC/AHA guidelines recommended starting beta-blockers for higher risk surgery, but the subsequent Perioperative Ischemic Evaluation (Poise) study found a higher mortality and stroke risk (40,41). Initiating beta-blockers in high-risk patients (three or more risk factors or positive stress evaluations), and continuing beta-blockers in patients already taking them, are current recommendations (29). Ideally, beta-blockage therapy should be started several weeks before elective surgery and should be at a dose to lower the resting heart rate to 50 to 60 beats per minute. The therapy is relatively contraindicated for patients with asthma or bronchospasm, or who have a baseline heart rate less than 55, systolic blood pressure less than 100, or have a type II second-degree or third-degree heart block. Starting a patient with cardiac abnormalities on beta-blockade may be daunting for the otolaryngologist. Consultation with the primary care physician, the preoperative clinic, or use of standardized hospital protocol may be of help. Preoperative oral medication options can include metoprolol, 25 to 50 mg, twice daily; bisoprolol, 5 to 10 mg, daily; or atenolol, 50 to 100 mg, daily. Metoprolol and atenolol can be given IV in patients who cannot take oral medications.

Hypertension

Antihypertensive medications should be continued to the morning of surgery and resumed immediately postoperatively (42–44). As mentioned above, beta-blocking agents should be continued until surgery and resumed immediately postoperatively because sudden cessation can produce a withdrawal syndrome with sinus tachycardia, hypertension, myocardial ischemia, or tachydysrhythmias. The symptoms may mimic a variety of cardiac abnormalities, but they respond rapidly to resumption of IV beta-blockers, such as labetalol or metoprolol, or enalapril, an angiotensin-converting enzyme (ACE) inhibitor. Clonidine-withdrawal syndrome can be characterized by a hypertensive crisis that may need IV nitroprusside or phentolamine for control (42–44). Beta-adrenergic antagonists, such as propranolol, atenolol, and metoprolol, should not be used in clonidine withdrawal because the resulting unopposed alpha-adrenergic activity may precipitate a hypertensive crisis. Monoamine oxidase inhibitors and guanethidine should be discontinued 2 weeks before surgery because of the possibility of severe drug interactions or interference with circulatory reflexes.

Virtually all anesthetic agents are vasodilators and negative ionotropes, which may create the necessity for fluid infusion in excess of fluid losses during surgery. Pharmacologic agents may be needed to control blood pressure during surgery (43). On emergence from anesthesia, sympathetic tone in the vessels is restored, and blood pressure can increase significantly. Postoperative hypertension is defined as systolic blood pressure greater than 200 mm Hg, an increase in systolic blood pressure greater than 50 mm Hg, or a diastolic blood pressure greater than 100 mm Hg. Prolonged or extreme postoperative hypertension may lead to myocardial failure or increased risk of intracranial bleeding in neurotologic or skull-base procedures. In urgent situations, the pharmacologic agent of choice has been nitroprusside, but nicardipine, an easily titratable calcium channel blocker, is an attractive alternative because it does not carry a cyanide risk (Table 3.6). Esmolol, a beta-blocker and fenoldopam, a dopamine receptor agonist, can be used effectively in the postoperative period (43).

TABLE 3.6 PERIOPERATIVE PHARMACOLOGIC CONTROL OF HYPERTENSION

Agent	Action	Dosage	Comment
Nitroprusside	Arterial and venous dilator	0.25–10 mcg/kg/min	Agent of choice for severe hypertension. Cyanide danger over 4 mcg/min
Labetolol	Combination alpha-, beta-blocker	20–80 mg q 5–10 min to max 300 mg in 24 h or 0.5–2 mg/min IV infusion	Avoid in negative inotropic states (e.g., heart failure, heart block) or asthma
Nitroglycerin	Antianginal agent (coronary vasodilator)	Initial 5 mcg/min IV infusion pump increased by 5 mcg/min every 3–5 min to max 100 mcg/min	Used when nitroprusside contraindicated for severe coronary insufficiency, advanced renal or hepatic disease
Esmolol	Beta-blocker	500 mcg/kg/min for first minute then 50–200 mcg/kg/min	Does not increase cerebral blood flow and intracranial pressure
Fenoldopam	Dopamine agonist	0.03–1.6 mcg/kg/min	Preferred in renal disease

In postoperative hypertension, it is extremely important to search for a cause rather than simply treat the hypertension with pharmacologic agents. The most common cause of postoperative hypertension is pain, but the differential diagnosis should include hypervolemia, ventilatory or respiratory failure, residual effects of anesthesia or intraoperative pressor agents, anesthetic-induced hypothermia and shivering, distended stomach or bladder, or manifestations of preexisting hypertension. Treatable causes of postoperative hypertension should be corrected before pharmacologic agents are given because severe hypotension may result if simultaneous antihypertensive medications and treatment of the underlying cause of hypertension are undertaken.

Postoperative Hypotension

As in hypertension, precipitating factors for hypotension must be found and treated. Hypovolemia secondary to inadequate fluid replacement or hemorrhage is the most likely cause of postoperative hypotension (45,46). Others include preoperative and intraoperative anesthetic agents and medications, pain, sepsis, cardiac dysfunction (e.g., dysrhythmias, infarction, failure), pulmonary problems (e.g., inadequate ventilation, emboli, pneumothorax), and electrolyte abnormalities. Postoperative hypotension may have components of hypovolemic, inflammatory, and neurogenic shock. All are treated with fluid replacement to start, usually a crystalloid solution such as normal saline. Colloids are used less frequently, and, if necessary, expanders such as hydroxyethyl starch are used more commonly than albumin, which is expensive, more difficult to obtain, and has some potentially detrimental effects (45,46). If a central venous line is not available to monitor intravascular volume, a fluid challenge consisting of 20 mL/kg of normal saline can be given over a 10- to 15-minute period (45). Clinical examination of the jugular venous pressure can guide replacement, and the infusion may be repeated once or twice. If no improvement is evident, a complete cardiac and pulmonary evaluation is indicated. The patient should have a chest radiograph, ECG, arterial blood gas sample, blood cultures if febrile, and insertion of monitoring catheters (e.g., central venous, arterial, and pulmonary artery lines). Vasopressor medication is indicated if significant hypotension is present (systolic pressure less than 100 mm Hg) and the patient manifests symptoms of decreased profusion, such as obtundation, cardiac

TABLE 3.7 PHARMACOLOGICAL CONTROL OF PERIOPERATIVE HYPOTENSION

Agent	Action	Dosage	Comment
Dobutamine	Beta-adrenergic	2–20 (max 40) mcg/kg/min	Increased cardiac output with minimal effect on heart rate and total peripheral resistance
Dopamine	Primarily beta- and lesser alpha-adrenergic agonist	1–20 (max 50) mcg/kg/min: increased cardiac output without vasoconstriction	Higher than usual doses needed for vasoconstriction and increased cardiac output
Norepinephrine	α_1 and β_1 agonist	Initial 0.5–1 mcg/min then 8–30 mcg/min titrated for response or weight based: 0.01–0.3 mcg/kg/min	Use only when vasoconstrictors are needed to maintain blood pressure
Phenylephrine	Alpha and beta agonist	IV bolus: 0.1–0.5 mg IV infusion: 100–180 mcg/min or 0.5 mcg/kg/min	Neurogenic shock

insufficiency, or decreased urinary output (Table 3.7). Pharmacologic treatment of hypotension is most effective in the neurogenic component of shock, and should be used cautiously since vasoconstriction has a detrimental effect on organs that are already compromised by ischemia (45).

Dysrhythmias

Acute cardiac disease, hypoxia, hypotension, acid–base abnormalities, hypokalemia, and central venous or pulmonary artery catheter stimulation of the heart are common causes of dysrhythmias (47,48). Hypokalemia may be worsened by intraoperative hyperventilation and resultant respiratory alkalosis and by intraoperative fluid replacement and fluid shifts. The underlying causes of cardiac dysrhythmias must be evaluated rapidly and corrected. The goal is to control ventricular rate and maintain normal sinus rhythm.

When a dysrhythmia is present, the clinician must determine if the patient is hemodynamically stable (47–49). Some dysrhythmias, such as nodal rhythm and bradycardia, are common during general anesthesia and usually do not require treatment. Sinus tachycardia is the most common postoperative rhythm abnormality, usually as a physiologic response to surgery, and requires no treatment if the patient is stable. Others can be hemodynamically significant and may be tolerated poorly by a heart already affected by the negative inotropic action of the anesthetic agent. The most obvious example is asystole, which requires cardiopulmonary resuscitation. Cardioversion (100 to 400 J) is the initial immediate treatment of choice for all other dysrhythmias in hemodynamically unstable patients (47). In the hemodynamically stable patient, a full 12-lead ECG should be performed to diagnose the dysrhythmia accurately. The treatment of bradycardia (heart rate less than 60 beats per minute) continues to be atropine, 0.5 mg IV, repeated every 2 minutes as necessary, followed by external or internal pacemaker if the bradycardia is prolonged. For tachydysrhythmias (heart rate greater than 100 beats per minute) with a wide QRS complex greater than 0.08 seconds, ventricular dysrhythmia is suspected and cardioversion is performed, followed by lidocaine, 100 mg IV. For narrow QRS tachyarrhythmias, an IV calcium channel blocker, such as verapamil 1 mg/min or diltiazem 0.25 mg/kg (15 to 20 mg) over 2 minutes repeated at 0.35 mg/kg 10 to 15 minutes later, is given until the heart rate slows, and then digitalization is begun. If the width of the QRS is uncertain, adenosine, 6 mg IV, can be given twice, and if the rate does not slow, cardioversion is performed. With calcium channel blockers, caution must be used in patients who are also taking beta-blockers, as a third-degree heart block may develop, although unusual. As well, with calcium channel blockers, since they are also peripheral vasodilators, hypotension may occur if the patient reverts to sinus rhythm, so adenosine may be preferred (47).

The pharmacologic agents available for tachydysrhythmia have continued to evolve (47,48). Amiodarone is an antidysrhythmic drug that prolongs the myocardial action potential and delays cardiac nodal conduction. It is widely used for treatment and prevention of ventricular tachydysrhythmias and can control atrial dysrhythmias, but does have significant side effects. The loading dose is 150 mg over the first 10 minutes followed by 360 mg for the next 6 hours and 540 mg over the following 18 hours. A maintenance infusion of 0.5 mg/min can be continued for up to 3 weeks, but the patient can also be converted to an oral regimen of 400 to 1,600 mg/day. Magnesium, 100 mg/kg IV over a 1- to 3-hour period, may be effective in the treatment of ventricular dysrhythmias, although the mechanism is unknown. Any of these serious bradydysrhythmias or tachydysrhythmias mandates observation telemetry in the cardiac care unit.

PULMONARY DISORDERS

General Management

Pulmonary problems are the most common complication after surgery (50–52). Anesthesia and surgery have profound effects on pulmonary function. All lung volumes, especially vital capacity and functional residual capacity, are decreased, reducing lung compliance and increasing the work of breathing. The result is alveolar hypoventilation with atelectasis, VQ abnormalities, and hypoxemia. Extravascular lung water also may be increased from increased hydrostatic pressure secondary to fluid overload and low plasma oncotic pressure. If the pulmonary capillary endothelium also is damaged from exposure to toxic products from injury, infection, or the surgical procedure, increased capillary permeability may increase lung extravascular water. In otolaryngologic procedures, impaired laryngeal protective mechanisms, airway edema, and foreign bodies such as blood clots may promote aspiration.

Treatment is initiated in the preoperative period with preventive measures and identification of the patients who may be at a higher risk for pulmonary problems (50–52). Historic symptoms, such as dyspnea on exertion, cough, sputum production, and cigarette smoking, indicate the need for further evaluation. The physical examination should include auscultation during maximal inspiration and forced expiration. Observation of the patient climbing stairs remains a valuable adjunct to clinical estimation of pulmonary and cardiac reserve. The preoperative chest radiograph can demonstrate pathology, but it is more important when used for postoperative comparison. A preoperative chest radiograph in asymptomatic patients is recommended for known pulmonary or cardiac disease, age older than 40 years, high risk for postoperative pulmonary complications, and a positive tuberculin test or high risk for unsuspected tuberculosis. Pulmonary-function tests can give the clinician an idea of the degree of alveolar ventilation and the ability to clear secretions in the

postoperative period. This is especially important in major head and neck resections in which aspiration may be common. The best overall predictor of postoperative pulmonary difficulties may be the maximal voluntary ventilation (MVV) test, which is the largest volume that can be breathed by voluntary effort per minute, extrapolated from rapid breathing into a spirometer during a 15-second interval (50). This test measures lung function, compliance of the chest wall, strength of the respiratory muscles, and patient motivation and ability to cooperate. An MVV value of less than 50% of predicted value has been correlated with postoperative pulmonary complications.

Preoperative arterial blood gases provide mainly a comparison for postoperative measurements, are not predictive of postoperative pulmonary insufficiency, and are not routinely indicated. Any patient with arterial oxygen tension less than 60 to 70 mm Hg usually has a significant VQ mismatch. An arterial carbon dioxide tension greater than 45 mm Hg indicates significant alveolar hypoventilation and is associated with an increased incidence of postoperative complications. Reversible causes, such as bronchospasm or bronchitis, should be corrected preoperatively.

Preventive measures are begun as soon as a decision to operate is made and are carried through the entire postoperative course. Predisposing factors for lung complications, such as smoking or obesity, and underlying pulmonary conditions, such as chronic bronchitis, chronic obstructive pulmonary disease, and reactive airway disease, are corrected insofar as possible before surgery. Ideally, pulmonary exercises that will be performed postoperatively should be practiced before surgery. These include deep breathing and the use of incentive spirometry. The main thrust of postoperative care is deep-breathing exercises to enhance alveolar aeration and ventilation. Unless secretions are a major problem, coughing may not need to be encouraged and may be detrimental in skull-base procedures with an increased chance of a spinal fluid leak. Mechanical assistance such as intermittent positive pressure breathing (IPPB) can be used in the weak patient but are not usually necessary. Bronchodilators are used in chronic obstructive lung disease.

The choice of anesthesia is important. Although local anesthesia may seem preferable, general endotracheal anesthesia gives the best control over the airway. Maintaining a large tidal volume of 10 to 15 mL/kg and slow respiratory rate with frequent sustained inflation to 20 mL/kg or to an airway pressure of 30 cm H_2O should be performed to prevent alveolar collapse. Intravenous crystalloid solutions should be given conservatively and blood or plasma replacement products should be given with large blood and plasma losses to help maintain normal intravascular colloid pressure and prevent pulmonary edema. Diuresis is indicated for significant fluid overload.

Preventive measures should be continued in the postoperative period. The endotracheal tube should be kept in place as long as necessary to maximize alveolar ventilation. Immediately after endotracheal tube removal, deep-breathing exercises, clearance of respiratory secretions, and frequent turning of the patient are begun. Supplemental oxygen should only be used for a few hours, unless dictated by arterial blood gases, in order to avoid respiratory suppression of deep breathing (52). If the patient is unable to perform maximal inhalation exercises or incentive spirometry, continuous positive airway pressure or IPPB may be of help in preventing atelectasis.

Management of Postoperative Pulmonary Insufficiency

Dyspnea, tachypnea, tachycardia, and cyanosis in the postoperative period are signs of acute pulmonary insufficiency (51,52). Atelectasis, bronchospasm, pulmonary edema, and aspiration are the most common causes. Exacerbations of preexisting pulmonary problems, mechanical limitations of breathing, acute bronchospasm, pulmonary embolization, congestive heart failure, and hypovolemia also should be considered. In head-and-neck procedures, mechanical limitations to breathing may be caused by gastric distention, pneumothorax, aspiration, or phrenic nerve injury with hemidiaphragmatic paralysis, in addition to any laryngeal or pharyngeal manipulation. If pulmonary insufficiency is suspected, supplemental oxygen should be given immediately to increase oxygen saturation to greater than 90% on pulse oximetry while a pertinent history, physical examination, arterial blood gases, and a chest radiograph are obtained. The patient should be in a comfortable sitting position. Nasogastric tube placement is considered to empty the stomach of any further gastric acid. Bronchospasm may be present and respond to bronchodilators.

Treatment of atelectasis is aimed at re-expanding the collapsed segment. Deep-breathing exercises, incentive spirometry, continuous positive airway pressure, and IPPB can be used. Adequate pain medication should be provided to promote mobility and deep breathing. Increased hydration, mist, nebulized bronchodilators, and mucolytic agents should be given through the airway to liquefy thickened secretions that may be blocking the involved bronchus. Coughing is not helpful in preventing postoperative pulmonary problems. Paradoxically, coughing does not clear mucus from collapsed airways because no air is distal to the mucous plug. Immediate treatment consists of mechanical removal of any foreign substance from the upper airway. Tracheal suction may be successful in removing retained secretions but should be performed only if deep breathing is not successful and then with caution because it may produce increased vagal tone and hypoxemia. Oxygen can be connected to the nasotracheal catheter and 5 mL of saline can be injected through the catheter to help liquefy secretions and facilitate aspiration through the catheter. Suction should be applied for no longer than 10 seconds before oxygen flow is resumed to prevent cardiac dysrhythmia. During tracheal suctioning, ECG monitoring should be

performed with atropine available for bradycardia. Flexible bronchoscopy allows direct visualization of the bronchial tree, removal of debris, and culture of sections. The same precautions as for tracheal suctioning are used. If adequate ventilation (respiratory rate less than 30/minute and oxygen saturation greater than 92%) cannot be restored by these methods, endotracheal intubation and mechanical ventilation are indicated. Supplemental oxygen should be kept as low as possible to avoid nitrogen displacement from alveoli and exacerbation of atelectasis.

Pulmonary edema is caused by an increase in lung water, and treatment is directed at decreasing the excess water (51,52). Treatment is directed toward decreasing extracellular fluid, decreasing pulmonary capillary bed hydrostatic pressure, and increasing plasma oncotic pressure. Furosemide is the diuretic of choice because it promotes venodilation and diuresis. Treatment in younger or previously healthy patients may simply involve fluid restriction and the use of diuretics as necessary. For patients with cardiopulmonary or renal disease, dobutamine, dopamine, or both may be required for low cardiac output and to increase renal perfusion. Nitroprusside may be necessary for patients with high systemic vascular resistance to reduce the cardiac afterload. Intravenous nitroglycerin may help patients who have coronary insufficiency. If hypoxemia or hypercapnia persists after these measures, ventilatory support may be necessary.

A flow-directed pulmonary artery catheter can help distinguish high- from low-pressure pulmonary edema. Cardiogenic pulmonary edema, on the one hand, is usually associated with a pulmonary artery wedge pressure greater than 25 mm Hg. In cardiogenic pulmonary edema, interstitial edema progresses to alveolar edema. Adult respiratory distress syndrome, on the other hand, is manifest as pulmonary edema in the presence of normal pulmonary artery wedge pressure. Lung damage is indirect and usually caused by infection, inflammation, or tissue destruction elsewhere in the body. It manifests as severe hypoxemia and decreased lung compliance, and it shows diffuse bilateral pulmonary infiltrates on chest radiograph. Management is directed at treating the underlying cause, with specific attention to aggressive antibiotic treatment of presumed infection. Severe hypoxemia and hypercapnia may need mechanical ventilation with positive end-expiratory pressure. Inspired oxygen content should be kept low to minimize oxygen toxicity while maintaining the hemoglobin oxygen saturation above 90%. Intravascular volume is kept low; dobutamine or dopamine may be needed for inotropic support.

GASTROINTESTINAL DISORDERS

Stress Ulcers

In patients who do not have a history of peptic ulcer disease, the most common cause of postoperative upper gastrointestinal bleeding is stress ulceration of the gastric mucosa (53). These ulcers develop as a result of trauma, surgery, medications such as corticosteroids or NSAIDs, or the stress associated with severe illness. The ulcers are usually painless, and the clinical presentation may be limited to a bloody aspirate from an indwelling nasogastric tube, melena, or an unexplained decrease in hematocrit. Predisposing conditions include coagulopathy and mechanical ventilation (54).

The main thrust of management should be prevention, and prophylactic measures should be considered in all major head-and-neck cases. Prevention of stress ulceration is aimed at reducing gastric acidity (above pH of 4 to 5), which may be accomplished by histamine (H_2)-receptor antagonists, cytoprotective agents, the mucosal protective effect of early enteral feedings, or antacids. Currently the preferred method is with proton-pump inhibitors (PPIs) such as omeprazole, which can be given IV or an oral dose of 40 mg, b.i.d (53–55). The IV dose of H_2-antagonist cimetidine is 50 mg/h or 300 mg every 6 hours, and the dose for ranitidine is 6.25 mg/h or 50 mg every 8 hours for the continuous or bolus injections, respectively. A continuous IV infusion may be more effective than bolus injections. The alteration in gastric pH caused by H_2-receptor antagonists and PPIs may predispose to gastric bacterial colonization and nosocomial pneumonia. Cytoprotective agents, such as sucralfate suspension, maintain the integrity of the stomach mucosal barrier without lowering pH. Sucralfate must be activated by gastric acid so cannot be used with PPI, H_2 blockers, or antacids (53). The dose is 1 g in 10 to 20 mL of sterile water infused into the stomach every 6 to 8 hours via nasogastric tube. Antacids are effective, but must be taken every 1 to 2 hours. If *Helicobacter pylori* is present, antibiotics should be given.

If stress ulcers develop, treatment methods are similar to those used in prophylaxis. Basic resuscitation is started, and blood tests sent for CBC and coagulation studies. Emergencies (e.g., hypovolemia) must be managed immediately with fluid or blood replacement. In the bleeding patient, an IV PPI, such as pantoprazole, 40 to 80 mg every 12 hours, is given. A large-bore nasogastric tube can be placed to decompress the stomach, to provide access for saline lavage, and to examine gastric aspirate. Esophagogastroduodenoscopy is the procedure of choice, gives direct visualization of the gastric mucosa for diagnosis, and allows an attempt at endoscopic control of hemorrhage by such methods as thermal coagulation or laser photocoagulation. If no site of bleeding is seen endoscopically, arteriography is performed to determine the bleeding site. Arterial embolization or selective injection of vasopressin into the left gastric artery has been used. Barium studies of the bowel are quite common, but the barium may interfere with tests such as CT or arteriography. Surgical intervention may be necessary for patients with persistent bleeding or ulceration despite conservative therapy, although the mortality of gastric resection for postoperative hemorrhage is high.

Adynamic Ileus

Ileus is much more common after abdominal procedures than after head-and-neck procedures. The otolaryngologist, however, must certify that intestinal motility exists before beginning postoperative feeding, especially hyperosmolar tube feeding. Adynamic ileus should be suspected in any patient with obstructive symptoms of constipation, prolonged vomiting, abdominal pain and distention, or an absence of bowel sounds (55). Abdominal upright and supine radiographs show a diffuse gas pattern and distended loops of bowel. The most common cause is the perioperative administration of pharmacologic agents, including anesthetic agents, opioids, sedatives, adrenergic agonists, anticholinergics, calcium channel blockers, and antihistamines. The differential diagnosis must include hypokalemia, distal obstruction (e.g., fecal impaction, neoplasm), sepsis, and an acute abdominal event, such as exacerbation of diverticulosis. Endoscopy or contrast enema may be necessary to rule out bowel obstruction. The treatment is directed at the underlying cause. The patient usually responds to supportive measures of avoidance of oral intake, discontinuation of narcotics, administration of intravenous fluids, correction of electrolyte abnormalities, and nasogastric suction. Sympathetic blockade or parasympathetic stimulation with bethanechol, neostigmine (2 mg IV over 3 to 5 minutes), or metoclopramide is rarely used and is contraindicated if a mechanical obstruction is present. Erythromycin, 200 mg IV, stimulates upper gastrointestinal motility and is an alternative (55). With these measures, the ileus usually resolves within a period of several days.

Diarrhea

The most significant exudative diarrhea is antibiotic-associated diarrhea and colitis (54,55). The severity of antibiotic-related diarrhea varies from mild diarrhea to pseudomembranous colitis with severe systemic manifestations. Antibiotics frequently used in otolaryngology patients may precipitate the syndrome. Clindamycin and ampicillin are the most common causes, but cephalosporins, erythromycin, penicillin, and trimethoprim–sulfamethoxazole also have been implicated. With persistent diarrhea, a stool examination is paramount. Fecal leukocytes suggest a bacterial infection or an antibiotic-associated pseudomembranous colitis. The stool should be evaluated for enteric pathogens, *Clostridium difficile*, and intestinal parasites (if the patient has been to an endemic area). More than 90% of patients with antibiotic-associated pseudomembranous colitis test positive for *C. difficile* toxins.

Management is both supportive and specific. Fluid and electrolyte balance must be monitored closely and may require measurement of electrolyte levels in stool samples. Potassium and bicarbonate losses may be large and may require IV replacement with up to two ampules of sodium bicarbonate in each liter of 5% dextrose in water. If cessation of the causative antibiotic does not relieve diarrhea, then treatment with appropriate antibiotics is guided by stool culture. Metronidazole (500 mg orally three times daily) is given for 10 to 14 days for patients who tolerate oral intake. Recurrences are common and are treated with a second course of metronidazole. Vancomycin (125 to 500 mg, PO, q.i.d.) is reserved for resistant bacteria or for patients who do not tolerate metronidazole. Intravenous metronidazole is less effective but can be used in patients who cannot take enteric medications. Intravenous vancomycin is not effective, but intracolonic irrigation has been tried. Antiperistaltic medicines should be avoided because decreased intestinal motility promotes bacterial overgrowth. Other causes of diarrhea such as osmotic, secretory, and altered intestinal motility, such as "bacterial overgrowth syndrome," should be considered if resolution is not prompt.

RENAL DISEASE

Two considerations are important in the perioperative management of renal disease. The first is treatment of patients with known renal disease, and the second is the prevention or recognition of acute renal failure in the postoperative period (18,23,31).

Chronic Renal Failure

Dialysis (renal replacement therapy) must be continued before and after surgery to minimize uremic complications such as acid–base, fluid, and electrolyte imbalances (56–58). In the elective situation, the patient is dialyzed on the day before and the day after surgery. The surgeon must take into account the need for heparin as an anticoagulant during dialysis, but this effect is minimal in 6 to 8 hours.

Other problems specific to chronic renal failure should be addressed. Baseline hematocrits in the 20% to 25% range should be adequate for surgery unless large blood losses are expected. Platelet dysfunction in renal disease is corrected only partially by dialysis. For patients with active bleeding secondary to uremic platelet dysfunction, administration of DDAVP at a dose of 0.3 mg/kg or platelet transfusion should be considered. Hypertension should be controlled with diuretics and dialysis, if necessary, for restoration of normal intravascular volumes.

An effort should be made to avoid medications with known renal toxicity, including anesthetic agents. Some volatile anesthetic agents, such as enflurane, produce fluoride and can lead to fluoride-induced kidney damage. Halothane can be used as an inhalation agent and propofol can be used as an infusion agent for general anesthesia (58). The neuromuscular blockers and anticholinesterases, especially succinylcholine, may potentiate hyperkalemia and acidosis.

Intraoperatively, the goal should be to prevent further kidney damage (56–58). An effort should be made to optimize renal profusion by correcting volume deficits and maintaining adequate cardiac output. In patients who are not anuric, urinary output should be maintained at a level of at least 0.5 mL/kg/h. Renal blood flow can be augmented with low-dose dopamine (1 to 5 mg/kg/min). Diuresis can be stimulated with mannitol or a loop diuretic like furosemide in an effort to maintain preoperative urine outputs. Urgent treatment of hyperkalemia can be accomplished with initial infusion of calcium chloride, 5 to 10 mL of 10% solution; sodium bicarbonate, 44 mEq in 2 minutes as needed for associated metabolic acidosis; and insulin, 10 U over a 30-minute period, concurrently with dextrose, 250 mL of 20% solution.

After surgery, fluids, electrolytes, acid–base balance, and hematocrit should be watched closely. In severe abnormalities, urgent hemodialysis may be necessary despite the need for heparin. In chronic renal failure patients, postoperative congestive heart failure may develop secondary to ischemic heart disease or hypotension secondary to volume depletion, decreased cardiac output, or abnormal receptor function. Nutritional support with a diet high in carbohydrates and essential amino acids is important. Adequate caloric intake (1,800 to 2,500 kcal/day or 35 kcal/kg/day) is provided to avoid endogenous protein catabolism. Protein is restricted to 1.0 to 1.4 g/kg daily of high-biologic-value protein. Prophylactic antibiotics and careful wound management are indicated because of decreased immune function.

Acute Renal Failure

Acute renal failure, also termed "acute kidney injury" (AKI), is an acute decrease over hours to days in renal function and glomerular filtration rate (GFR) with a rise in creatinine of 0.5 mg/dL in normal patients or a 25% rise of creatinine in preexisting renal disease. In hospitalized patients, even a rise of 0.3 mg/dL is significant (56). Diminished urine output (i.e., <0.5 mL/kg/h or <400 mL/day in adults, and <1.0 mL/kg in children weighing <10 kg) should prompt an investigation to eliminate renal causes. Difficulty in voiding, with resultant urinary retention, may be caused by perioperative medication. Placement of a bladder catheter may be necessary to relieve urinary retention and to monitor adequate urinary output. If a postrenal obstruction is suspected, ultrasonography is performed. Continued low urinary output through the bladder catheter demands immediate action in an attempt to prevent renal damage and acute renal failure (56–58). Clinical assessment should be used to differentiate between hypovolemia and decreased cardiac function. Prerenal hypovolemia or hypotension is the most common cause of low urine volume in head-and-neck surgery patients. The urine is low in volume, sodium, and chloride and high in osmolarity. Urine sodium is less than 20 mEq/L in prerenal hypovolemia and greater than 40 mEq/L in intrinsic renal failure. The fractionated urinary excretion of sodium (FE_{NA}), a similar measure, is less than 1% in prerenal failure and greater than 3% in renal causes, whereas values between 1% and 3% suggest a combination of prerenal and intrinsic renal failure. In hypovolemia, treatment should be directed toward increasing renal perfusion by rapid infusion of intravenous fluids to increase the central venous pressure to at least 10 mm Hg. The intravenous fluid bolus should be 500 to 1,000 mL of normal saline. Blood may be used for this bolus if significant blood loss occurred during surgery. Controversy exists concerning the use of diuretics and osmotic agents such as mannitol because they have not been shown to decrease the mortality from renal failure. Administration of these agents hinders the use of urine volume and electrolytes, described earlier, as a measure of renal function for at least 24 hours. However, diuretics can convert an oliguric to a nonoliguric renal failure, which may have a higher survival rate. If diuretics are used, 40 mg of furosemide is administered intravenously with observation for increased urinary output over the next 60-minute period. In the volume depleted with prerenal failure, NSAIDs, which inhibit the vasodilatory effects of prostaglandins, ACE inhibitors, and angiotensin receptor blockers, which can cause efferent arteriolar dilation and drop in GFR, and nephrotoxic medications such as aminoglycosides, should also be avoided (57). Dopamine, which improves renal blood flow, has not been found to prevent the development of AKI (56).

The most common postoperative intrinsic renal cause of acute renal failure is acute tubular necrosis secondary to ischemia or nephrotoxicity. It is characterized by oliguria, an increasing serum creatinine, and examination of urinary sediment demonstrates classic pigmented granular casts. Urinalysis demonstrates a hypo-osmolar urine with a high sodium and FE_{NA} content and a low urinary-to-plasma creatinine ratio. After a tentative diagnosis of acute tubular necrosis or other renal cause of acute renal failure is made, baseline laboratory and clinical values, such as body weight, blood pressure, chemistry and hematologic profile, urinary chemistry and sediment examination, and consideration for renal imaging studies or ultrasonography, should be performed. Early nephrology consultation should be obtained. Conservative management may be successful with a high-carbohydrate and low-protein diet, fluid and electrolyte management, and careful reevaluation of all medications. If hyperkalemia, volume overload, acidosis, or uremia develops, dialysis may be necessary.

NEUROPSYCHIATRIC PROBLEMS

Postoperative Seizures

The goals of therapy for postoperative seizures are to control the seizure and to determine the underlying cause (59,60). Typical seizures for patients with known seizure

disorders may simply require supportive measures and continuation of anticonvulsant medications. Atypical seizures in a known seizure patient or new seizures in a previously asymptomatic patient require immediate investigation for a treatable underlying cause.

Metabolic imbalances such as hyperglycemia or hypoglycemia, hypoxia, acid–base disturbances, hypernatremia or hyponatremia, or other electrolyte abnormalities may cause seizures. Head trauma, fever (especially in children), stroke, subarachnoid hemorrhage, central nervous system infections, drug and alcohol withdrawal, cardiac dysrhythmias, hypotension, and certain drugs and toxins can precipitate a seizure. Overdosage of cocaine and local anesthetics like lidocaine are of particular concern to the otolaryngologist. The patient's history should highlight any previous neurologic disease, possible drug reactions, and fluid and electrolyte abnormalities. Complete general and neurologic and physical examinations should be performed, with special attention to any seizure sequelae such as trauma, aspiration, or rhabdomyolysis. Characteristics of the seizure also should be noted. If the seizure is self-limited, the laboratory evaluation should include a rapid glucose determination, CBC, blood chemistries including calcium and magnesium, oxygen saturation, and ECG. If an immediate cause for the seizure is not found, then an electroencephalogram, lumbar puncture, and an imaging study of the head with contrast are performed.

Status epilepticus is the condition of continuous or repeated seizures, usually lasting longer than 5 to 20 minutes, and is a true medical emergency (59,60). More prolonged seizures tend to become more refractory to treatment (60). The condition produces acidosis, hypotension, relative hypoglycemia, rhabdomyolysis, autonomic and cardiovascular dysfunction and may produce cerebral damage from local hypermetabolism and prolonged hypoxia. An abbreviated search for underlying causes is important, but the primary goals are to stop the seizure, maintain the airway and ventilation, avoid hypoxia, and avoid complications, such as an injury to the operative site. An intravenous catheter is placed, and blood should be drawn for the aforementioned tests. Serum anticonvulsant drug levels and arterial blood gases also should be tested. Metabolic and ventilation abnormalities should be corrected. Immediate treatment can be started with empiric IV injection of thiamine, 100 mg, and a glucose injection, 50 mL of 50% dextrose, should be given if the fingerstick glucose is low or not available. Pharmacologic control is obtained with benzodiazepines, phenytoin, and barbiturates (Table 3.8). Because high doses may be required, the clinician should be ready to support ventilation. Intubation may be necessary to protect the airway. The antiseizure duration of action of diazepam is relatively short: about 20 minutes. Lorazepam also may be used, and the duration of action is somewhat longer. Phenytoin should be used in addition to the benzodiazepines and will be used as the long-term therapy. No significant central nervous system depression occurs with phenytoin, but rapid administration may cause cardiovascular toxicity. The longer-duration action of phenytoin supplements the initial control obtained by the benzodiazepines. Fosphenytoin, expressed as phenytoin equivalents (PEs), is preferred to phenytoin for parenteral injection because of less venous irritation. Phenobarbital also can be used if phenytoin is not tolerated or is contraindicated, but it leads to depression of consciousness and respiration. Blood levels should be checked to monitor treatment levels for phenytoin and phenobarbital. For a patient refractory to IV medications, phenobarbital coma, propofol, or other general anesthesia with neuromuscular blockade may be used to control the status epilepticus.

TABLE 3.8 PHARMACOLOGIC MANAGEMENT OF STATUS EPILEPTICUS

Agent	Dosage
Diazepam	
Adults	IV bolus of 5–10 mg at 1–2 mg/min or 0.15 mg/kg at 5 mg/min (max 30 mg)
Children	1 mg/y of age to total dose of 5–10 mg
Lorazepam	2–4 mg IV, 2 mg/min, q5–10 min, usual maximal dose: 8 mg
Phenytoin	
Adults	Loading dose of 15–20 mg/kg at 30–50 mg/min (max dose 30 mg/kg)
Children	Loading dose of 10–20 mg/kg at 0.5–1.5 mg/kg/min
Phenobarbital	Loading dose of 10–20 mg/kg IV (initial bolus 200–300 mg), repeat in 20 min
Propofol	1–2 mg/kg loading dose, then 1.5–10 mg/kg/h (intubation required)
Supportive	
Glucose	
Adults	50 mL of a 50% solution
Children	1–2 mL/kg of a 25% solution
Thiamine	100 mg IV
Calcium gluconate	1–2 amps for recent thyroid or parathyroid surgery

Myasthenia gravis: Multiple factors may increase muscular weakness for patients who have myasthenia gravis in the perioperative period (61). Anticholinesterase preparations like pyridostigmine or neostigmine should be maintained preoperatively and reinstituted on the first postoperative day. For patients who are unable to resume postoperative oral or tube feedings, neostigmine and pyridostigmine can be given as a continuous IV infusion. Certain medications, including quinidine, curare, lithium, beta-adrenergic blockers, phenytoin, and aminoglycoside antibiotics, may increase weakness and should be avoided. Vital capacity can be used to monitor pulmonary function. Increased weakness of the respiratory muscles may be caused by surgical stress and may require assisted

ventilation or tracheostomy if vital capacity falls to 15 mL/kg (62). Corticosteroids, immunosuppressive agents such as azathioprine or cyclosporin, or plasmaphoresis is used to supplement the benefit of anticholinesterases, but the ultimate therapeutic benefit in myasthenia gravis may not be seen for several weeks or months.

Cognitive impairment: Cognitive function or general mental status may decrease after surgery (63,64). Patients aged over 60 years or who have addictions to alcohol or drugs, major organ system disease, preexisting or family histories of psychosis, or even auditory or visual impairment are predisposed to perioperative cognitive impairment. Even a simple otologic procedure with a mastoid head dressing may prevent the use of hearing aids and glasses and add to disorientation. The entire hospital environment of sensory overload, sleep deprivation, anxiety, and pain contribute to disorientation and decreased cognitive function. Underlying medical conditions should be treated promptly, routine medications continued, excessive use of narcotics or benzodiazepines (e.g., diazepam) avoided, and a comfortable hospital routine established.

An attempt should be made to classify the type of cognitive impairment. Delirium should be differentiated from dementia, depression, mania, and other organic brain disorders. Dementia is a clinical syndrome that has a protracted course and is characterized by loss of cognitive abilities, personality disorganization, and decreased ability to perform daily activities without disturbance of consciousness. It is usually present in the elderly (e.g., Alzheimer disease) with a presumed organic cause. Depression, mania, and other functional disorders (e.g., schizophrenia) are true psychiatric disorders. The otolaryngologist is more likely to see delirium, a transient organic mental disorder characterized by the acute onset of impairment in attention and arousal. Restlessness, insomnia, irritability, frightening dreams, difficulty in thinking, disturbed consciousness, urinary incontinence, focal neurological signs, nystagmus, and loss of motor coordination all are seen in delirium. Causes of delirium can include drug intoxication, drug withdrawal (especially alcohol, discussed below in a separate section), metabolic disturbances, acute cerebral disorders (e.g., stroke, transient ischemic attack), infections, hemodynamic disturbances (e.g., hypovolemia, congestive heart failure), respiratory disorders, nutritional and vitamin deficiencies, and trauma. Psychiatric consultation may be necessary to help differentiate the type of cognitive impairment and guide the discovery of underlying causes.

Communication with, and management of, the patient in delirium is difficult. Agitation is pronounced. Conservative therapy can include removal of known precipitating factors, orientation to the environment with special attention to the use of a hearing aid and glasses, and pain control. If reassurance is not sufficient, medications may be necessary. Haloperidol is most often used, starting with 0.25 mg, and repeated every 30 minutes up to a loading dose of 5 mg/day. Atypical antipsychotic agents, such as risperidone or quetiapine, may have fewer extrapyramidal and sedative side effects. The anticholinesterase inhibitor donepezil may be useful with patients with delirium coexisting with dementias such as Lewy body (64). Recovery from postoperative delirium can be prolonged with some lasting effects.

GENERAL CONSIDERATIONS

Postoperative Fever

Body temperature is set by the thermoregulatory center in the anterior hypothalamus. In hyperthermia, such as heat stroke or malignant hyperthermia of anesthesia, the thermal-regulation mechanisms fail, and heat production exceeds heat loss. In a patient with fever, cytokines from mononuclear cells, important in the early-phase response to infection and inflammation, act directly on the hypothalamus to increase the "thermal set point." When the thermal-regulation set point is elevated in fever, this increased body temperature is maintained by limiting heat loss from the body by vasoconstriction and increasing heat production by mechanisms such as shivering. This explains why patients with new extremely elevated body-set temperatures feel cold even in the environment of a mildly elevated temperature. If the current body temperature is less than the elevated set point, the patient feels cold, vasoconstricts, and shivers in an effort to raise body temperature to the new temperature set point.

Although common, inflammation and infection are not the only causes of postoperative temperature elevation (65,66). Numerous noninfectious factors may cause temperature elevation, especially in the first 48 to 72 hours after surgery (Table 3.9). Infectious causes of fever usually occur 3 to 7 days after surgery, somewhat later than noninfectious causes (Table 3.9). Sinusitis and otitis may develop in the postoperative period, either from primary head-and-neck surgery or from blockage caused by nasal tubes. The otolaryngologist may be consulted by other services to exclude these common and potentially serious postoperative infections.

Evaluation of the postoperative fever should include a complete history and physical examination rather than a protocol format of blindly ordering cultures from the most common infectious sites (65,66). The first step should be a repeated rectal temperature to evaluate core body temperature. It is difficult to give an absolute definition of fever, but any elevation of 1 °C to 2 °C that occurs over a short period or an absolute elevation over 38.5 °C (101.3 °F) should be investigated. In the physical examination, special attention should be paid to the wound, chest, and signs of phlebitis in extremities. The following procedures should be performed if no obvious site is found: a leukocyte count and urinalysis; Gram stain of sputum, urine, and wound exudate; cultures of blood, sputum, urine, wound, and blood; chest radiograph; and removal and culture of intravenous

TABLE 3.9 POSTOPERATIVE CAUSES OF FEVER

Noninfectious causes
- Hematoma and tissue trauma
- Atelectasis
- Nonseptic phlebitis and DVT
- Drug or anesthetic allergies
- Transfusion reactions
- Presence of drains or catheters

Less common noninfectious causes
- Activation of inflammatory disease (lupus, rheumatoid arthritis)
- Endocrine excess (thyroid storm)
- Hypothalamic abnormalities

Infectious sites
- Wound
- Urinary tract
- Respiratory
- Intravascular catheter and site
- Infected prosthesis or foreign body
- Meningitis (especially in skull-base surgery)
- Sinusitis or otitis media
- Diarrhea: antibiotic-associated colitis

catheters. After neurotologic procedures, consideration should be given to examination and culture of spinal fluid. In general, the history, physical examination, and a few selected tests should suffice to evaluate the febrile patient. The clinician should not forget that unexplained fever in the postoperative period is common and does not mean an infection is impending.

Nosocomial infection, defined as an infection acquired in the hospital, is a major concern for the otolaryngologist. Surgical site infection (SSI) is the third most common type of nosocomial infection, and is defined as an infection within 30 days of surgery, or within 1 year of an implanted prosthesis (67–69). The use of prophylactic antibiotics for prevention of SSI has evolved to a single dose treatment, given within 30 to 60 minutes prior to the surgical incision (65–68). Cefazolin, at a simplified preoperative dose of 2 g for all adult patients, is the current recommended antibiotic, and may need to be repeated every 4 hours or for extensive blood loss. Antibiotics should not be continued longer than 24 hours, and there is good evidence that any prophylactic prevention of SSI for the most common bacteria is achieved in the first few hours. For patients with a penicillin allergy, clindamycin is the alternative, and metronidazole is a consideration for anaerobic coverage (65–67). The risk of infection in most head-and-neck surgery is low, and prophylactic antibiotics may not be needed except for cases that will last longer than 2 hours or where the oropharyngeal area will be entered or a prosthesis placed. Special circumstances include the patient who has cultured positive for methicillin-resistant staphylococcus, where intranasal mupirocin may be given. Additional measures to help prevent infection include glucose control, avoidance of hypoxemia, maintenance of normothermia, use of hair clippers instead of blade shaving, and cleansing with antibacterial solutions such as chlorhexidine (not approved for ears or contact with meninges).

Treatment is based on the underlying cause and an understanding of the physiology of temperature regulation. SSIs should be treated with drainage first, cultured, and appropriate antibiotics if necessary. Pulmonary atelectasis requires aggressive pulmonary toilet, and in the event of progression to pneumonia, antibiotics and possible bronchoscopy are indicated. If no obvious cause is discerned or while waiting for laboratory confirmation, treatment is directed toward lowering body temperature and the comfort of the patient. Mild temperature elevations are usually well tolerated and do not require specific treatment. Elevations over 39°C (102.2°F) increase the body's metabolic demands and may be accompanied by tachypnea, tachycardia, and malaise. In this situation, the body temperature set point should be reduced by antipyretics (aspirin or acetaminophen, PO or rectally, 325 to 650 mg, every 4 hours, is the preferred medication). Other treatments, such as removing bed covers, cool or ice-water sponge baths, reducing room temperature, or increasing air flow over the patient add a cold stress to the patient and are not necessary unless the core body temperature exceeds 40°C (104°F). If the body set point is not reduced by the antipyretics before these adjunctive measures are used, counterproductive vasoconstriction and shivering will attempt to maintain the elevated temperature set point. Meperidine, currently not given for postoperative pain, is a preferred medication for shivering, although benzodiazepines are also effective. Other abnormalities, such as electrolyte imbalances, should be corrected, and an adequate supply of glucose to meet the higher metabolic demands of the fever should be administered. In life-threatening elevations of body temperature (41°C or 105.8°F), special attention must be given to the cardiorespiratory reserve. Rapid cooling of the body temperature can be achieved in this situation by placing the patient in an ice bath or even on partial cardiopulmonary bypass with a heat exchanger if necessary.

Malignant Hyperthermia

Malignant hyperthermia occurs in anesthetized patients and is, if untreated, highly lethal. Because a genetic predisposition exists, all preoperative patients should be asked whether any family relative has had the condition. In malignant hyperthermia, abnormal sarcoplasmic reticulum release of calcium in skeletal muscle occurs, causing a sustained contraction with increased oxygen consumption and heat production. Patients with the condition are sensitive to the inhalation agents (e.g., halothane or enflurane) and the muscle relaxant succinylcholine chloride.

TABLE 3.10 TREATMENT OF MALIGNANT HYPERTHERMIA

Signs
- Sharp increase in core body temperature
- Cardiac arrhythmias
- Excessive bleeding
- Rise in end-tidal carbon dioxide concentration

Management
- Stop succinylcholine and inhalation agent immediately
  - 100% oxygen
- Dantrolene sodium, 2.5 mg/kg IV q5–10 min to max dose of 10 mg/kg
- Sodium bicarbonate, 1–2 mEq/kg IV for acidosis (monitor blood gases)

Support therapy
- Remove drapes
- Lower core temperature with iced saline (IV, rectally, or intragastrically)
- Application of ice to exposed body parts
- Watch for hyperkalemia, acidosis, myoglobinuria, arrhythmias, and posttreatment hypothermia

Signs usually occur shortly after the onset of anesthesia (Table 3.10). The specific treatment is dantrolene sodium, which inhibits the release of calcium in the endoplasmic reticulum of the skeletal muscle. Marked hyperkalemia from potassium released from muscle cells, acidosis, and malignant dysrhythmias may need urgent treatment.

TABLE 3.11 PHARMACOLOGIC MANAGEMENT OF POSTOPERATIVE PAIN

Drugs	Initial Dose
Opioids	
Morphine (agonist)	IV: 2.5–10 mg, duration 3–4 h Continuous IV infusion: 3 mg/h (loading dose 5–10 mg) PCA: Lock out 5–10 min Adults: 0.5–3.0 mg Children: 0.01–0.03 mg/kg, max 0.15 mg/kg/h
Hydromorphone (agonist)	IV: 1–2 mg, q4-6h PCA: Lock out 5–10 min Adults 0.05–0.25 mg Children: 0.003–0.005 mg/kg, max 0.02 mg/kg/h
Buprenorphine (partial agonist)	IV/IM: 0.3 mg, repeat in 30–60 min, then q4-6h
Tramadol	PO: 50–100 mg q4-6h, max daily 400 mg Nonurgent: initial 25 mg/d, increase 25 mg/every 3rd day
Nonsteroidal anti-inflammatory drugs	
Ibuprofen	200–400 mg, PO, q6h
Indomethacin	50–100 mg, PO, q6-8h
COX-2 inhibitor	
Celecoxib	400 mg initial dose, then 200 mg twice daily
Other	
Acetaminophen	500–1,000 mg, PO, q6h (max daily dose: 4,000 mg)

Postoperative Pain

Postoperative pain is often inadequately controlled as a result of a variety of factors, including fear of side effects (e.g., respiratory depression, nausea), fear of addiction, or failure to give medicine as prescribed. The otolaryngologist should give consideration to pain control in both the preoperative and postoperative periods. A complete explanation of the procedure to the patient and a discussion of the plan for pain control can alleviate anxiety that contributes to pain. Continuing concern and reassurance postoperatively also are important in the psychologic management of pain relief (69).

Pharmacologic treatment of postoperative pain revolves around the administration of systemic opioids (29,69) (Table 3.11). Patient-controlled analgesia (PCA) is a safe and reliable method of delivering postoperative pain relief without the delay associated with formulating IV or IM injections. Morphine remains the drug of choice for analgesia in severe pain. Meperidine is no longer recommended because of the buildup of a metabolite, normeperidine, which can cause central nervous system excitation and seizures, even for patients with normal renal function. Buprenorphine is a mixed narcotic agonist and antagonist that has a longer duration of action than morphine. To be effective, systemic opioids must be given in adequate dosage in the immediate postoperative period. Consideration should be given to IV administration, which is more reliable than IM or oral administration. The principal side effect in the postanesthetic period is respiratory depression, and it may be particularly pronounced in elderly patients. Respiratory depression can be treated with 0.4 mg of naloxone given intravenously. In a mixed agonist–antagonist like buprenorphine, naloxone may have less effect, and 2 mg/kg of doxapram, a respiratory stimulant, given intravenously is preferable. Opioids may cause vasodilatation and secondary hypotension, which can initially be treated with elevation of the feet.

An essential part of postoperative pain control is use of nonnarcotic medications on a regular dosing scale to provide a baseline level of pain relief. Current American College of Surgeons guidelines recommend that acetaminophen be given as a component of multimodal pain relief (69). Acetaminophen is present in many oral medications used when the patient is capable of oral intake (e.g., acetaminophen with oxycodone or codeine).

The total dose of acetaminophen should not exceed 4 g daily, to lessen the chance of liver toxicity. NSAIDs and selective COX-2 inhibitors can also play an important adjunctive role in postoperative pain relief. The combination of NSAIDs and opioid potentiates analgesia. NSAIDs are anti-inflammatory, antipyretic, and decrease platelet adhesion. The side effects of gastrointestinal bleeding or renal toxicity are low, but are a concern. In most otolaryngology operations, the routine use of NSAIDs should be considered as soon as the risk of bleeding at the operative site is minimal. COX-2 inhibitors do not cause platelet dysfunction, but there is concern about cardiovascular complications in long-term use, and they are not used in patients undergoing cardiac bypass.

The injection of a long-lasting local anesthetic, such as bupivacaine, into the incision can help reduce immediate postoperative pain. This can help improve early mobilization, especially important in the outpatient surgical setting common to many otolaryngology procedures. Other adjunctive procedures, such as transcutaneous electrical nerve stimulation, cryoanalgesia, and epidural-intrathecal opioid administration, are treatment modalities used in other specialties but less frequently in head-and-neck surgery. In patients with difficult or refractory pain management, consultation with a pain service is beneficial.

SURGERY IN THE CHEMICALLY DEPENDENT OR ALCOHOLIC PATIENT

The most common substances of abuse exhibiting a withdrawal syndrome are depressants, stimulants, and opioids (70). Even therapeutic medications, such as aspirin, anticoagulants, and beta blockers, can also have a withdrawal syndrome characterized by the opposite effect of the drugs. For example, rapid or overcorrection of anticoagulation can lead to a hypercoagulable state. No purposeful attempt to "withdraw" the substance abuse patient should be made during the perioperative period. Instead, the medical treatment should be designed to support the addicted patient. Stimulant withdrawal, such as from cocaine, is managed with dopaminergic agents such as amantadine, or antidepressant drugs such as desipramine, with lorazepam, 2 mg, used for more acute agitation. Perioperative treatment of depressant drug withdrawal (other than alcohol) to medicines such as the benzodiazepines or barbiturates usually involves reinstituting the abused medicine at a lower dose, and gradually weaning off over 5 to 6 weeks. In opioid abuse, narcotic analgesics should be used for pain control in the immediate postoperative period. Thereafter, support can be maintained by a number of different withdrawal schemes. Clonidine, 0.1 mg, orally every 4 hours, initially, for the first 36 hours, followed by gradual weaning, helps minimize the opiate abstinence syndrome (70). As an alternative, methadone 10 to 30 mg, orally is given initially with subsequent doses every 8 to 12 hours, depending on symptoms. Naloxone, 0.4 mg, i. v., should be available to reverse narcotic overdosage.

The alcoholic has several specific abnormalities that should be addressed. After only a few hours without alcohol, the patient may begin to show signs of mild withdrawal, including irritability, tremulousness, and nausea. In addition to reassurance, chlordiazepoxide, 25 to 100 mg, orally every 6 hours, may help prevent the onset of more severe delirium tremens, which usually starts 48 to 72 hours after alcohol cessation and lasts 3 to 5 days (70,71). Delirium tremens is an unwanted complication in the otolaryngology patient, especially for patients who have undergone a major head-and-neck resection, tracheostomy, and flap reconstruction. Delirium tremens develops in 5% to 10% of patients with alcohol withdrawal, characterized by increased irritability, agitation, hallucinations, fever, tachycardia, and disorientation, and can have mortality up to 15%. Seizure activity may be present but usually of short duration and not requiring antiepileptic medications. Medical treatment includes increasing chlordiazepoxide to 100 mg, IV or PO, every 2 to 6 hours, up to 500 mg in the first 24 hours, and tapering thereafter, depending on symptoms. In older patients, shorter-acting lorazepam, 1 to 2 mg IV or PO, every 6 to 8 hours, can be used, and oxazepam, which is excreted by the kidneys, can be used in patients with hepatic failure, at a dose of 15 to 30 mg, PO, every 6 to 8 hours.

The alcoholic also has medical problems pertinent in the surgical patient. Hemostasis in the alcoholic patient can be altered significantly. The patient may have prominent bleeding problems secondary to insufficient or abnormal platelets found in alcoholism, in addition to decreased coagulation factors if alcoholic liver disease is present. All alcoholic patients should have thiamine, 100 mg, and folic acid, 1 mg, IV, followed by oral thiamine, 100 mg, daily with a multiple vitamin containing folic acid and vitamin B_{12}. Metabolic problems also are important in alcoholic patients, who are especially susceptible to hypoglycemia because of depleted glycogen stores. For this reason, all preoperative alcoholic patients should have intravenous fluids with glucose and a minimal fasting period before surgery. Phosphate, magnesium, and potassium are frequently low and should be measured and replaced as necessary.

HIGHLIGHTS

- Routine preoperative laboratory evaluation is not productive in healthy patients, has minimal predictive value for postoperative complications, and should evaluate known medical conditions.
- Correction of hemostatic disorders requires the replacement of specific clotting factors, FFP, or platelets rather than the use of whole blood.

- Prevention is the best form of therapy for DVT, and it involves mechanical methods and consideration of low-dose anticoagulant therapy.
- In the diabetic, adequate carbohydrates are provided during and after surgery to prevent protein catabolism and lipolysis. Serum glucose is controlled by monitoring blood glucose and giving supplemental regular insulin as needed. A sliding scale for insulin dosing is not routinely used.
- Thyrotoxic storm is treated with medications to block production or release of thyroxine (e.g., PTU, iodides), control cardiac symptoms (e.g., propranolol if tachycardia, diuretics and digitalis if heart failure), and replace other deficiencies (e.g., hydrocortisone).
- A search for the underlying cause for postoperative hypotension or hypertension should be sought rather than instituting treatment only with pharmacologic agents.
- Pulmonary problems are the most common postoperative complication, and deep breathing, clearance of secretions, and frequent turning are begun immediately after surgery.
- Stress ulceration is the most common cause of postoperative gastrointestinal bleeding. Reduction in gastric acidity by histamine blockers, PPIs, and early enteral feedings are the most effective prophylactic measures.
- The most important intraoperative consideration in chronic renal failure is to maximize renal perfusion and minimize further kidney damage.
- The primary goals in treating postoperative seizures are to stop the seizure, avoid hypoxia, and avoid injury to the operative site. Benzodiazepines, phenytoin, and phenobarbital are pharmacologic agents of choice.
- Noninfectious causes of postoperative fever are common, especially in the immediate postoperative period.

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Operative Technologies

4

Paul G. van der Sloot *Runhua Hou*

INTRODUCTION

The nature of surgery is such that operative technologies provide impetus for change and progress with improved operative outcomes. Operative technologies are numerous and diverse, maybe more so in otolaryngology than any other surgical specialty. This chapter represents an overview of operative technologies in otolaryngology. It is by no means comprehensive. An array of technologies are presented that include new technologies that have come into widespread practice, developing technologies that are at the cusp of general use and old technologies for which new applications have been recently developed.

DISSECTION/HEMOSTASIS TECHNOLOGIES

A number of recent tools have been developed that provide the ability to dissect and achieve hemostasis virtually simultaneously. These instruments tend to be most useful in operative cases where space is limited and a clean operating field is particularly important. These include cases like parotidectomy, thyroidectomy, parathyroidectomy, tonsillectomy, and microvascular free flap harvest.

Tonsillectomy

In the case of tonsillectomy, technologies have been adopted that attempt to minimize pain associated with conventional cautery without increasing the risk of post-tonsillectomy bleeding. Coblation involves the dissociation of isotonic saline into sodium ions between the electrodes of the coblator, which breaks molecular bonds between cells. The temperatures generated by the coblator are between 45°C and 85°C as compared to 400°C and 600°C with electrocautery. This, along with the fact that coblation tonsillectomy is usually performed using an intracapsular technique, has been shown to decrease the duration of postoperative pain and speed the return to a normal diet (1). The disposable coblator components do create an added cost for the procedure. Coblation has also been used for a variety of nasal surgeries like turbinate reduction, hemostatic debulking of tumors to allow endoscopic visualization, and the removal of encephaloceles.

Other techniques that have been used successfully include argon plasma scalpels where argon gas is ionized by an electrode creating a beam of argon plasma through which current flows allowing for tissue dissection using molecular resonance technology where alternate current high-frequency electron waves at well-defined and varying wavelengths create electron energy quanta, which, when in resonance with cell molecular bonds, causes them to break (2,3). The main thrust of these technologies is to decrease pain without increasing the risk of hemorrhage in the postoperative period.

Thyroidectomy and Parotidectomy

Ultrasonic shears (or the harmonic scalpel) involve the use of ultrasonic blade vibrations at 55,000 Hz that denature proteins and create a coagulum that seals vessels. Vessels of up to 2-mm diameter can be sealed using this technique. Because no electrical energy is transferred to the patient, it may be ideally suited for areas of dissection near nerves. Some studies have suggested decreased blood loss and decreased frequency of facial nerve injury are seen with the use of ultrasonic shears for superficial parotidectomy (4). Similar results have been obtained for thyroidectomy. Despite the common use of this instrument for these procedures, basic science researchers have shown that activation of the shears near the nerve, particularly closer than 2 mm or when it is activated in the vicinity for greater than or equal to 3 seconds, does result in a change in peak latency for the recurrent laryngeal nerve in a rabbit model (5).

Microvascular Free Tissue Harvest

Several donor sites for free tissue harvest involve the harvest or division of large muscle bellies. The fibular osteocutaneous free flap and the anterolateral thigh myofasciocutaneous flap with or without significant vastus lateralis muscle are commonly used donor sites that require substantial muscle division. Vascular perforators in the muscle at irregular intervals make the muscle division tedious, and conventional harvest can be prolonged with blood loss hampering field visualization. Increasingly, ultrasonic shears are used to limit time required to harvest, decrease blood loss, and improve field visualization.

TECHNOLOGIES TO IMPROVE VISUALIZATION OF THE OPERATIVE FIELD

Sinus Surgery

Endoscopes with variably angled lenses have been in conventional use for sinus surgery for many years. They have paved the way for less morbid surgery by allowing the sinus surgeon to visualize the tissues more precisely. The surgeon is thus able to limit trauma to those areas of the nose and sinuses that have no bearing on the desired outcome of surgery. In this way, it has decreased the morbidity of sinus surgery while improving outcomes.

Skull Base Surgery

The combination of improved endoscopes and cameras coupled with image-guided navigation and even real-time imaging has expanded the bounds of endoscopic skull base surgery (6). Although the basic instruments are similar to sinus surgery instruments, more varied angles for cutting and grasping instruments, extended guards for drills, and other modifications like endoscopic bipolar cautery have all contributed to the advancement of endoscopic skull base surgery. Self-irrigating endoscope technology has also allowed for more efficient surgery by limiting the need for scope removal and cleaning during the procedure. Although robotic surgery has not become a standard for skull base surgery at this point, increasing miniaturization of instruments and cameras as well as work on multiply articulated instruments may make robot-assisted surgery of the skull base a standard in the future (7).

Thyroid and Parathyroid Surgery

Minimally invasive procedures of the thyroid and parathyroid glands have evolved as a result of a desire for improved cosmesis, particularly in certain cultural groups, and a desire to limit pain and hospital stay. Video-assisted thyroidectomy involves a reduced central neck incision, subsequent blunt dissection to divide the muscular raphe in the midline, blunt dissection over the capsule of the thyroid, and subsequently the use of a 5-mm 30-degree laparoscope combined with the harmonic scalpel to take down the superior pole vessels and subsequently identify the recurrent laryngeal nerve. The remainder of the lobe is then separated from the parathyroids, Berry's ligament is divided, and the lobe is dissected off the trachea. Nodules greater than 3 cm and a history of thyroiditis may limit this technique, but with appropriately selected patients, complication rates that are comparable to conventional surgery are quoted in the literature (8,9).

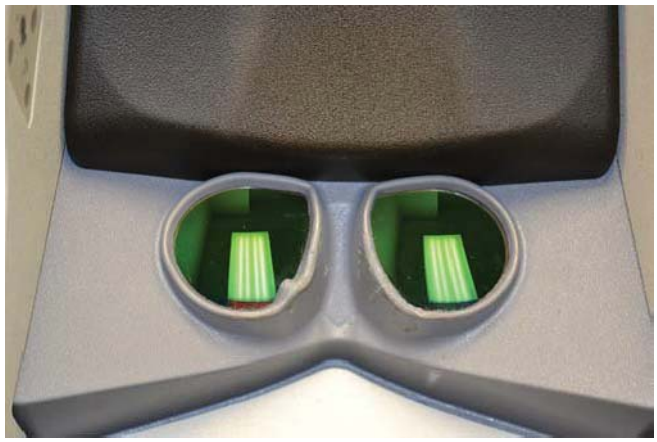


Figure 4.1 Robot stereo viewer.

An extension of the desire to limit any visible scar is the transaxillary thyroidectomy, often done with robotic assistance. The da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA) provides binocular (Fig. 4.1), three-dimensional (3D) magnification, tremor filtration, and greater degrees of freedom in the mobility of instruments. The surgeon, after preparing the surgical field, sits in a console with 3D visualization of the field and ergonomic hand and foot controls. Scaling of movement up to 5 to 1 can be set, and any tremor is filtered as the surgeon's movements in the console are transferred in real time to the instruments in the patients (Fig. 4.2). Clutching of the wrist



Figure 4.2 Robot master hand controller.

rotational movements allows for 360 degrees of rotation for a given instrument. In the case of transaxillary thyroidectomy, the patient station is docked on the contralateral side. The 30-degree endoscope is used facing downward through 5- to 6-cm vertical incision in the ipsilateral axilla. Dissection is in a subcutaneous plane until the sternocleidomastoid muscle is identified. It is subsequently carried down between the two heads of the muscle. Indications for this approach include small nodules less than 2 cm including well-differentiated malignancies without extracapsular spread. High BMI may be a contraindication to this approach (10).

Transoral Robotic Surgery

Historically, tumors of the oropharynx, particularly those of the base of tongue, required extended access procedures to be able to visualize and remove tumors at these locations. Often, a lip and mandibular split procedure was required. Subsequent patient function and cosmesis was at the very least temporarily impaired. This was one of the driving forces behind the move toward organ-preserving therapy. Robotic surgery has been used as a minimally invasive approach for urologic surgery for some time. More recently, this technology has been applied to tumors of the oropharynx to provide a surgical alternative to nonsurgical organ-preserving therapies. Transoral robotic surgery (TORS) has been successfully used for tumors of the oropharynx in particular. The potential benefits of the technology are listed above.

Patient selection is critical for these cases. Mouth opening must be adequate and paralysis intraoperatively is usually required. Usually, a Feyh-Kastenbauer or Dingman retractor is used to keep the mouth open. A second assistant at the head of the bed is also required for additional retraction and occasional help with hemostasis. Thirty-degree binocular endoscopes are usually used for the tongue base. Zero-degree endoscopes are often used for the tonsillar fossa (Fig. 4.3). Recent studies have shown that even when combined with adjuvant therapy, functional outcomes 12 months posttreatment including swallowing, speech, and diet are not significantly different from pre-op assessments (11). Human papillomavirus–related oropharyngeal malignancy, with its increasing incidence and brighter prognosis, has prompted work on deintensification of therapy. TORS appears to have a role to play in maintaining oncologic outcomes while minimizing long-term morbidity.



Figure 4.3 Basic setup for the robot with central camera arm and lateral instrument arms.

VIDEO (ROBOTIC RESECTION ORO/HYPOPHARYNGEAL LESION)

Oncologic Tools

Photodynamic Therapy

The basic idea behind photodynamic therapy is administration of a photosensitizing drug followed by the application of light causing a photochemical reaction that results in tissue damage. Intraoperatively, needles are placed in a tumor and optical fibers are threaded through these needles. Guidance for needle placement can include endoscopy, ultrasound, and CT and MRI technologies. Temoporfin is a commonly used photosensitizing agent that is typically given IV 90 minutes prior to light therapy. A 652-nm diode laser is then used at 20 J per location. This technique has been shown to decrease tumor bulk and improve functional status in unresectable and recurrent tumors (12). Photodynamic therapy shows particular promise for dysplasia and carcinoma in situ.

High-Resolution Microendoscopy and Confocal Microscopy

High-resolution microendoscopy is showing promise as an adjunctive measure for evaluation of margins in head and neck epithelial malignancies. The technology involves direct contact between a high-resolution endoscope and an epithelial surface. Prior to contact, the epithelium is painted with a contrast agent like proflavin. Excitation light is delivered through the fiberoptic bundle. Fluorescence emission from the epithelial surface is then captured by a charge-sensitive camera, and digital images are obtained. Differences in the obtained images allow for differentiation of normal mucosa from dysplasia and carcinoma with good histologic correlation (13). Laser scanning microscopy (confocal microscopy) with endoscopes has been combined with the utilization of laser light to produce topographical images of the epithelium. When combined with rigid endoscopes, evaluation of tissue just below the surface epithelium can also be obtained. Differentiation between normal, dysplastic, and cancerous epithelium shows good correlation with histologic analysis (14).

Lasers

Lasers have been utilized in a number of ways in the field of otolaryngology. We focus on relatively recent developments that have had an impact on the practice of otolaryngology

Angiolytic Lasers

Photoangiolysis involves the ablation of small superficial blood vessels by targeting hemoglobin. The potassium titanyl phosphate (KTP) laser has a wavelength of 532 nm, which correlates closely with the peak absorbance of hemoglobin. By ablating the supporting microcirculation of a lesion, whether it is benign or even malignant, the growth of the lesion is terminated. Delivery through flexible fibers permits use with rigid or flexible endoscopes. This makes ideal for in-office procedures.

This technology has been particularly useful in the treatment of a variety of laryngeal lesions including vascular ectasias, papilloma, polyps, and granulomas. It shows promise in the treatment of dysplasia and early glottic cancers as well (15).

CO_2 Laser (Flexible Fiber Delivery)

Through the combination of CO_2 laser energy and near-perfect mirrors, a flexible delivery system has been designed that allows for broader application of the CO_2 laser (Omniguide, Cambridge, MA). A hollow core delivering a cooling flow of inert gas allows for a cleaner field, improved coagulation, and cooling of the treated tissues, limiting thermal injury. Of course, it can be delivered with a flexible scope but also with a variety of hand pieces. This technology is used in variety of otolaryngologic procedures from stapedectomy and cholesteatoma removal to laryngeal papilloma and cancer removal. It also has proved very useful in tracheal surgery to debulk tumors and to make radial cuts for tracheal stenosis. Furthermore, work is currently being done on coupling the flexible CO_2 laser with robotic technology.

Image-Guided Navigation

Image guidance has now been used since the early 1980s and has become routinely used in revision sinus surgery and complex endoscopic skull base surgery. There are several platforms available. In general, a preoperative CT scan is performed and images are referenced to fixed points placed close to the surgical site. This provides for an increased margin of safety relative critical structures at risk during these procedures. In general, these systems do not provide real-time evaluation of the patient's anatomy. However, compact, portable CT scanners are available that can couple real-time CT images with existing image guidance systems to give up-to-date information as surgery modifies existing anatomy (16).

Topical Hemostatic Agents

Topical hemostatic agents are commonly used in otolaryngology. In general, they can be divided into four categories: fibrin sealants, gelatin-based products, oxidized cellulose, and collagen products. Fibrin sealants are now commonly used in otolaryngologic surgeries. Tisseel (Baxter) is the most commonly used product. It comes in two vials. The first vial is composed of human fibrinogen and bovine aprotinin, an inhibitor of proteases including plasmin. The second vial contains human thrombin and calcium chloride. The two vials are combined to form a solid fibring sealant. Crosseal (Ethicon) is a more recently developed product and contains human fibrinogen and thrombin but no bovine aprotinin. These products have been successfully used in the context of parotidectomy and rhytidectomy to reduce the potential for hematoma and ecchymosis (17).

Gelatin-based products have hemostatic properties that are not linked to the clotting cascade and are thought to be physical rather in chemical in nature. Gelfoam (Baxter) is made of purified pork skin gelatin and typically is used in sponge form, often combined with purified thrombin. An important property of gelatin sponge is its ability to absorb up 40 times its weight in fluid and expand its volume up to 200%. Depending on the application, this may be a positive or negative attribute. Floseal (Baxter) combines human thrombin with bovine gelatin matrix granules. These are mixed at the time of application. Volume expansion is minimal, and because it comes in liquid form, it is easy to apply in limited access procedures. Surgiflo (Ethicon) has a similar constitution and utilization.

Oxidized cellulose, like Surgicel (Ethicon), has long been used as a topical hemostatic agent. It is produced as a knitted fabric from regenerated plant-derived cellulose, which is oxidized. It acts as a scaffold for clot formation. Surgicel comes in a number of different forms, from a thick woven product to lightweight tufted layers depending on the nature of the application. Besides its hemostatic properties, it has bacteriocidal properties. Surgicel is used extensively as a topical hemostatic agent for epistaxis and with intranasal surgical procedures.

Microfibrillar collagen products like Avitene (Davol, Inc.) are made by purifying bovine collagen and processing it into microcrystals. Collagen products induce the intrinsic pathway of the coagulation cascade. They have been in use since the 1970s. Developments have been made recently in the format of these products. They are now available in powder, woven–knit, and sponge form. In some randomized control trials, microfibrillar collagen has been shown to be a superior topical hemostatic agent than oxidized cellulose (18).

Wound Adhesive/Hemostatic Agents

Cyanoacrylate adhesives were developed in the 1940s by Kodak. As early as 1965, they were used for tympanic

membrane repair. Liquid cyanoacrylate monomers polymerize to form long chains in the presence of hydroxyl ions. Water from human tissues activates the polymerization reaction and the "glue" rapidly sets. Although it is mainly used for closure of small skin incisions, it has been used for corneal perforations, varices, and other vascular repairs, as well as skin grafting. Besides their adhesive properties, cyanoacrylate adhesives also have good antimicrobial properties.

Tissue Substitutes

Dural Substitutes

Repair of dural defects, although usually performed with autologous tissues, is sometimes performed with engineered tissues. In most cases, this is performed using collagen-based dural substitutes. Duragen (Integra, Life Sciences) is cross-linked collage foam produced from bovine Achilles tendon. Duraguard (Synovis) is a cross-linked collagen product produced from bovine pericardium. Durarepair (Integra, Life Sciences) is a non–cross-linked bovine collagen implant derived from bovine fetal dermis. Durarepair and Duraguard are stronger materials that are usually sutured in place. Duragen is more fragile, and although it can be sutured in place, it is usually used as an onlay graft. Duragen is typically absorbed by 1 month, while both Durarepair and Duraguard are still identifiable but integrated by 6 months implantation. Duragen is quickly penetrated by native cells, whereas Durarepair and Duraguard take much longer to integrate. In short, the physical properties of Duraguard and Durarepair are useful where a long-term dural substitute is required. Duragen is more useful for the repair of small defects, not requiring the mechanical strength of native dura (19).

Skin Substitutes

The definition of "skin substitutes" varies widely. We define them as materials containing normally occurring skin elements that are incorporated into native skin. Skin substitutes can be categorized into the skin layers being replaced. Epidermal replacements contain keratinocytes. Allogenic keratinocytes can be harvested from fresh human donor skin, neonatal foreskin, and occasionally other harvested skin. One to two months following placement, autologous keratinocytes have replaced the allogenic cells. The use of these epidermal substitutes is relatively limited. More commonly, dermal skin substitutes are used for skin replacement. These can be divided into acellular and cellular substitutes, the latter usually containing fibroblasts and endothelial cells. Alloderm (Life Cell Corporation) is a commonly used acellular dermal replacement containing collagen and elastin derived from human donor skin. Apligraf (Organogenesis) is an example of a cellular product containing collagen, glycosaminoglycans, allogenic keratinocytes, and allogenic fibroblasts derived from bovine tendon and neonatal foreskin. Whether acellular or cellular, these materials provide a scaffold for the invasion of fibroblasts. These fibroblasts produce extracellular matrix and cytokines, which eventually lead to the replacement of the skin substitute. This substitution can take place over weeks, months, or years depending on the material (20).

HIGHLIGHTS

- Temperatures generated by the coblator are about 1/10 those of electrocautery when used for tonsillectomy.
- Ultrasonic shears denature proteins, creating a coagulum that seals vessels.
- Video-assisted thyroidectomy may be limited to nodules less than 3 cm in greatest dimension.
- Robotic surgery benefits from binocular magnification, 360 degrees of wristed motion, and scaled movements with tremor suppression.
- TORS in selected oropharyngeal cancer patients reduces functional morbidity by avoiding lip-splitting, mandible-splitting surgery and by reducing the dose of radiation or even eliminating it entirely.
- Photodynamic therapy using light-sensitizing agents and light can reduce bulk in unresectable tumors and shows promise in the treatment of dysplasia and carcinoma in situ.
- Confocal and high-resolution microendoscopy show promise in identifying dysplasia and cancer on epithelial surfaces.
- Photoangiolysis with the KTP laser can be used to ablate the supporting microcirculation of an array of laryngeal lesions by utilizing a wavelength that closely corresponds to the peak absorbance of hemoglobin.
- Topical hemostatic agents can be divided into fibrin sealants, gelatin-based products, oxidized cellulose preparations, and microfibrillar collagen products.
- Dermal skin substitutes can be divided into cellular and acellular products. In both cases, the material provides a matrix for invasion by native fibroblasts that induce further incorporation into the surrounding skin.

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Critical Care

5

Jon D. Simmons *Kimberly A. Donnellan*

The field of critical care medicine is complex and rapidly changing. The goal of this chapter is to familiarize the otolaryngologist with some of the basic principles of critical care medicine and provide evidence for common postoperative complications often seen in the intensive care unit (ICU). This chapter increases a general understanding of critical care medicine while facilitating a good working relationship with the intensivist.

TISSUE OXYGENATION AND ORGAN PERFUSION

Many physicians struggle with understanding the difference between tissue oxygenation and organ perfusion. Although these topics are often regarded as synonymous, they are not. This misunderstanding is likely the reason for inappropriate fluid resuscitation and blood transfusions, and emphasizes the importance of understanding their differences and treatment.

OXYGEN DELIVERY

In general terms, oxygen delivery (DO_2) refers to the amount of oxygen that is delivered to the tissue. It does not refer to the amount of oxygen uptake at the cellular level. The lack of oxygen delivered into the tissues can be due to several defects including: respiratory failure, inadequate delivery to the tissues, and defective uptake into the tissue. DO_2 to the peripheral tissues can be calculated by using the following formula.

$$DO_2 = CO \times 1.34 \times Hb \times SaO_2 + (PaO_2 \times 0.003)$$

where CO, cardiac output; Hb, hemoglobin; SaO_2, oxygen saturation; and 1.34 is a conversion factor that relates how much oxygen can bind to hemoglobin. (PaO_2 × 0.003) describes the amount of oxygen that is dissolved in blood and not bound to hemoglobin.

Notice the amount of oxygen delivered to the peripheral tissues as dissolved oxygen that is not attached to hemoglobin is miniscule (PaO_2 × 0.003). Therefore, when the oxygen saturation of hemoglobin is high, it does not help to provide excess supplemental oxygen. The CO, Hb, and SaO_2 all have equal contributions to the amount of oxygen delivered to the peripheral tissue. Therefore, CO and Hb are as important as the oxygen content in the blood.

OXYGEN EXTRACTION

Oxygen extraction (VO_2) refers to the amount of oxygen that is extracted from the blood into the peripheral tissues at the capillary level and utilized by the cell. Since oxygen is not stored in the cell, extraction (consumption) is equal to the amount of oxygen utilized by the cell. The rate of oxygen extraction is expressed by the following formula:

$$O_2 = CO \times 1.34 \times Hb \times (SaO_2 - SvO_2)$$

where CO, cardiac output; Hb, hemoglobin; SaO_2, arterial oxygen saturation; SvO_2, venous oxygen saturation; and 1.34 is a conversion factor that relates how much oxygen can bind to Hb.

The most important concept to understand in tissue oxygenation is that delivery (DO_2) and extraction (VO_2) are not the same. The rate of oxygen extraction from the blood into the peripheral tissues (VO_2) is done at a constant rate. In normal circumstances (a normal DO_2), only 25% of the oxygen in the blood is extracted into the tissues. Therefore, 75% of the oxygen in the blood is not extracted into the tissue and is considered "extra." The amount of oxygen extracted into the tissue is better described as the oxygen extraction ratio (O_2ER).

$$O_2ER = VO_2 / DO_2$$

The O_2ER reveals that as the delivery of oxygen to the tissue (DO_2) decreases, the amount of oxygen extracted into the cell is the same (no change in VO_2). However, the O_2ER will increase (more oxygen disassociation from Hb) to provide the constant transfer of oxygen into the cell.

At some point, the delivery of oxygen (DO_2) will be low enough not to provide the constant flow of oxygen into the cell, which is needed for aerobic metabolism. This is the point that must be identified by the physician. This level is often referred to as the critical DO_2. This is the level that cellular metabolism changes from aerobic to anaerobic metabolism. Therefore, increasing the delivery of oxygen without a level below the critical DO_2 is often unnecessary and may carry the risk associated with the treatment (i.e., inappropriate blood transfusions).

Since the DO_2 is irrelevant until it reaches the critical DO_2 signifying a drop in tissue oxygenation (VO_2), the decrease in VO_2 is the important factor. The measurement of the oxygen consumption (VO_2) requires invasive devices, like a Swan-Ganz catheter or Metabolic cart, that are not readily available in all situations. However, the O_2ER is closely linked to the oxygen consumption (VO_2) and can be easily measured since most critically ill patients have a central venous catheter. We know from many human and animal studies that the oxygen consumption (VO_2) starts to drop with an O_2ER of approximately 50%. The O_2ER can be calculated by subtracting the amount of oxygen in the venous blood from the oxygen in the arterial blood. Since the peripheral tissues do not store oxygen, this difference of oxygen content between the arterial and venous blood is the amount of oxygen extracted at the cellular level. This can be expressed as:

$$O_2ER = SaO_2 - SvO_2$$

where SaO_2, arterial oxygen saturation; SvO_2, venous oxygen saturation.

The SaO_2 is easily measured with noninvasive devices such as a pulse oximeter. The SvO_2 is most accurate when obtained in the pulmonary artery that is distal to where the coronary sinus empties desaturated venous blood into the right atrium from the myocardium. A Swan-Ganz catheter is needed to obtain this "mixed venous" (SvO_2) measurement in the pulmonary artery. However, the venous oxygen saturation taken from the superior vena cava ($ScvO_2$) from the tip of a "central line" is in close proximity to the pulmonary artery oxygen saturation (SvO_2). The average variation between these measurements is about 5% (1). So the oxygen saturation from a central venous catheter ($ScVO_2$) can fairly accurately replace the mixed venous saturation (SVO_2), especially when following trends. This allows the physician to fairly accurately predict the oxygen consumption without a Swan-Ganz catheter.

ANAEROBIC METABOLISM

As stated previously, the switch from aerobic to anaerobic metabolism occurs at the point where the supply of oxygen (DO_2) cannot meet the metabolic demands (VO_2) at the cellular level. This occurs at an O_2ER below approximately 50%. Another indirect marker of anaerobic metabolism is lactate. The serum lactate level can be an effective marker of cellular oxygenation but using this to solely determine end-organ perfusion can be problematic. Since lactate is cleared by the liver, its clearance is variable and therefore is not the best immediate marker to guide therapy.

BLOOD TRANSFUSIONS IN THE ICU

Blood transfusions are often a lifesaving therapy in surgical ICUs. However, blood transfusions are also one of the most misused resources available to physicians. We will describe the indications, side effects, and evidence surrounding the use and misuse of blood transfusions in the ICU.

The effect that packed red blood cells (PRBCs) have on tissue oxygenation is often misunderstood. As described earlier, the delivery of oxygen to the tissues is dependent upon cardiac output, amount of hemoglobin, and the oxygen saturation. In normal individuals, only 25% of delivered oxygen (DO_2) to the peripheral tissue is utilized (VO_2). Therefore, an excess of oxygen is delivered to the tissue. As the DO_2 decreases (i.e., decrease in hemoglobin), the amount of oxygen extracted from hemoglobin increases, but the oxygen uptake into the tissues (VO_2) remains unchanged. So, giving a blood transfusion when the extraction ratio is above 50% will not increase the amount of oxygen utilized by the cell. In fact, giving a blood transfusion in the setting of isovolemic anemia will often decrease the VO_2 due to the increased viscosity of PRBCs causing a decrease in perfusion of the microcirculation.

Blood transfusions are analogous to a "Blood Transplantation" and the side effects of blood transfusions are similar to most other transplanted organs from another human (allograft). The previous concerns for the infectious risk of hepatitis and human immunodeficiency virus are now very uncommon (2). The most notable side effects consist of immunosuppression and rejection. The immunomodulating effects of receiving a blood transfusion increase the risk of the recipient to developing nosocomial infections, acute respiratory distress syndrome (ARDS), and possible development of autoimmune diseases later in life (3,4). However, the most important immunomodulating effect of blood transfusions in postoperative oncologic patients is the significant increase in cancer recurrence and death (5–7). Most of the evidence regarding cancer recurrence is in colorectal cancer but some studies have specifically examined the recurrence rate after squamous cell carcinoma (SCC) of the head and neck (8,9). Jones et al. (6) examined the recurrence/metastasis rate in Stage 3 SCC in the head and neck in regards to blood transfusions. They found the recurrence/metastasis rate of SCC to be significantly higher in the group that received a blood transfusion (64% vs. 22%). This reason alone should prompt careful consideration prior to giving a blood transfusion in postoperative patients.

More recently it has been shown that not all units of PRBCs are equal (9) and that the length of storage makes a significant difference in the quality of PRBCs that are transfused. Longer storage times are associated with ATP depletion, decreased 2,3 DPG, protein oxidation, and loss of membrane flexibility. The combination of the membrane flexibility and decreased 2,3 DPG would conceptually reduce the quality of the PRBC transfusion the most. The loss of membrane flexibility limits the ability of the red blood cell (RBC) to pass through the microvascular circulation, and the decrease in 2,3 DPG will cause a left shift in the oxygen–hemoglobin disassociation curve causing less off-loading of oxygen to the peripheral tissues. The loss of membrane flexibility and increased viscosity of PRBCs are often cited as being the culprits for decreasing the DO_2 following the administration of PRBC. This is best displayed in a study examining the progressive normovolemic hemodilution in canine skin flaps (10). The authors progressively infused a colloid solution while removing blood from the canine to drop the hemoglobin while maintaining adequate intravascular volume and cardiac output, which effectively decreased the viscosity of the blood (normovolemic hemodilution). As the hemoglobin dropped, the authors measured the tissue oxygenation on the skin flaps. They found that as the hemoglobin decreased, the tissue oxygenation actually improved instead of the decline. The tissue oxygenation of the normal skin continued to improve until the canine reached a hemoglobin of 4.

In 1942, Adam and Lundy (11) suggested a hemoglobin level of less than 10 should prompt a blood transfusion. Since that time, study after study has attempted to find the optimal hemoglobin level that would necessitate a blood transfusion in the nonhypovolemic patient. Thus far, the Transfusion Requirement in Critical Care (TRICC) trial is the only prospective randomized controlled trial with an adequate sample size to examine this issue. The TRICC trial (12) examined the difference between a hemoglobin transfusion trigger of 7 versus 10 in euvolemic patients in the ICU. The authors concluded "A restrictive strategy of red-cell transfusion is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina." This was later confirmed in another prospective randomized controlled trial (13). In 2006, Marik et al. (14) performed a systematic review of the literature and concluded "the need for a PRBC transfusion should be individualized based on a patient's clinical circumstances rather than an arbitrary hemoglobin concentration."

SHOCK

The term shock is used very commonly throughout the medical field but is often poorly understood. In simple terms, shock is synonymous with tissue dysoxia. The treatment of shock is guided by correcting the variables in the DO_2 equation that are abnormal (CO < 6 L/min, Hb < 7, and oxygen saturation < 90%). There are two situations in which shock is not caused by decreased DO_2: mitochondrial dysfunction (sepsis, cyanide, etc.), and vasodilatory states (systemic inflammatory response syndrome, sepsis, spinal shock, etc.). There is no treatment for the mitochondrial dysfunction seen in sepsis other than supportive care. Vasopressors are likely the optimal treatment for vasodilatory states (i.e., systemic inflammatory response syndrome) in the setting of normovolemia.

VASOACTIVE AGENTS IN THE ICU

The use of vasoactive infusions in the ICU is not uncommon and their use can be lifesaving. However, severe complications can be associated with the use of vasopressors. There is not good evidence to support which vasopressor to use in a given situation or if they improve outcomes in shock. However, we will review commonly used vasopressors in the ICU and the ideal situations in which they should be applied (see Tables 5.1 & 5.2).

There are several things in which a physician should consider prior to initiating vasopressor infusion. These considerations should include: cardiac output, volume status, peripheral vascular resistance, and causes of hypotension. All four of these considerations are very important and must be known prior to initiating any vasopressor for hemodynamic support.

Common Pitfalls to Avoid with Vasopressors

Systolic Left Ventricular Failure

In patients with severe systolic dysfunction, a rapid increase in peripheral vascular resistance will cause increased myocardial work and worsening cardiac output with rapid decline. These patients may benefit from inotropic support or decreased peripheral vascular resistance rather than a vasoconstrictor.

Diastolic Dysfunction

Diastolic dysfunction is often misunderstood. A simplistic view of diastolic dysfunction is to imagine a muscular bodybuilder that cannot straighten his arms due to the tight bicep muscle. This bicep muscle is very strong but it cannot completely relax. This is analogous to a hypertrophied left ventricle in diastolic dysfunction. The left ventricle is unable to stretch and accept enough preload to generate sufficient cardiac output despite being able to contract normally. It is a preload problem; therefore, the ejection fraction is normal despite a low cardiac output. Although ventricular hypertrophy is the most common type of diastolic dysfunction, any disease process that limits the ability of the ventricle to relax is considered diastolic dysfunction. Patients with severe diastolic

TABLE 5.1 CARDIOVASCULAR EFFECTS OF VASOACTIVE AGENTS

		Hemodynamic Effects[a]				
Agent	**Dose Ranges[b]**	**HR**	**MAP**	**PAOP**	**CI**	**SVR**
Dopamine	1–3 µg/kg/min	↑	↔/↓	↓	↔/↑	↔/↓
	3–10 µg/kg/min	↑↑	↑	↔	↑	↔
	>10–20 µg/kg/min	↑↑↑	↑↑	↔	↑	↑
Norepinephrine	0.01–1 µg/kg/min	↑	↑↑	↑	↔/↑	↑↑↑
Epinephrine	0.01–1 µg/kg/min	↑↑	↑↑	↑	↑↑	↑↑
Phenylephrine	0.5–1 µg/kg/min	↔/↓	↑	↑	↔/↓	↑↑
Vasopressin	0.01–0.04 units/min	↔/↓	↑↑	↑	↔	↑↑
Dobutamine	2–20 µg/kg/min	↑↑	↓/↑	↓	↑	↔/↓

[a]Hemodynamic effects may vary among patients.
[b]The maximum dose should be based on individual institutional policies.
HR, heart rate; MAP, mean arterial pressure; PAOP, pulmonary artery occlusion pressure; CI, cardiac index; SVR, system vascular resistance.

dysfunction can be very difficult to manage perioperatively. If the patient is underresuscitated and placed on a vasoconstrictor in the setting of severe diastolic dysfunction, the cardiac output will quickly decrease as the vasopressor infusion is quickly titrated upward to maintain hemodynamic stability. This type of patient must get adequate volume resuscitation prior to starting a vasopressor for hemodynamic support.

Cardiac Valve Disease

Cardiac valvular disease can be difficult to treat or diagnose without imaging studies (i.e., echocardiogram). Vasopressor therapy can dramatically worsen valvular abnormalities such as but not limited to aortic/mitral stenosis and insufficiency. The immediate clue that a cardiac valve abnormality may be significantly contributing to the hemodynamic instability is a murmur on cardiac auscultation. The presence of a murmur in the setting of hemodynamic instability should prompt an immediate echocardiogram.

Tachycardia

Vasopressors with high beta-adrenergic activity can be highly arrhythmogenic. These medications can create a variety of arrhythmias including: ventricular ectopy, ventricular tachycardia, and sinus tachycardia. Tachycardias that reach rates above 130 often create a decrease in ventricular filling time (decreased preload) that exacerbates the tachycardia. Epinephrine, dobutamine, and dopamine are the usual culprits. Tachyarrhythmias may be indication to decrease the dose or switch to another agent.

Rapidly Increasing Vasopressor Requirements

Any time a vasopressor is initiated and the patient starts to rapidly decompensate or the vasopressor requirement steadily increases, the diagnosis and intravascular volume should be reevaluated immediately. This should always make the physician question the cause of hypotension. Inappropriate use of vasopressors can cause rapid hemodynamic decomposition and can be fatal.

TABLE 5.2 RELATIVE RECEPTOR ACTIVITY OF VASOACTIVE AGENTS

		Relative Receptor Activity				
Agent	**Dose Ranges[a]**	**α**	**β_1**	**β_2**	**Dopamine**	**Vasopressin**
Dopamine	1–3 µg/kg/min	0	+	0	++++	0
	3–10 µg/kg/min	+	++++	++	+++	0
	>10–20 µg/kg/min	+++	+++	+	+	0
Norepinephrine	0.01–1 µg/kg/min	++++	+++	+	0	
Epinephrine	0.01–1 µg/kg/min	+++	+++	++	0	0
Phenylephrine	0.5–1 µg/kg/min	+++	0	0	0	0
Vasopressin	0.01–0.04 units/min	0	0	0	0	+++
Dobutamine	2–20 µg/kg/min	+	++++	+++	0	0

[a]The maximum dose should be based on individual institutional policies.

Types of vasopressors:

Epinephrine: Epinephrine is a naturally occurring catecholamine that has potent β_1 and α_1 properties. The combination and potency of these properties often limit its use in the ICU.

Norepinephrine: Norepinephrine is the most widely used vasopressor in surgical ICUs. It possesses the same α_1 properties as epinephrine but has limited β_1 properties. The reduced β_1 properties limit the associated tachycardia and ectopy that is seen with other β_1 agonists. Norepinephrine is considered the first choice vasopressor in most situations requiring hemodynamic support.

Vasopressin: Vasopressin is identical to antidiuretic hormone, which is secreted by the posterior pituitary. Vasopressin affects V_1 and V_2 receptors as an agonist. The V_1 receptor is found on peripheral blood vessels that causes vasoconstriction. There is some evidence to suggest vasopressin is beneficial as a second vasopressor when the hypotension is refractory to norepinephrine. It should not be used at a dose greater than 0.04 μg/kg due to mesenteric ischemia.

Dobutamine: Dobutamine is a pure other β agonist. Therefore, it has potent inotropic (increased contractility) and chronotropic (increased heart rate) activity. It is often the drug of choice when inotropic activity is needed. However, its potent β_1 activity can create tachycardia and ventricular ectopy at higher doses. The β_2 properties often cause hypotension, which can be counteracted with avoidance of hypovolemia or addition of an α_1 agonist.

Dopamine: Dopamine is still one of the most widely used vasopressors despite the common side effects of tachycardia and ectopy. Due to these side effects, most intensivists use it as an alternative to norepinephrine. Dopamine may be beneficial in early sepsis but is contraindicated in septic shock. The cardiovascular effects and target receptors are dependent upon the dose administered (Tables 5.1 and 5.2). It is important to remember these ranges are approximate and vary in each patient.

Phenylephrine: Phenylephrine is a pure α_1 agonist. It is often used following spinal cord injuries that cause vasodilation. Phenylephrine often causes a reflex bradycardia secondary to the acute vasoconstriction and should be used with caution in patients with bradycardia.

MECHANICAL VENTILATION

The first form of mechanical ventilation was introduced as the "iron lung" in the 1920s. Modern ventilators introduced in the mid-1980s have changed critical care medicine as a specialty. Ventilators are very complex machines with a simple function, to breathe for the patient. Although the concept is simple, the complexity of the interaction between the patient and ventilator can take an entire career to completely understand. Ventilator dysynchrony ("Bucking the Vent") is common and the correct treatment almost never involves sedation. A skilled or experienced intensivist can often immediately determine the etiology of the dysynchrony. The correct treatment for dysynchrony is simple—fix the cause. This involves knowing the intricacies of the ventilator and understanding the different modes available.

Modes of Mechanical Ventilation

Volume Control

Volume control (VC) is a mode of mechanical ventilation commonly used in the medical ICUs. The respiratory rate and tidal volume are set by the physician. When the patient initiates a breath, the ventilator will give the prescribed volume. If the patient does not initiate a breath, the ventilator will give the same prescribed volume. Therefore, the minute ventilation in VC is determined by the respiratory rate multiplied by the prescribed tidal volume (which is not true for synchronized intermittent mechanical ventilation [SIMV]).

Pitfalls with VC

Breath-stacking can be a dangerous complication of VC. This occurs when the patient or ventilator initiates a breath before complete exhalation of the previous tidal volume. By stacking several breaths on top of one another, the mean airway pressures may reach levels high enough to cause barotrauma, pneumothorax, or pulseless electrical activity (PEA). Anytime a patient suddenly develops high airway pressures, PEA, or desaturation; the physician should first disconnect the ventilator from the endotracheal tube to equalize mean airway pressures. This same concept ("air-trapping") often applies to patients with obstructive lung disease who often have prolonged expiratory times.

Synchronized Intermittent Mechanical Ventilation

SIMV is the most frequently used ventilator mode in the surgical ICU. The surgical ICU, unlike the medical ICU, rarely initiates mechanical ventilation for primary respiratory failure (e.g., pneumonia or chronic obstructive pulmonary disease exacerbation). SIMV is very similar to VC except that a patient initiated breath will not be given the prescribed tidal volume. The physician sets a respiratory rate and a prescribed tidal volume that will only be given if the ventilator initiates the breath. SIMV differs from the older IMV models by "synchronizing" a patient initiated breath that is very close to a ventilator initiated breath. For instance, if the patient initiates a breath very close to a predetermined ventilator breath, the ventilator will fully support this patient initiated breath with the prescribed tidal volume and not give the predetermined ventilator breath. The advantage to SIMV is that it is difficult to create breath-stacking or airway-trapping. However, if the patient

initiated breaths do not generate sufficient tidal volumes to maintain minute ventilation, the patient will quickly become tachypneic and fatigued. This can be avoided by adding pressure support ventilation (PSV) to each patient initiated breath to increase the tidal volumes.

Pressure Control Ventilation

Pressure control ventilation (PCV) is very similar to VC and SIMV except the ventilator will stop the inspiratory flow at a prescribed pressure rather than a prescribed volume. This mode of mechanical ventilation was developed to prevent high airway pressures when the patient has poor lung compliance.

Pitfalls of PCV

The inspiratory volumes are different with every breath in PCV so the minute ventilation also varies. Also the lung compliance can improve, which will increase the tidal volumes that can create volutrauma. The patient should be closely supervised when using PCV.

Pressure Support Ventilation

Pressure support ventilation (PSV) is a commonly used mode of mechanical ventilation used in all ICUs. It can be used as the primary mode or used in addition to another mode of mechanical ventilation. In a nutshell, PSV supports a patient initiated breath. In PSV, the ventilator delivers a flow-rate sufficient to reach the prescribed airway pressure and the ventilator will terminate the inspiration when the flow rate decreases by 25% which signifies that the patient has stopped inhaling. All breaths that are spontaneously initiated by the patient will be supported to the amount of pressure prescribed by the physician. PSV is an excellent method of weaning mechanical ventilation. The advantages of PSV are that the patient can determine their minute ventilation, which minimizes ventilator dysynchrony when compared to VC, SIMV, or PC.

Pitfalls of PSV

Since there are no mandatory ventilator breaths with PSV, hypoventilation can be problematic in patients on sedatives due to decreased respiratory drive.

Pressure Regulated Volume Control

Pressure regulated volume control (PRVC) is a complex mode of mechanical ventilation that is most often used in patients with poor lung compliance (acute lung injury or ARDS). It can be used with VC or SIMV. PRVC is a volume cycled mode (inspiratory flow stops at prescribed volume), which will constantly adjust the inspiratory flow rate during the inspiration of each delivered breath. The adjustment of the inspiratory flow rate allows more inspiratory volume at lower airway pressures. Similar to other volume cycled modes of mechanical ventilation (e.g., VC or SIMV), PRVC will stop the inspiratory flow if the peak airway pressure reaches a predetermined value.

Airway Pressure Release Ventilation

Airway pressure release ventilation (APRV) is often referred to as a newer mode of mechanical ventilation. It was actually first introduced in the late 1980s. Although many physicians struggle with understanding APRV, it is merely continuous positive airway pressure (CPAP) with occasional releases. It offers the advantage of allowing the patient to spontaneously breathe without additional inspiratory flow from the ventilator. Allowing spontaneous breathing offers many benefits. It decreases ventilator dysynchrony while improving oxygenation and cardiac output. There are many studies that reveal the improvement of oxygenation and cardiac output when compared to standard mechanical ventilation. However, despite these improvements there has been no proven survival benefit when using APRV. Also, the improved patient-to-ventilator interaction often requires less sedation.

High-Frequency Oscillation

High frequency oscillation (HFO) is used primarily as a rescue mode of mechanical ventilation in refractory hypoxemia seen in ARDS. This unconventional mode of mechanical ventilation improves oxygenation by maintaining an increased mean airway pressure (similar to APRV), which enables recruitment of collapsed alveoli. The constant mean airway pressure maintains alveolar recruitment, which reduces shunting and prevents high peak pressures. Like APRV, HFO significantly improves oxygenation without changing mortality.

Pitfalls of HFO

Only experienced providers should use HFO due to its complexity. The patient often has to be completely sedated secondary to the extreme discomfort experienced with this unconventional mode of ventilation. Hypercarbia (high CO_2) can be problematic due to the small tidal volumes seen in HFO.

Proportional Assist Ventilation

This newer mode of mechanical ventilation was developed to limit ventilator dysynchrony. In general terms, proportional assist ventilation (PAV) is a newer generation of PSV. PAV differs from PSV by adjusting the inspiratory flow-rate during each breath to attain the percentage of effort that is prescribed by the physician. The physician prescribes the amount of "work" that is done by the ventilator compared to the patient. The ventilator will calculate the "work" or energy in joules required for each inspiration. The ventilator will provide enough flow to match the prescribed "work." This mode should allow for rapid weaning and reduced ventilator dysynchrony. However, the available literature has not revealed an advantage over PSV.

Discontinuing Mechanical Ventilation

It is clear that prolonged intubation or mechanical ventilation is linked to increased mortality, morbidity, length

of stay, and costs; thus, it is important to extubate the patient when appropriate. Most authors would suggest that a 10% reintubation rate is appropriate. This number may be inflated for surgical patients since the ventilator is usually not for pulmonary dysfunction that is often seen in the medical ICU. It is also clear that reintubation in the ICU carries a significant increase in morbidity and mortality. These factors are why the decision for extubation is both important and difficult.

Factors to consider when contemplating extubation represent both pulmonary and nonpulmonary origins. The first consideration for extubation is to be sure the primary reason for intubation has been resolved. Other nonpulmonary contributors would include: neurologic status, ability to clear secretions, hemodynamic stability, nutrition, and acid–base status. The acid–base status is a very important consideration. The respiratory system is the first compensatory mechanism to correct metabolic acidosis/alkalosis. For instance, in metabolic acidosis the patient will become tachypneic in order to increase the pH. This tachypnea increases dead-space ventilation while also increasing energy expenditure in a patient that may have a predilection for respiratory fatigue. The opposite is true for metabolic alkalosis in which the primary compensation is hypoventilation.

There are many methods of weaning from mechanical ventilation. In 1995, Esteban et al. (15) compared four methods of weaning from mechanical ventilation. They revealed that patients managed with spontaneous breathing trials at least once daily were the best protocol for weaning. Ely et al. (16) later demonstrated that combining the daily wean screen with spontaneous breathing trials further decreased time of mechanical ventilation. Common measures used to determine the likelihood of successful extubation are displayed in Figure 5.1.

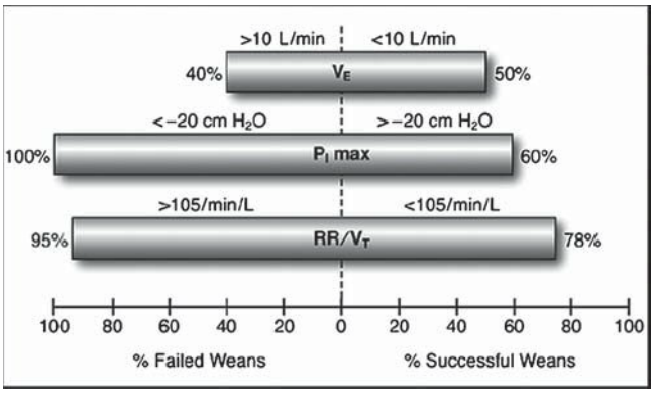


Figure 5.1 The predictive value of selected measurements obtained during spontaneous breathing. VE, minute ventilation; Pi_{max}, maximum inspiratory pressure; RR/VT, ratio of respiratory rate to tidal volume. (Data from Yang K, Tobin MJ. A prospective study of indexes predicting the outcome of weaning from mechanical ventilation. *N Engl J Med* 1991;324:1445–1450; Marino P. *The ICU book*, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2007, with permission.)

Common Protocols (17) for Discontinuation of Mechanical Ventilation

1. Spontaneous daily awakening (18)
2. Wean screen (16)
3. Spontaneous breathing trials (19)
4. Pulmonary mechanics (see Table 5.3)

Timing of Tracheostomy

The optimal timing of tracheostomy in a patient receiving prolonged mechanical ventilation is controversial. A recent examination of the National Trauma Databank revealed large variations in the timing of tracheostomy during prolonged mechanical ventilation (20). In 1984, Whited (21) noticed subglottic damage from the endotracheal tube/cuff was evident at 7 days. A short time later, the National Association of Medical Directors of Respiratory Care recommended tracheostomy to be performed in patients that required mechanical ventilation greater than 3 weeks (22). Since that time, many observational studies have suggested early tracheostomy is beneficial. However, these studies have mixed results. One concern with the available literature is that many studies use different terminology to describe early versus late tracheostomy.

The perceived advantage of early tracheostomy would include: decreased sinusitis, decreased tracheal stenosis, decreased mechanical ventilation, decreased ventilator associated pneumonia (VAP), better secretion clearance, and decreased mortality. However, not all of these are supported by the literature and there is no evidence that early tracheostomy improves long-term mortality. A recent randomized controlled trial examined tracheotomy at 6 to 8 versus 13 to 15 days in 600 ICU patients (23). There were more VAPs in the 13- to 15-day group but this did not reach statistical significance ($p = 0.07$). This study also found the early group required less time on the ventilator and decreased ICU stay. There was no change in mortality at 28 days. Interestingly, 39% of patients that received a tracheostomy had a complication associated with its placement. The authors concluded, "considering that anticipation for tracheotomy of

TABLE 5.3 STEPS OF TROUBLESHOOTING A NONFUNCTIONING NGT

Make sure the NGT is on continuous suction and air port is unobstructed
Turn off suction
Flush the gastric tube with saline
Flush the air port with air
Put on continuous suction
Repeat steps 3 and 4
If unable to make the NGT functional. Notify the attending. Consider replacing the NGT, upsizing it to a larger size, or placing on intermittent suction

1 week increased the number of patients who received a tracheotomy, and more than one-third of the patients experienced an adverse event related to the tracheotomy, these data suggest that a tracheotomy should not be performed earlier than after 13 to 15 days of endotracheal intubation."

Percutaneous Versus Open Tracheostomy

The percutaneous dilational tracheostomy (PDT) was first introduced in the 1960s. It did not become popular until Ciaglia provided physicians with a better system to facilitate safe placement via a dilational technique. Since that time, the methods and experience with placing PDTs have enhanced its utilization. As physicians were learning this new technique, there proved to be a learning curve that was not without complications, which is well documented in the literature. One crucial addition to the method of PDT was the simultaneous use of bronchoscopy (24,25). The use of bronchoscopy has proven to prevent many of the major complications that were initially seen with PDT.

In 1999, a meta-analysis revealed the PDT had more complications than the open technique (26). However, a more recent large meta-analysis of 17 randomized controlled trials showed that PDT was superior to open tracheostomy (27). This study revealed less wound infections, bleeding, and mortality. The differences seen in these two large studies may be the time period in which they were performed. As stated above, the techniques and experience with the PDT have improved greatly over the past 25 years.

The cost difference between the two techniques may be dependent upon the location (ICU vs. operating room) in which they are performed. With the wide variety of techniques involving PDT among providers, it is difficult to assess the incidence of wound infections in clinical trials and it is likely that a smaller incision/dissection will provide lower wound infection rates. The one complication that is not completely understood is the rate of tracheal stenosis with the PDT. The incidence of tracheal stenosis following a PDT is not known. Many believe the PDT will often crush the anterior trachea, which produces a fracture of the tracheal rings. The inward displacement of the fractured rings may create a significant stenosis. A more proximal fracture occurring at the level of the first tracheal ring would be very likely to cause a symptomatic subglottic stenosis. In one postmortem study (28), patients with PDT demonstrated an anterior fracture to the tracheal rings, which produced significant stenosis in 11 of 12 patients. Another study examined the rate of tracheal stenosis after PDT by performing endoscopic examinations on 146 patients referred to a rehabilitation center. The authors found that 23.8% of patients who received PDT had greater than 50% stenosis compared to 7% who had an open tracheostomy (29). It is likely the tracheal stenosis rate is significantly higher with PDT, however, the rate of symptomatology exhibited by the stenosis is difficult to determine because of the low functional reserve of patients receiving a PDT.

Due to conflicting results of many randomized controlled trials, it is difficult to recommend which of the two techniques is superior. Therefore, the physician should use the technique in which they have the most experience. If the preferred technique is PDT, it should be performed under bronchoscopic guidance. Open tracheostomy is still the preferred technique for select patients with thyroid hyperplasia, short neck, tracheomalacia, obesity, previous neck operation, and for children (30).

MAINTAINING A FUNCTIONAL NASOGASTRIC TUBE

The nasogastric tube (NGT) was first placed by John Hunter in the 1600s to feed a patient. It was not until the early 1930s before physicians routinely used the NGT for gastric decompression. The current NGTs actually contain two separate lumens that are fixed together (Fig. 5.2). The large lumen is for the passage of gastric contents. The smaller (often blue) port is for air only. The sump NGT works by allowing continuous suction applied to the larger tube to pull air through the blue tube, which creates a continuous cycle of air being pulled from the atmosphere into the stomach and back into the wall suction. This constant flow of air prevents the tip of the NGT from suctioning directly on the mucosa causing ulceration/perforation. If air is not allowed through the air tube in a continuous manner, the tip of the NGT will suction directly on the mucosa and create ulceration and may lead to perforation. Therefore, nothing should ever obstruct the air tube and the NGT should always be on continuous suction. Common mistakes that obstruct the continuous flow of air include: intermittent suction, fluid in the air port, putting a cap on the blue port, and tying the blue tube in a knot. All of these increase the chance of the patient suffering a severe iatrogenic complication.

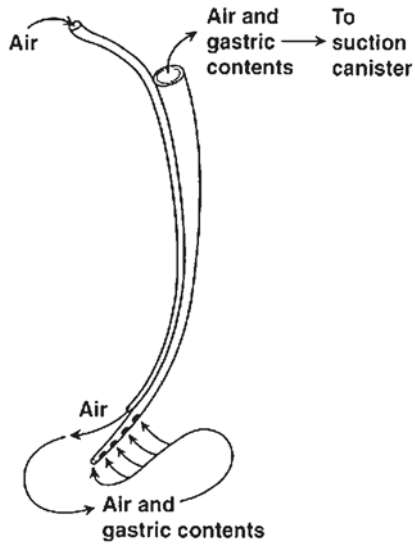


Figure 5.2 Nasogastric tube. (From Blackbourne LH. *Surgical recall*, 6th ed. Philadelphia, PA: Lippincott Williams and Wilkins, 2012, with permission.)

One way to know the NGT is not working properly (suctioning directly on the mucosa) is when gastric contents back up through the air tube (blue port). This simply means the NGT is not functional and the problem must be fixed to prevent iatrogenic mucosal injury. One problem is the described backup of gastric contents into air tube is considered a nuisance. In fact, the NGT companies have devised a one-way valve to prevent this from happening. This is a dangerous situation because it implies that it is OK to have a nonfunctional NGT on continuous suction. It is ill advised to allow any type of cap or one-way valve to be placed on the air tube. The backup of gastric contents is the easiest way to tell if the NGT is functional and not causing direct injury to the gastric mucosa. The steps for troubleshooting a nonfunctioning NGT are listed in Table 5.3.

OLIGURIA IN THE POSTOPERATIVE PERIOD

Oliguria in the postoperative period is very common and is generally defined as urine output of less than 0.5 mL/kg/h. There are many potential causes and the physician must quickly determine the correct diagnosis to direct appropriate treatment. The reported mortality associated with acute kidney injury (AKI, formerly called acute renal failure) varies but is routinely reported as approximately 50%. It is very important for the physician to remember that AKI is usually a secondary event. The predicted mortality or morbidity for AKI is likely more accurately represented by the process that caused the AKI.

There are many potential causes and they can be grouped into three categories: prerenal, intrarenal (intrinsic), and postrenal (Table 5.4).

TABLE 5.4 COMMON CAUSES OF AKI

Prerenal	Hypovolemia
	Decreased cardiac output
	Renal artery obstruction/stenosis
	Hepatorenal syndrome
	Medications (ACE inhibitors, NSAIDs, ARBs)
	Aortic dissection
Intrarenal	ATN
	Sepsis
	CIN
	Myoglobinuria
	Antibiotics (penicillin, sulfonamide, and allopurinol)
	Vasculitis
	Embolus
Postrenal	Urinary catheter obstruction
	Ureter obstruction
	Bladder

The diagnostic workup should be focused on the common causes of postoperative AKI. The most common postrenal cause of AKI is an obstructed urinary catheter, which can be easily diagnosed by flushing the urinary catheter with saline. After quickly ruling out the most common cause of postrenal obstruction, the focus should be to determine if the cause is prerenal or intrarenal. The most common cause of AKI in the postoperative period is acute tubular necrosis (ATN) from previous hypotension/hypovolemia. A careful review of the history combined with a thorough physical exam will often point to the correct diagnosis rather quickly. The diagnosis may then be confirmed while directing appropriate therapy. The most important category to quickly diagnose is prerenal, because the intervention will benefit other organ systems as well (i.e., if the kidneys are receiving decreased blood flow, so are the other organs).

The physical exam should focus on signs of perfusion. Signs of perfusion may be evident by warmth of peripheral tissues and strength of distal pulses. Auscultation of a new cardiac murmur or abdominal bruit may also be helpful. One should be careful of trying to measure intravascular volume based on patient change in weight or peripheral edema as these are very unreliable determinates of intravascular volume.

Laboratory and diagnostic data will help confirm the diagnosis. A renal ultrasound can be a valuable noninvasive diagnostic test that can rule out multiple diagnoses including: renal artery stenosis, infarction, and all postrenal causes of AKI. Important laboratory studies include: hemoglobin, serum and urine chemistry, urinalysis and urine microscopy. Other helpful laboratory studies include an arterial blood gas with a lactate to rule out acidosis or anaerobic metabolism (shock).

The most commonly used measure of renal function is serum creatinine. Creatinine is a byproduct of muscle breakdown and its production is not constant. Also, creatinine is filtered in the glomerulus and reabsorbed in the distal tubule. Therefore, the production and clearance make its accuracy in predicting AKI problematic in the acute setting and should be used with caution. The fractional excretion of sodium (FE_{Na}) has been considered a very accurate test to differentiate between prerenal disease and ATN. The accuracy of FE_{Na} has been recently questioned. A similar test, fractional excretion of urea (FE_{UN}), may be a better predictor of glomerular filtration. One study (31) revealed that FE_{UN} was more sensitive and specific for diagnosing prerenal AKI when compared to FE_{Na} (Table 5.5).

ATN is the most common cause of postoperative AKI. This is classically due to intraoperative or postoperative hypotension. The oliguria in ATN is usually seen after the hypotensive episode but the increase in serum creatinine can take days to weeks later. The hypotension causes ischemia of the proximal renal tubules, which creates sloughing of the tubular epithelium. As the dead cells slough, they create a blockage that will cause a backup of urine. As the urine backs up into the glomerulus, the glomerular

TABLE 5.5 PRERENAL VERSUS ATN

	Prerenal	ATN
Urine Na	<20	>40
BUN/Creatinine	>20	<10
Urine specific gravity	>1.020	<1.010r
Urine osmolality	>500	<250
$FE_{Na} = U_{Na} \times P_{Cr} \div U_{Cr} \times P_{Na}$	<1%	>1%
$FE_{UN} = U_{UN} \times P_{Cr} \div U_{Cr} \times P_{UN}$	<35%	>35%

filtration rate decreases. Urine microscopy will reveal multiple granular casts. A recent study in 2008 reveals that examination of urine microscopy accurately differentiated ATN from prerenal AKI (32). The treatment of ATN is supportive care focusing on the avoidance of electrolyte abnormalities and hypovolemia.

ANALGESIA

Virtually all postoperative patients require analgesia and commonly used analgesics in the ICU during the postoperative period are described. The indications and route of administration is beyond the scope of this chapter.

OPIATES

This category of medications is derived from the opium poppy plant and has been used for centuries. Many patients and physicians commonly associate opioids with addiction and may limit the appropriate dosing schedules despite evidence suggesting that opioid addiction in hospitalized patients is extremely rare (33). The classic opioid is morphine. Opioids act on the μu opioid receptor (μu stands for "morphine"). The majority of μu receptors are found in the brain and spinal cords. Although the most potent effect of opioids is analgesia, they also cause some degree of sedation, decreased respiratory drive, and hypotension. The majority of these side effects can be avoided at lower doses. The incidence of these side effects among opiates varies between medications. Despite the side effect of sedation at high doses, opiates do not cause amnesia. Most of the opiates are metabolized in the liver and then excreted by the renal system. Several reports suggest that opiates with active metabolites (morphine and codeine derivatives) cause significant narcosis and respiratory depression when used during renal insufficiency (34,35).

MORPHINE AND MEPERIDINE

In a 2007 survey, morphine was the most frequently used opiate in the ICU (36). However, morphine and meperidine have many side effects that other available opiates do not have. Morphine and meperidine have active metabolites that limit prolonged administration in the setting of renal insufficiency. Some of the metabolites of the two medications are more potent than the parent compound. The dose of morphine and meperidine should be reduced to 50% in the setting of renal insufficiency. Morphine and meperidine also cause histamine release which produces hypotension. This hypotensive effect is most exaggerated with large doses that are given rather quickly. Meperidine is used much less frequently than morphine due to its side effects (including euphoria) and the active metabolite normeperidine. Naloxone will reverse the respiratory depression caused by most opioid drugs but will not alter this effect when caused by normeperidine.

FENTANYL

Fentanyl is a synthetic opiate that has 100 times the potency of morphine. It also demonstrates a shorter time of onset and half-life when compared to morphine. Fentanyl does not activate histamine release and is the opioid of choice during relative hypotension making fentanyl a more attractive choice than other opiates in the ICU. It can also be used in renal insufficiency because it has no active metabolites. However, it is much more lipid soluble than morphine, which can contribute to accumulation and prolonged effect when used for extended periods of time or in patients with obesity.

HYDROMORPHONE

Hydromorphone is a semisynthetic derivative of morphine. Therefore, it demonstrates many of the same side effects as morphine. Hydromorphone has active metabolites but does not exhibit histamine release seen with morphine. Because of the active metabolites, the half-life of hydromorphone can increase by 20-fold with renal insufficiency. Due to its potency and half-life, it is often used in patients with a high pain tolerance in patients without liver or renal insufficiency (Table 5.6).

SEDATIVES IN THE ICU

The use of sedatives in the ICU have changed dramatically over the past decade. It was once thought to be cruel to allow patients to remain awake while receiving mechanical ventilation. Despite the perceived advantages, continuous sedative infusions for critically ill patients have been shown to increase the duration of mechanical ventilation and length of intensive care stay (38,39). Many studies have shown a linear relationship between ventilator days and ICU length of stay with mortality. More recently, there has been a large interest in the relationship between the overuse of sedation and delirium. High doses of benzodiazepines have been shown to cause delirium and one study described a 100% transition rate to delirium with

TABLE 5.6 COMMONLY USED OPIATES FOR ADULTS IN THE ICU

Medication	Strength[a]	Route	Typical Dose[b]	Typical Frequency[b]	Active Metabolite	Histamine Release
Morphine	1	IV, IM, SQ	0.1–0.2 mg/kg	q3h	Yes	Yes
Meperidine	0.1	IV, IM, SQ	1–2 mg/kg	q2h	Yes	Yes
Fentanyl	100	IV, IM, SQ	1–2 µg/kg	q1h	No	No
Hydromorphone	5	IV, IM, PO	1–2 mg	q4h	Yes	No

[a]The strength is based on equivalency to intravenous morphine.
[b]The appropriate dose and frequency will vary significantly between patients. The physician should always start at the lower dose and titrate to pain scores (37).

continuous lorazepam infusions (40). In 2004, Ely et al. (41) reported a significant increase in mortality in patients with delirium. This study and others have prompted a recent flurry of evidence suggesting that the routine use of continuous sedation for mechanical ventilation is not needed and increases adverse events including death.

Benzodiazepines

Benzodiazepines are $GABA_A$ agonists. GABA is the major inhibitory neurotransmitter mediating the inhibitory actions of neurons in the brain and spinal cord. Although it increases GABA throughout the body, the most prominent effects are on the central nervous system. The notable effects include: sedation, anxiolytic, anterograde amnesia, muscle relaxation, and anticonvulsant activity. Benzodiazepines do not tend to cause cardiovascular or respiratory problems at therapeutic doses unless they are given in addition to narcotics or other sedatives. They have no intrinsic analgesic properties. However, they are known to potentiate the pain relief when used in combination with opiates. Most benzodiazepines undergo hepatic metabolism followed by renal excretion and should be used with caution in patients with liver or kidney disease. There are three main types of benzodiazepines used in the ICU. They are diazepam, lorazepam, and midazolam (see Table 5.7).

Diazepam

Diazepam is a long-acting fat-soluble benzodiazepine that is not frequently used in the ICU because of its unpredictable absorption and active metabolites. Therefore, it is rarely used in the ICU as a bolus and should not be used as an infusion. Diazepam also contains the preservative propylene glycol, which can cause metabolic acidosis with accumulation.

Lorazepam

Lorazepam has the lowest fat solubility of the benzodiazepines listed here. This property creates a slower onset of action with a prolonged duration. However, its metabolism by glucuronidation makes the clearance the most predictable in the setting of liver dysfunction. Like diazepam, it contains propylene glycol that can accumulate with prolonged use.

Midazolam

Midazolam has a fast onset of action with the shortest half-life of the benzodiazepines frequently used in the ICU. It is this quality that makes it the most frequently used benzodiazepine infusion. However, the effective half-life can increase significantly with prolonged infusion. Like diazepam, midazolam also has an active metabolite that may potentiate its accumulation during renal failure.

TABLE 5.7 BENZODIAZEPINES COMMONLY USED IN THE ICU

Medication	Onset (min)	Half-Life (h)	Active Metabolite	Bolus Dose (mg)	Infusion Dose[a]
Diazepam	<5	20–40	Yes	5–10	Not recommended
Lorazepam	<20	10–20	No	1–2	0.5–10 mg/h
Midazolam	<5	3–5	Yes	1–2	0.5–10 mg/h

[a]Maximum infusion doses should be based on individual institutional protocols.

Propofol

Propofol is a very potent fat-soluble sedative that has rapid onset and rapid clearance when used as a bolus. These properties have made it the induction agent of choice for many anesthesiologists. As with any fat-soluble medication, prolonged use as an infusion can create accumulation. The mechanism is not completely understood but it most likely potentiates GABA. It produces sedation and amnesia but does not exhibit analgesic properties. It is hepatically conjugated to an inactive form, which makes it an attractive choice in the setting of renal insufficiency. Despite all of its good qualities, it can demonstrate severe side effects. The most common is hypotension. Hypotension is most often seen with a large bolus but can also be present with low-dose infusions. Because propofol is formulated in an emulsion containing purified egg phospholipids, the sedative should not be used if the patient has an allergy to eggs. However, the most feared complication is propofol-related infusion syndrome (PRIS). PRIS is a rare complication associated with high doses or prolonged use greater than 48 hours. Although it is rare (probably <1%), it is often deadly. Symptoms include metabolic acidosis, rhabdomyolysis, hypotension, and dyslipidemia. There is no effective treatment other than discontinuing the propofol infusion and providing supportive care. Therefore, for patients requiring escalating doses or infusion greater than 48 hours should be closely followed for hyperlipidemia and lactic acidosis.

Dexmetomidine

Dexmetomidine is a centrally acting alpha-2 agonist that provides sedation and anxiolysis without respiratory depression. A recent double-blinded randomized controlled trial compared the use of dexmetomidine and midazolam in the ICU (42). It revealed that dexmetomidine significantly reduced delirium by 20% and ventilator use by 2 days when compared to midazolam. However, it did exhibit more bradycardia while patients with midazolam had tachycardia and hypertension more frequently. The sedative and sympatholytic effects without respiratory depression make this a very attractive option in postoperative patients. However, this medication is very expensive making it difficult for many institutions to justify the costs.

THE USE OF PERIOPERATIVE BETA BLOCKER PROPHYLAXIS IN THE ICU

Perioperative beta blockade has been the standard of care in the ICU for many years but the recent guidelines have changed. Several small studies published in the late 1990s suggested that prophylactic beta blockade may be useful in preventing cardiovascular complications in the perioperative period (43,44). Despite the potential flaws of these studies (45), perioperative beta blockers became the standard of care for patients with cardiovascular risk factors and are still used as benchmarks for defining the quality of care given to surgical patients. Using a beta blocker to decrease myocardial ischemia in the noncardiac surgical patient seems to make sense. The pathologic rise in catecholamines following a major surgical procedure causes excess tachycardia and increased myocardial oxygen demand.

In 2006, the metoprolol after vascular surgery (MAVS) study did not reveal a benefit for beta blockade in high-risk vascular surgery patients and the group that received the beta blocker had significantly more bradycardia and hypotension that required treatment (46). The results of the MAVS trial and others (47) not only questioned the benefit of beta blocker prophylaxis, but also revealed potential side effects. This led to the POISE trial, which was published in 2008 (48). This randomized controlled trial enrolled over 8,000 patients with evidence of a major cardiovascular risk factor to examine the effect of metoprolol that was started preoperatively and continued for 30 days after surgery. Although the metoprolol group had fewer myocardial infarctions, the drug also resulted in a significant excess risk of death, stroke, and clinically significant hypotension and bradycardia. The POISE trial called into question the safety of routine perioperative beta blockers. In 2008, the American College of Cardiology and American Heart Association released a focused update to the previously released 2007 guidelines for perioperative beta blocker therapy (49). Table 5.8 shows the perioperative risk of a cardiovascular complication for different surgical procedures. Table 5.9 shows the changes in recommendations for beta blocker prophylaxis from the previous guidelines.

TABLE 5.8 CARDIAC RISK STRATIFICATION FOR NONCARDIAC SURGICAL PROCEDURES[a]

Risk Stratification	Procedure Examples
Vascular (reported cardiac risk often >5%)	Aortic and other major vascular surgery
	Peripheral vascular surgery
Intermediate (reported cardiac risk generally 1%–5%)	Intraperitoneal and intrathoracic surgery
	Carotid endarterectomy
	Head and neck surgery
	Orthopedic surgery
	Prostate surgery
Low (reported cardiac risk generally <1%)	Superficial procedures
	Endoscopic procedures
	Breast surgery
	Ambulatory surgery

[a]Modified from the ACC and AHA Guideline (49).

TABLE 5.9 CHANGES MADE IN 2008 FROM PREVIOUS GUIDELINES ON PERIOPERATIVE BETA BLOCKADE (49)

2007 Perioperative Guideline Recommendations	2009 Perioperative Focused Update Recommendations	Comments
Class I evidence		
Beta blockers should be continued in patients undergoing surgery who are receiving beta blockers to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA Class I guideline indications. (Level of evidence: C)	Beta blockers should be continued in patients undergoing surgery who are receiving beta blockers for treatment of conditions with ACCF/AHA Class 1 guideline indications for the dr ugs. (Level of evidence: C)	2007 recommendation remains current in the 2009 update with revised wording
Beta blockers should be given to patients undergoing vascular surgery who are at high cardiac risk owing to the finding of ischemia on the preoperative testing. (Level of evidence: B)		Deleted/combined recommendation (class of recommendation changed from I to IIa for patients with cardiac ischemia on preoperative testing).
Class IIa		
Beta blockers are probably recommended for patients undergoing vascular surgery in whom preoperative assessment identifies coronary heart disease. (Level of evidence: B)	Beta blockers titrated to heart rate and blood pressure are probably recommended for patients undergoing vascular surgery who are at high cardiac risk owing to coronary artery disease or the finding of cardiac ischemia on preoperative testing. (Level of evidence: B)	Modified/combined recommendation (working revised and class of recommendation changed from I to IIa for patients with cardiac ischemia on preoperative testing)
Beta blockers are probably recommended for patients in whom preoperative assessment for vascular surgery identifies high cardiac risk, as defined by the presence of more than one clinical risk factor. (Level of evidence: B)	Beta blockers titrated to heart rate and blood pressure are reasonable for patients in whom preoperative assessment for vascular surgery	Modified recommendation (level of evidence changed from B to C)
Beta blockers are probably recommended for patients in whom preoperative assessment identifies coronary heart disease or high cardiac risk, as defined by the presence of more than one clinical risk factor, who are undergoing intermediate risk or vascular surgery. (Level of evidence: B)	Beta blockers titrated to heart rate and blood pressure are reasonable for patients in whom preoperative assessment identifies coronary artery disease or high cardiac risk, as defined by the presence of more than one clinical risk factor, who are undergoing intermediate risk surgery. (Level of evidence: B)	2007 recommendations remain current in 2009 update with revised wording.
Class IIb		
The usefulness of beta blockers is uncertain for patients who are undergoing either intermediate-risk procedures or vascular surgery, in whom preoperative assessment identifies a single clinical risk factor. (Level of evidence: C)	The usefulness of beta blockers is uncertain for patients who are undergoing either intermediate-risk procedures or vascular surgery in whom preoperative assessment identifies a single clinical risk factor in the absence of coronary artery disease. (Level of evidence: C)	2007 recommendations remain current in 2009 update with revised wording
The usefulness of beta blockers is uncertain in patients undergoing vascular surgery with no clinical risk factors who are not currently taking beta blockers. (Level of evidence: B)	The usefulness of beta blockers is uncertain in patients undergoing vascular surgery with no clinical risk factors who are not currently taking beta blockers. (Level of evidence: B)	
Class III		
Beta blockers should not be given to patients undergoing surgery who have absolute contraindications to beta blockade. (Level of evidence: C)	Beta blockers should not be given to patients undergoing surgery who have absolute contraindications to beta blockade. (Level of evidence: C)	2007 recommendations remain current in 2009 update with revised wording.
	Routine administration of high-dose beta blockers in the absence of dose titration is not useful and may be harmful to patients not currently taking beta blockers who are undergoing noncardiac surgery. (Level of evidence: B)	New Recommendation

TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME

The incidence of alcohol withdrawal syndrome (AWS) after abrupt discontinuation of alcohol is variable but can be as high as 50%. Symptoms often follow a continuum starting with tremulousness and ending with delirium tremens (DTs). The term "DTs" is often thought to be synonymous with AWS. This is incorrect. It is rare that the symptoms of AWS progress to this magnitude. DTs are the last stage of AWS and carry significant mortality. The key to diagnosing DTs is the combination of hyperadrenergic activity and a change in sensorium (Table 5.10).

Chronic alcohol ingestion leads to enhanced activity of the inhibitory neurotransmitter GABA. The neurologic system compensates by upregulating *N*-methyl D-aspartate excitatory receptors to balance the affects of enhanced GABA. Therefore, abruptly removing the alcohol also decreases GABA to cause an excitatory and hyperadrenergic state causing symptoms of AWS. Therefore, the common treatment modalities for AWS target the GABA receptors.

Currently, benzodiazepines are the best treatment for AWS. The type of benzodiazepine does not seem to matter, so the choice should be based on the pharmacokinetics of the medication. There are many studies examining various medications (including alcohol) as prophylactic agents to prevent AWS. The results are mixed at best. Many show no evidence that alcohol or benzodiazepines are effective at preventing AWS and it appears that symptom-driven dosing is better than scheduled prophylactic dosing (50,51). These studies reveal that symptom-driven treatment requires less benzodiazepine administration, a shorter duration of treatment, and up to 40% of patients never require any treatment. This method seems to be the current trend for many ICUs. However, the prevention and/or treatment of AWS at your institution will likely depend on the beliefs and individual interpretation of the available data. For more information on AWS, a recent review of AWS in the ICU was published in *Critical Care Medicine* (52).

TABLE 5.10 CONTINUUM OF SYMPTOMS IN AWS

Minor Withdrawal (24–72 h)
- Anxiety
- Diaphoresis
- Fluctuating tachycardia
- Mild cognitive impairment

Major Withdrawal (24–72 h)
- Sustained tachycardia
- Confusion

DTs (72–96 h)
- Severe tachycardia
- Severe hypertension
- Fever
- Agitation
- Hallucinations

Note: Isolated seizures and hallucinations without hyperadrenergic activity generally occur at 24–48 hours and are associated with AWS but do not carry the same mortality as DTs.

Gastric Acid Suppression

Gastric stress ulcers are not uncommon in the ICU. However, only a small percentage of these ulcers produce significant bleeding. The reported incidence of gastric stress ulceration varies significantly. This is likely because of the difference in the mechanism of diagnosis and study population presented in the literature. However, the incidence of stress ulcers may be up to 15% in high-risk patients. Patients with stress ulcers and significant bleeding can have mortality rates up to 45%. Therefore, prevention of stress ulcers in the ICU is important. The perception that all ICU patients need prophylaxis is not correct. A large multicenter prospective study revealed only two major risk factors for significant gastrointestinal bleeding in the ICU. They included the use of mechanical ventilation greater than 48 hours and coagulopathy (odds ratio of 15.6 and 4.3, respectively) (53). The incidence of significant bleeding was about 3% with one or both of these risk factors compared to 0.1% with neither risk factor. Large burns and neurologic injuries have long been considered high risk for stress ulcers. Many of the larger trials excluded these injuries because of their high risk. So many providers still consider these factors as high risk for developing stress ulcers.

There are many options for stress ulcer prophylaxis. Currently, the standard of care is the use of proton pump inhibitors (PPI) or histamine receptor blockers (H_2 blockers). One large meta-analysis revealed no significant difference in ulceration between the PPIs and H_2 blockers (54). However, many studies suggest that a PPI may be slightly better than H_2 blockers. Both of these drug classes seem to increase the rate of VAP. The mechanism of VAP is likely linked to gastric bacterial overgrowth from the increase in gastric pH. Esophageal reflux and microaspiration in the setting of gastric bacterial overgrowth leads to colonization of esophageal and tracheal lumens with pathogenic bacteria. PPIs may have a slight increase in VAP rates compared to H_2 blockers, although not significantly different. The cost of H_2 blockers tend to be much less than PPIs. Therefore, many intensivists use H_2 blockers instead of PPIs unless the patient is on a PPI prior to hospitalization. There have also been recent suggestions that PPIs may cause an increase in *Clostridium difficile* (CDif) colitis and other infections (55,56). Other prophylactic medications include sucralfate and traditional antacids. Sucralfate is a mucosal coating agent that is delivered via NGT four times per day. It is considered inferior to PPI and H_2 blockers but has a lower incidence VAP. Sucralfate also must be used carefully in patients with renal failure due to aluminum toxicity. Very importantly, sucralfate should not be used in combination with H_2 blockers and other select medications due to the inhibition of absorption.

Gastric feeding has also been shown to decrease stress ulcers without the use of antacids. One observational study of burn patients revealed that early gastric feeding resulted in decreased ulceration compared to H_2 blockers alone (57). This study also revealed an increase in mortality in the group that received both early gastric feeds plus a H_2 blocker. However, this study population consisted of both high- and low-risk patients. Therefore, one should be careful interpreting the results and many physicians feel that early gastric feeds should not prevent the use of H_2 blockers or PPIs until further evidence is available. This is, however, another great reason to resume enteral nutrition as soon as possible.

PPIs or H_2 blockers should be first line agents for stress ulcer prophylaxis. The physician must weigh the risks, benefits, and costs associated with each to determine which medication should be used. The most important consideration is to only give stress ulcer prophylaxis when needed and discontinue the prophylaxis when appropriate. See Table 5.11 for indications for stress ulcer prophylaxis in the ICU.

Contrast-Induced Nephropathy

The concern about contrast-induced nephropathy (CIN) is warranted due to the high prevalence of renal insufficiency seen in the ICU. CIN is likely due to medullary vasoconstriction and direct cytotoxic/osmolar injury to the proximal tubules. This injury is considered immediate, so the only potential treatment is prevention. Therefore, dialysis before or after the contrast-load is not useful.

The rate of CIN varies according to each patient. There are many risk factors that are routinely associated with CIN that have not proven to be independent risk factors throughout the literature (see Table 5.12). It appears the most predictive risk factors for CIN are creatinine > 1.5 mg/dL and diabetes. Patients with this combination can have CIN in over 50% of cases.

TABLE 5.11 INDICATIONS FOR STRESS ULCER PROPHYLAXIS IN THE ICU[a]

Independent Predictors
Coagulopathy: Platelet count <50,000, INR > 1.5, or PTT > 2× control
Mechanical ventilation >48 h
Minor Predictors
Traumatic brain injury
Spinal cord injury
Burn >30%
Sepsis
Previous gastric ulcer within past year
Prolonged ICU stay
Corticosteroid therapy
Treatment
All ICU patients with at least one independent predictor or two minor predictors should receive stress ulcer prophylaxis

[a]Modified from ASHP Guidelines (58).

TABLE 5.12 RISK FACTORS FOR CIN[a]

Patient Related
Creatinine >1.5
Diabetes
Intra-aortic balloon pump
Ejection fraction <40%
Age
Hypertension
Low hematocrit
Hypotension
Not Patient Related
Contrast osmolar properties
Contrast volume

[a]Modified from Pannu N, Wiebe N, Tonelli M. Prophylaxis strategies for contrast-induced nephropathy. *JAMA* 2006;295(23):2765–2779.

The available data regarding the appropriate prophylactic treatment is conflicting. However, it is clear that increasing urine flow is beneficial. Therefore, any patient at risk for CIN should have intravenous volume expansion immediately prior and during contrast injection. It is not clear what type of intravenous infusion should be used to prevent AKI. However, it appears that isotonic solutions are more successful than hypotonic solutions at preventing CIN (59). Other popular strategies include administration of sodium bicarbonate or *N*-acetylcysteine (NAC).

Sodium bicarbonate ($NaHCO_3$) administration provides both alkalinization of the urine and provides intravascular volume expansion from the sodium. The alkalinization is thought to prevent free radical injury to the renal tubules. The most commonly used method of administration of $NaHCO_3$ is by adding 3 ampules of $NaHCO_3$ to 1 L of free water. Each ampule contains 50 mEq of Na^+ and 50 mEq of HCO_3. Adding 3 ampules of $NaHCO_3$ to 1 L of free water will create a relatively isotonic fluid. There are many randomized controlled trials examining the administration of $NaHCO_3$. The results in a few of the studies are equivalent, although the majority of studies reveal better outcomes compared to isotonic fluid administration. Thus, an isotonic $NaHCO_3$ solution should be provided when concerned for CIN *in lieu* of isotonic intravenous fluids alone unless otherwise contraindicated.

NAC is the most commonly studied intervention to prevent CIN. NAC is used for a variety of medical conditions including: pulmonary mucous retention, Tylenol toxicity, and CIN. The proposed mechanisms to prevent CIN are its antioxidant properties combined with the enhancement of the vasodilatory effects of nitric oxide. The results of studies examining the effect of NAC on CIN are mixed (60). However, due to the cost and safety profile of the medication, most authors suggest using oral NAC. This requires

beginning the administration of NAC up to 24 hours prior to giving the contrast agent. Due to the toxicity of the intravenous form, only the oral form of NAC should be used.

There are many contrast agents available to the radiologist. The incidence of AKI depends on the osmolality of the agent. The older ionic contrast agents have very high osmolalities, where the newer nonionic agents are closer to iso-osmolar. Although there are few comparisons between contrast agents, it appears the newer generation agents with lower osmolar gradients produce less CIN. The available literature suggests the contrast agents with lower osmolalities provide the most benefit when the creatinine is greater than 1.5 mg/dL with the presence of diabetes.

In summary, the only treatment for CIN is prevention. Each patient with renal insufficiency should be carefully examined for risk factors of CIN. Hyperosmolar contrast agents, dehydration, and medications that limit the glomerular filtration rate (ACE inhibitors, NSAIDS, etc.) should be avoided in high-risk patients if possible. There is a limited role for dialysis or diuretics. Although the literature is not completely clear, it appears that isotonic $NaHCO_3$ infusions are superior to isotonic saline alone in preventing CIN. The use of NAC may be helpful but should not replace isotonic $NaHCO_3$ infusions. (See Fig. 5.3 for a standard prevention strategy.)

Clostridium Difficile Colitis

CDif colitis is a commonly seen disease process in any ICU. The mortality of CDif colitis can be up to 30% in critically

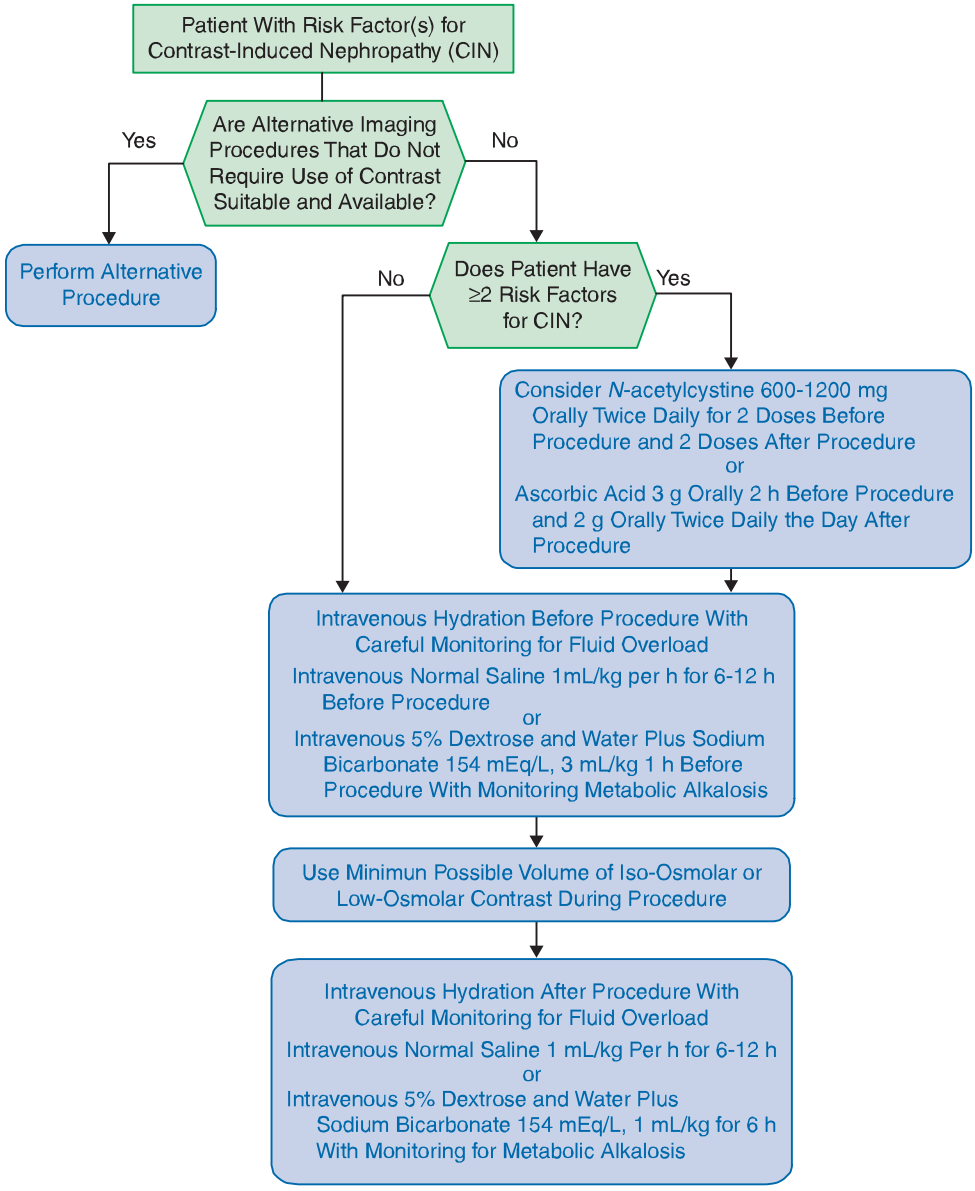


Figure 5.3 Strategy for management of patients with risk factors for contrast-induced neuropathy. (From Pannu N, Wiebe N, Tonelli M. Prophylaxis strategies for contrast-induced nephropathy. *JAMA* 2006;295(23):2765–2779.)

ill patients. The most common etiology of CDif colitis is from antibiotic administration. Although it is commonly secondary to long-term antibiotics, it can originate from a single dose of perioperative antibiotics.

CDif colitis is defined by the Centers for Disease Control as the passage of ≥3 loose stools per day and a positive diagnostic test or visualization of pseudomembranous colitis. The current methods of diagnoses are more accurate. The newer real-time stool PCR assay used to detect the toxin B gene are over 90% accurate. Therefore, empiric treatment with a negative PCR test should be rare. Stool testing should be performed prior to initiation of antibiotics. Stool examination for WBCs is not sensitive or specific for CDif and should be avoided.

The treatment of CDif colitis depends on its severity (see Table 5.13). Oral metronidazole is considered first line for uncomplicated disease and oral vancomycin is reserved for severe disease, pregnancy, and the second recurrent episode. The efficacy of intravenous metronidazole is not known and there is no role for intravenous vancomycin. Surgical intervention (i.e., colectomy) should be considered EARLY for patients who are hemodynamically unstable.

The rate of recurrence is not known. Historically, up to 25% can present with at least one episode of recurrence. This is most frequently due to failure to eradicate spores or acquisition of a new strain and can occur several weeks following the initial treatment. The first recurrence should be treated the same as the initial episode unless more severe. The second recurrence should be treated with oral vancomycin.

Prophylaxis against CDif only includes avoidance of offending agents. There is no role for prophylactic metronidazole. This may increase the incidence of CDif colitis while also increasing the resistant strains of CDif. Antibiotics that commonly cause CDif colitis are clindamycin, cephalosporins, and fluoroquinolones.

Perhaps the most important consideration in patients with CDif colitis in an ICU is infection control. Preventing the spread of CDif is very important. This highly infectious condition is spread easily by contact. Therefore, all patients with CDif colitis should be on contact isolation. The physician should wash their hands with soap and water before and after entering the patient room. The commonly used alcohol-based hand sanitizers are not useful for CDif spores.

Atrial Fibrillation

Atrial fibrillation (Afib) is a common complication seen in any ICU. The incidence in the postoperative patient varies according to the operation performed. There is a large amount of literature concerning postoperative cardiac and thoracic patients. However, the available evidence for noncardiothoracic surgical patients is scant. The incidence of atrial tachyarrhythmias can be seen in up to 50% of patients after cardiac surgery and 30% following thoracic

TABLE 5.13 CLINICAL MANIFESTATIONS AND TREATMENT FOR *CDif* INFECTION (61,62)

Infection Severity	Clinical Manifestations	Treatment[a]
Asymptomatic carriage	CDif antigen or PCR positive without diarrhea, ileus, or colitis	Do not treat. Treatment could promote resistance and recurrent disease
Mild or moderate	PCR positive with diarrhea but no manifestations of severe disease	Metronidazole 500 mg PO q8h
Severe	PCR positive with diarrhea and one or more of the following attributable to CDif infection: WBC > 15,000 ↑ creatinine >50%	Vancomycin solution 125 mg PO q6h. Solution is preferred over capsules
Severe complicated	Severe disease (see above) plus one of the following: Hypotension Ileus Colitis on CT scan Toxic megacolon Perforation Require ICU admission	Obtain surgical and infectious disease consultation. Vancomycin solution 500 mg PO q6h PLUS metronidazole 500 mg IV q8h. If unable to tolerate oral therapy or signs of ileus: Vancomycin 500 mg in 100 mL normal saline as retention enema PLUS metronidazole 500 mg IV q8h

[a]Duration of treatment should be at least 10–14 d.
Note: This table was modified from the Johns Hopkins Antibiotic Guidelines (61) with permission. This table can also be viewed at www.hopkinsmedicine.org/amp.

TABLE 5.14 STROKE RISK IN AFIB ACCORDING TO $CHADS_2$ SCORE

	Points		$CHADS_2$ Score	1-Y Stroke Rate (%)	Treatment
CHF	1		6	13.7	*High Risk*
Hypertension	1		5	12.3	Warfarin
Age > 75 y	1	SUM	4	10.9	*Moderate Risk*
Diabetes	1		3	8.6	Warfarin or Aspirin
Stroke	2		2	4.5	*Low Risk*
			1	2.2	Aspirin
			0	0.8	

This table was modified from Ref. 67.

surgery. The incidence following noncardiothoracic surgery is below 10% in most studies. This difference in the incidence of Afib between these operations likely suggests a different pathogenesis. In normal patients, the predominant regulator of heart rate is the vagal tone. The most probable cause of Afib in the noncardiothoracic patient is a sympathetic overstimulation from the stress response to surgery. The documented elevation of catecholamines causes overstimulation of the myocardial excitability, which creates tachycardia. Since the body does not need the increase in heart rate, it will try and slow itself by increasing vagal tone. The slowing of electrical conduction (vagal stimulus) during increased myocardial excitability (catecholamine surge) creates a perfect setup for ectopic foci and reentry phenomena. The prevention of Afib in the noncardiothoracic patient is not well studied. At this time, there is no evidence to suggest prevention is helpful, and in many cases, it is harmful. There is only one randomized controlled trial examining the pharmacologic treatment of postoperative Afib. This RCT found esmolol superior to diltiazem in the treatment of atrial tachyarrhythmias in the hemodynamically stable patient (63). Although many intensivists may use amiodarone acutely for Afib, the efficacy and side-effect profile of amiodarone is mixed in the available retrospective trials (64,65). With the available evidence, esmolol should be the first line agent for postoperative Afib in the hemodynamically stable noncardiothoracic patient. Amiodarone should be reserved for cases where a beta blocker is contraindicated (i.e., obstructive airway disease, etc.).

Following conversion to a sinus rhythm, continued treatment is not warranted unless otherwise indicated. It is uncommon that postoperative Afib does not convert to a sinus rhythm within 48 hours but occasionally this is the case. In this instance, the decision must be made for either rate or rhythm control with or without anticoagulation. The decision for rate versus rhythm control should be made by the cardiologist. The current literature regarding rate versus rhythm control would suggest they have similar rates of embolic events. Therefore, many cardiologists lean toward rate control unless rhythm control is otherwise indicated. The more important question for the physician is whether to start anticoagulation. Every patient with Afib does not need anticoagulation. The risk of stroke in patients with Afib is quite low in most studies. For example, the Framingham study revealed an annual stroke rate of 1.3% (66). Most cross-sectional studies reveal an annual stroke risk of less than 3%. Therefore, any treatment (i.e., anticoagulation) must have a favorable side-effect profile that does not exceed the benefit of the medication. The risks associated with embolic events are well documented. One of the more commonly used scoring systems to stratify the risk of embolization is the $CHAD_2$ score (67) (see Table 5.14). Although there have been modifications to the $CHAD_2$ score that improve the prediction of embolic events with Afib, the improved accuracy is not enough for the otolaryngologist to remember the more complicated formulas. Therefore, we recommend using the $CHAD_2$ Score for predicting embolic events with Afib (Table 5.14).

HIGHLIGHTS

- The three factors that determine the delivery of oxygen to the peripheral tissues are cardiac output, hemoglobin, and oxygen saturation.
- Prolonged use of mechanical ventilation has potential serious complications.
- The optimal timing of tracheotomy with use of prolonged mechanical ventilation is not known; however, strong consideration should be given after 2 weeks.
- The open and percutaneous tracheotomies both have advantages and disadvantages. The optimal surgical technique likely depends most on the surgeons experience with each method.
- ATN is the most common cause of postoperative renal failure. The treatment of ATN is supportive care focusing on the avoidance of electrolyte abnormalities and hypovolemia.

- Symptom-driven treatment of AWS requires less benzodiazepine administration, a shorter duration of treatment, and up to 40% of patients never require any treatment.
- The only independent risk factors for stress ulcer hemorrhage in the ICU are mechanical ventilation greater than 48 hours and coagulopathy.
- It appears that isotonic $NaHCO_3$ infusions are superior to isotonic saline alone in preventing CIN. The use of NAC may be helpful but should not replace isotonic $NaHCO_3$ infusions.
- Oral metronidazole is superior to intravenous metronidazole for the treatment of CDif colitis. Oral vancomycin should be reserved for the second recurrent episode or severe disease. There is no role for antimicrobial prophylaxis.
- The acute treatment of stable tachyarrhythmias in the noncardiothoracic postoperative patient is controversial. However, intravenous esmolol is more effective than diltiazem in conversion to sinus rhythm. There may be a role for amiodarone.
- Not all patients in Afib should be anticoagulated. Only patients with a CHADS2 score of 5 to 6 should be anticoagulated with warfarin if the risk a warfarin-associated complications is less than 10% per year.

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Dynamic Wound Healing

6

Gina D. Jefferson

INTRODUCTION

The otolaryngologist–head and neck surgeon encounters wound healing problems on a regular basis. An in-depth knowledge of the wound healing process and potential complicating factors is therefore imperative. There are several factors that may adversely affect the normal wound healing process including trauma, malignancy, history of radiation at the site of the wound, advanced age, metabolic diseases such as diabetes mellitus, and autoimmune disorders, just to name a few. Moreover, wounds are classified according to various criteria. *Acute wounds* follow a time course of healing within 30 days. The wounds repair themselves in an orderly fashion following the normal healing pathway. A *chronic wound* fails to progress through the normal phases of wound healing and is incomplete because it is often disturbed by various factors that impede the process.

The evolution in understanding wound healing began with single author publications in the late 1800s. These early reports were largely anecdotal experiences shared by individual surgeons. Various antiseptic agents were described. There were even reports of large rotational skin flaps utilized to prevent contraction scar deformities. In 1903, Cushing described nerve anastomoses for facial paralysis. Oschner reported in a symposium on the importance of septic techniques in 1904. In 1909, the surgeon John Stage Davis of Johns Hopkins Hospital published the first of many papers regarding wound closure, grafts, and flaps. Horsley discussed techniques for suturing blood vessels and recurrent laryngeal nerves in 1912. In 1919, Depage emphasized principles gleaned from experiences of World War I including antisepsis, delayed closure, and debridement with specific considerations for wounds of special areas. In 1925, Ravdin was the first to publish about the morbidity, mortality, and wound complication rate of a major surgical service (1).

During the 1930s, several papers appeared presenting observations of studies regarding wounds, wound healing, repair, and sepsis. The time course and various aspects of wound healing were discussed, and the Halstedian principles on operative technique were re-emphasized. In 1938, Ives and Hirshfeld relayed the importance of bacteria from a patient's skin as a source of postoperative wound healing complications. During the late 1930s, the improvement in the course of wound healing was noted to occur with vitamin C and vitamin A supplementation (1).

During World War II, papers appeared espousing the use of penicillin to prophylax against surgical infection as well as papers regarding wound shock management, anesthesia, and wound pain. Jenkins described a new hemostatic agent, Gelfoam, in 1946 experimentally used for liver hemorrhage. Growth-promoting factors in tissues were reported in 1946 as well. In the 1950s, the role of nutrition was investigated with respect to wound healing. In 1956, Dunphy published regarding the role of vitamin C in collagen synthesis and the biochemical phases of wound healing. In 1964, factors influencing the incidence of wound infection led to the classification of wounds as clean, clean-contaminated, contaminated, and dirty. In the 1970s, Dunphy and others continued their research into the biochemistry of wound healing and the role and origin of various chemical mediators in the inflammatory process (1).

Recently, extensive research regarding adverse circumstances affecting wound healing has occurred. This research may lead to advanced treatment methodology directed at various phases of wound healing that targets specific substances or actually provide specific factors to improve the wound healing process.

THE NORMAL WOUND HEALING PROCESS

The biologic process of wound healing involves the sequential occurrence of four phases that are continuous and naturally overlap. One region of the wound may exhibit a different phase than the dominant phase occurring in another region of that same wound bed. These four phases of healing signal the introduction of specific cell types into the wound bed as depicted in Figure 6.1. Tissue injury incites the first phase, which is the coagulative and hemostatic phase of wound healing. The second inflammatory phase follows shortly thereafter. The body initiates wound repair with phase three, proliferation. Wound healing culminates with tissue remodeling. Importantly, all phases of wound healing depend upon the presence of various cytokines in order to accomplish the goal as briefly outlined in Table 6.1.

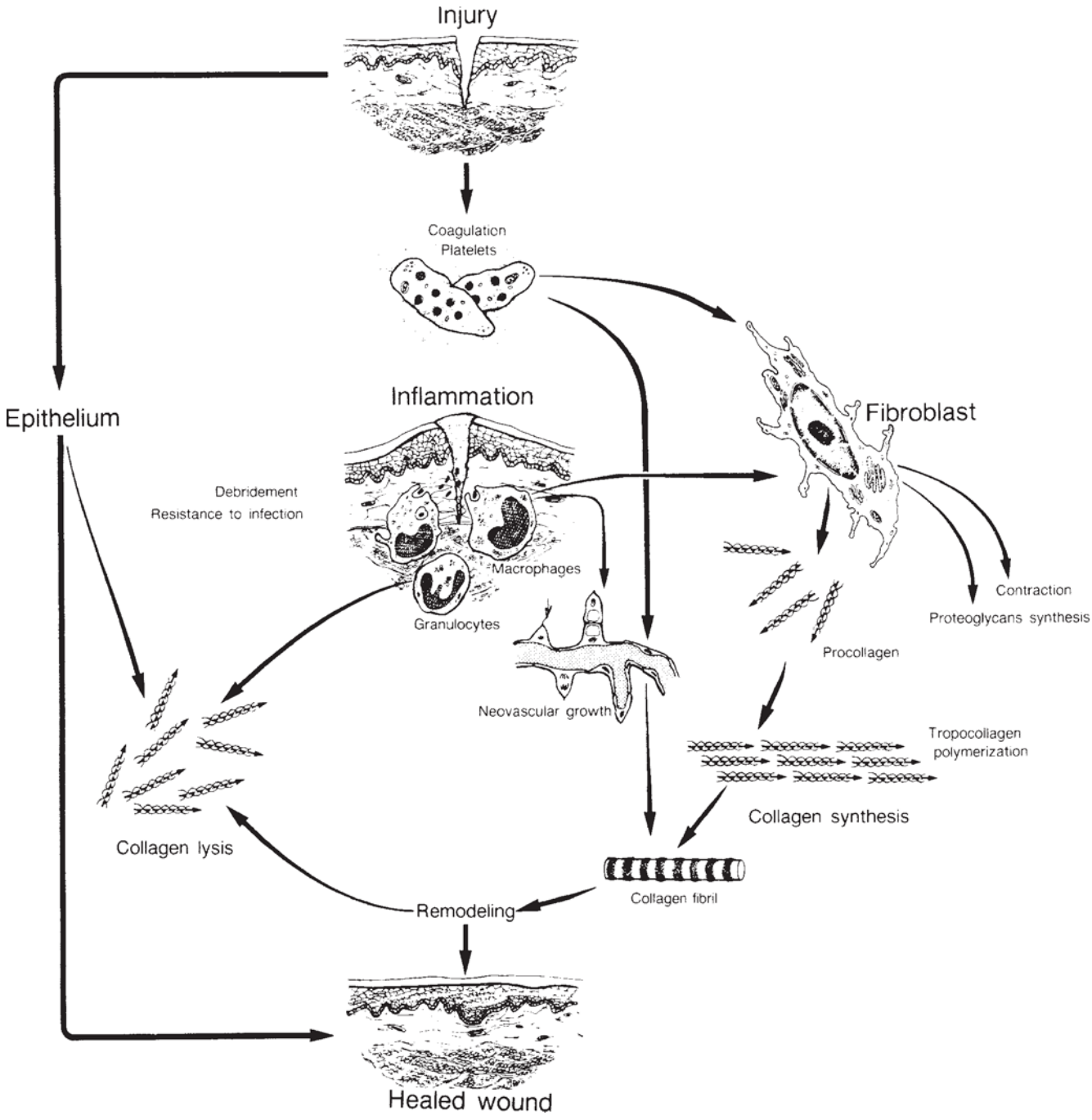


Figure 6.1 Brief depiction of the complexity of wound healing. (Modified and reprinted from Feinberg SE, Larson PE. Healing of traumatic injuries. In: Fonseca RJ, Walker RV, eds. *Oral and maxillofacial trauma*. Philadelphia, PA: WB Saunders, 1991, with permission.)

TABLE 6.1 CYTOKINES INVOLVED IN WOUND HEALING

Cytokine	Abbreviation	Source	Function
Human growth hormone	GH	Pituitary gland	Fibroblast proliferation; increases collagen content and tensile strength; anabolism; stimulates IGF-1
Epidermal growth factor	EGF	Platelets, bodily fluids (including saliva, urine, milk, and plasma)	Epithelial cell and fibroblast proliferation and migration; activates fibroblasts; angiogenic
Platelet-derived growth factor	PDGF	Platelets, macrophages, fibroblasts, endothelial cells, smooth muscle cells	Mitogenic for fibroblasts and smooth muscle cells; chemoattractant for neutrophils and macrophages; angiogenic
Fibroblast growth factors	FGF	Macrophages, brain, pituitary gland	Proliferation and migration of vascular endothelial cells; mitogenic and chemotactic for keratinocytes and fibroblasts
Transforming growth factors	TGF	Platelets, fibroblasts, neutrophils, macrophages, lymphocytes	Epithelial cell and fibroblast proliferation
Nerve growth factor	NGF	Schwann cell, muscle cells	Motoneurons, Schwann cells, muscle cells
Brain-derived neurotrophic factor	BDNF	Central nervous system, skeletal muscle, heart, lung	Support cranial and spinal motoneurons after axotomy
Ciliary neurotrophic factor	CNTF	Schwann cells	Promote survival and differentiation of neural and glial cells within the nervous system
Insulin-like growth factor 1	IGF-1	Fibroblasts, liver, plasma	Fibroblast proliferation, synthesis of proteoglycans and collagen
Tumor necrosis factor	TNF	Macrophages, mast cells, lymphocytes, other tissues and cells	Fibroblast proliferation
Interleukins	IL	Macrophages, lymphocytes, other tissues and cells	Fibroblast proliferation, neutrophil chemotaxis
Interferons	IFN	Fibroblasts, lymphocytes	Inhibition of fibroblast proliferation and collagen synthesis
Keratinocyte growth factors	KGF	Fibroblasts	Epithelial cell proliferation

Phase I: Coagulation and Hemostasis

The body's immediate response to tissue injury is to protect the vascular system and prevent exsanguination. In addition, this phase provides cells that serve as a matrix for other cells that eventually appear in the wound in the later stages of wound healing. Microvascular injury results in extravasation of blood into the wound. A reflex vasoconstriction occurs due to vascular smooth muscle contraction. This rapid reflex response can temporarily halt blood loss. After a few minutes, this environment becomes hypoxic and acidotic triggering vascular smooth muscle relaxation with the resumption of blood loss. Exsanguination is thwarted however by activation of the coagulation cascade.

The coagulation cascade (Fig. 6.2) assembles a platelet plug and clot via extrinsic and intrinsic pathways. Cellular injury extrinsically exposes a tissue factor lipoprotein ubiquitously present on cell membranes that leads to conversion of factor VII to an active protease and ultimately to the common pathway of the coagulation cascade. Likewise, the contact or intrinsic coagulation pathway creates a complex on exposed subendothelial collagen with factor XII, high molecular weight kininogen, and prekallikrein. These factors convert to active proteases after binding and together activate factor XI, which leads to the final common coagulation pathway via factor X activation. Factor X is activated by the calcium-dependent complex formed between factors VIII, IX, and X or directly by an activated factor VII. Finally, in the presence of calcium and phospholipid, factor V becomes activated, and in concert with activated factor X, prothrombin is converted to thrombin. Fibrinogen in turn is converted to fibrin, which ultimately cross-links and forms a stable platelet plug.

The platelet plug contains platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), epidermal growth factor (EGF), and insulin-like growth factor (IGF). These growth factors promote the activation and

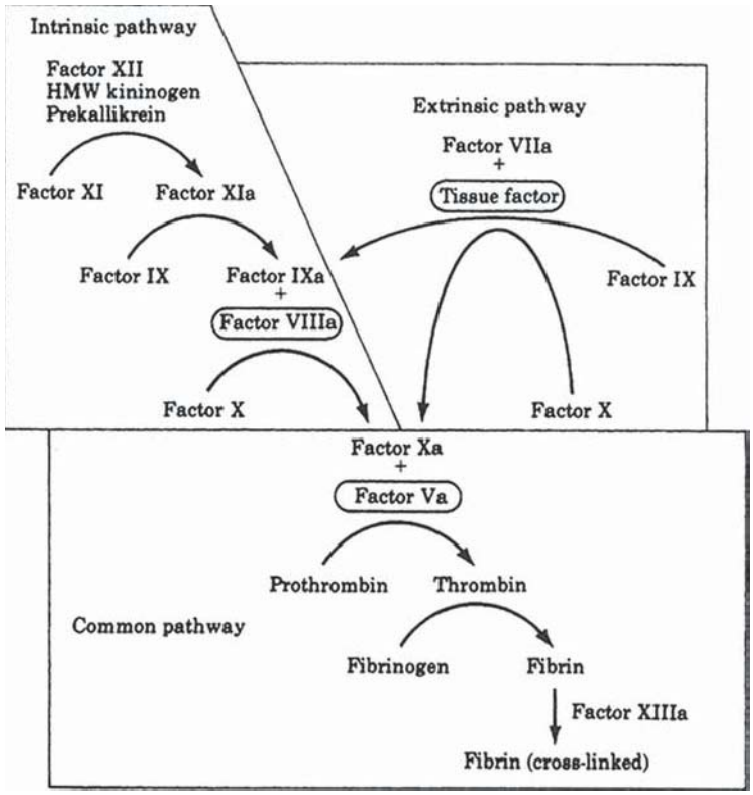


Figure 6.2 The coagulation cascade. (From Klingensmith ME. *Washington manual of surgery*, 5th ed. Lippincott Williams & Wilkins, 2005, with permission.)

chemotaxis of neutrophils, macrophages, endothelial cells, and fibroblasts. Platelets also contain vasoactive amines like serotonin that cause vasodilation and increased vascular permeability. Fluid extravasation occurs contributing the edema observed during the second phase of wound healing, the inflammatory phase (2,3).

Phase II: Inflammation

The inflammatory phase of wound healing functions to establish an immune barrier against invading bacteria. This phase is divided into an early phase and a late phase.

Early Inflammatory Phase

The early inflammatory phase of wound healing ensues during the late phase of coagulation during the first 24 to 36 hours after wounding occurs. This phase activates the complement cascade, which elaborates various chemoattractive factors such as C3a and C5a. These complement components synergistically act with local chemoattractive factors released from the activated platelets such as TGF-β to encourage neutrophil migration to the site of injury. Neutrophils are critical in performing phagocytosis to eliminate bacteria, foreign particles, and injured tissue components for the wound healing process to continue. Modification of surface adhesion molecules confers a sticky quality to neutrophils enabling the process of margination. Margination allows neutrophils to adhere to the endothelial cells of venules surrounding the wound bed. The endothelial cells secrete chemokines that activate a stronger adhesion system that is regulated by integrins. Through diapedesis, neutrophils migrate between endothelial cells to continue phagocytosis. Once neutrophils have completed their function of eliminating wound bacteria and foreign material, the products are extruded via apoptosis to the wound surface producing an exudate. This exudate is then further phagocytosed via macrophages (2,3).

Late Inflammatory Phase

The *late inflammatory phase* is heralded 48 to 72 hours of wounding with the appearance of macrophages. Macrophages originate as blood monocytes that undergo phenotypic changes upon arrival to the wound to become tissue macrophages. Macrophages have a longer lifespan than neutrophils and continue the function of phagocytosis of bacteria and foreign material within the wound bed. The macrophages are attracted to the wound by elaborated clotting factors, complement by-products, cytokines such as PDGF, TGF-β, leukotriene B_4, and platelet factor IV plus elastin and collagen breakdown products. Additional growth factors essential for the later phases of wound healing are released by tissue macrophages to influence the growth and behavior of fibroblasts, assist in wound revascularization, and produce factors to modulate proteins comprising the extracellular matrix (ECM) scaffold. These factors include transforming growth factor alpha (TGF-α), heparin-binding EGF, fibroblast growth factor (FGF),

and collagenase. Activated keratinocytes, fibroblasts, and endothelial cells also play a role (4).

The next cells to arrive at the site of injury are lymphocytes. After 72 hours, interleukin-1 (IL-1), complement components, and immunoglobulin G breakdown products all attract lymphocytes to the wound bed. Lymphocytes regulate collagenase, which is later needed for collagen remodeling and to assist in producing ECM components such as fibrin and fibronectin, as well as participate in their degradation (2,3).

Phase III: Proliferation

The proliferative phase of wound healing begins on day 3 after injury once hemostasis is achieved and an adequate immune response has occurred. This phase lasts for about 2 weeks. Fibroblasts originate from nearby connective tissue cells after growth factors released from tissue macrophages stimulate the mitosis and proliferation of fibroblasts for collagen synthesis. Fibroblasts migrate into the wound and synthesize a new ECM replacing the original fibrin–fibronectin matrix scaffold thereby providing the lattice for collagen synthesis. Granulation tissue represents this phase of wound healing. Importantly, unwounded dermis contains 80% type I collagen and 25% type III collagen. Early in wound healing, granulation tissue however contains 40% type III collagen rendering a lower tensile strength. Later in wound healing, this type III collagen is largely replaced by type I collagen; however, the maximum tensile strength achieved is 80% of the previously unwounded tissue (5).

Angiogenesis is also a component of proliferation. Angiogenesis is critical for the restoration of blood flow into a wound, for reoxygenation of the wound surface, and for the continuation of wound healing through all of its phases. The local tissue response to hypoxia is to increase the production of vascular endothelial growth factor (VEGF). In addition to VEGF, other angiogenic factors including FGF, PDGF, angiogenin, TGF-α, and TGF-β promote the proliferation and growth of endothelial cells. VEGF is secreted by macrophages and binds to endothelial cell receptor tyrosine kinases VEGFR1 and VEGFR2. Binding to these receptors initiates an intracellular signaling cascade to promote angiogenesis. The endothelial cells sprout capillary buds at the wound surface. Ultimately, these capillary buds form a network that join other networks sprouting from the wound bed (2,3).

Cellular migration is imperative for both angiogenesis and continued collagen formation and is dependent upon three processes: (a) protrusion at the cell front, (b) adhesion for the actin cytoskeleton to attach to the substratum, and (c) traction, which propels the trailing cytoplasm forward (2,3).

The cytoskeleton is anchored by cell–cell junctions and cell–ECM adhesions. The internal actin network reorganizes at the leading edge pushing the plasma membrane outward and forming a filopodia. The cyclic assembly and disassembly of actin filaments at the leading plasma membrane edge and behind the edge, respectively, permits unidirectional movement toward other capillary sprouting matrices and other forming ECM frameworks (2,3).

Integrins serve as the primary receptors for ECM proteins and are therefore necessary for cellular migration. Integrins also function in signal transduction and in the regulation and stimulation of cell migration. Increasing adhesion optimizes the rate of cellular migration; however, mobility declines with further attachment. After attachment to the underlying ECM, integrins signal a change in cellular morphology from an oval, spindle shape to an irregular, flat shape. This occurs initially at the leading migratory edge of the plasma membrane. Migration is fastest immediately after injury and slows to a steady state maintained during the remainder of the wound healing process. Traction is effected by contractile forces transmitted through the integrin–cytoskeletal connections. These connections allow the cell to pull its cytoplasm forward. It is the interaction between myosin and actin fibers that pull the cell body forward (2,3).

Epithelialization also begins shortly after injury. This starts from the wound periphery as a single layer of cells forming over the defect. There is a marked increase in epithelial cell mitotic activity around the wound edges, and cells migrate across the wound by attaching to the underlying provisional matrix. When advancing epithelial cells come into contact with one another, migration ceases and basement membranes begin to form.

Phase IV: Remodeling

New epithelium forms in this phase of wound healing along with final scar tissue formation. This phase may last as long as 1 or 2 years. Normal wound healing occurs with the establishment of a balance between degradation and synthesis. The collagen fibers increase their diameter, while hyaluronic acid and fibronectin are degraded. There are three important stimuli inciting the deposition of collagen: (a) high lactate content in the wound, (b) adequate oxygen levels, and (c) growth factors, namely, TGF-β. The collagen fibers initially appear in a haphazard orientation within the wound but eventually become more oriented and cross-linked. The oriented, cross-linked collagen may regain about 80% of the original strength of the wounded area in comparison to the unwounded condition. The synthesis and breakdown of collagen and ECM components occur continuously and simultaneously, equilibrating during the third week postinjury as the rate of collagen synthesis is maximal during the first 2 weeks after injury. Matrix metalloproteinases produced by neutrophils, macrophages, and fibroblasts at the wound site carry out the task of degradation.

Further wound organization occurs during the final stages of the remodeling phase via wound contraction that began during the proliferative phase. The wound's bed

TABLE 6.2 MAJOR COMPONENTS OF ECM

Component	Structure	Function
Collagen	Triple helical glycoprotein	Strength, support, and structure for all tissues and organs
Elastin	Stretchable hydrophobic protein	Expansion and contraction of tissues
Fibronectin	Large double-chain adhesive glycoprotein	Cell adhesion, locomotion, and differentiation
Laminin	Large cross-shaped adhesive glycoprotein	Cell and connective tissue adhesion, cell differentiation
Proteoglycans	Glycosaminoglycans covalently linked to a protein core	Regulation of connective tissue structure and permeability
Hyaluronic acid	Nonsulfated glycosaminoglycan	Fluid environment for cell movement and differentiation

of connective tissue shrinks thereby bringing the wound edges closer together. This is facilitated by fibroblast activity with the ECM scaffold. The main elements of the ECM are listed in Table 6.2. The ECM is comprised of proteoglycans, glycosaminoglycans, and mucoproteins made by fibroblasts. Fibronectin is produced by fibroblasts, endothelial cells, and platelets and forms the substrate for migration and ingrowth of cells initially and later serves as the template for collagen production and contributes to the debridement of wounds during this phase of remodeling. Apoptosis removes the fibroblasts and macrophages as the wound continues to heal, and the density of wound capillaries also declines resulting in a matured scar with a decreased number of cells and an increase in tensile strength.

All of the phases of wound healing are dependent upon various growth factors. These peptides promote cell growth, division, migration, and recruitment into injured tissue. Growth factors are synthesized by a variety of cells including platelets, macrophages, neutrophils, endothelial cells, and fibroblasts. The major growth factors that play a role in fibroblast activity are FGF, TGF-β, and PDGF. VEGF and cysteine-rich protein 61 (Cyr61) are the major proteins involved in regulating angiogenesis (2,3).

FGF exists in several different types, but acidic FGF-1, basic FGF-2, and keratinocyte growth factor are the dominant types contributing to wound healing. Dermal fibroblasts secrete FGF-1 and FGF-2, and their target of action are cells of mesodermal and neuroectodermal origin. They are responsible for the induction and acceleration of the proliferation of fibroblasts, vascular and capillary endothelial cells, keratinocytes, chondrocytes, and myoblasts (2).

TGF-β1 is synthesized by fibroblasts, platelets, macrophages, lymphocytes, and endothelial cells. It stimulates the migration of inflammatory cells and promotes the synthesis of ECM components collagen-1, glycosaminoglycans, and fibronectin. TGF-β1 also regulates the activity of growth factors FGF, PDGF, and EGF (2).

PDGF is stored in and secreted from the platelet alpha granules. PDGF is critical for the synthesis of connective tissue matrix and wound remodeling. It has a mitogenic effect on fibroblasts and stimulates the synthesis of glycosaminoglycans and proteoglycans (2).

VEGF is the principal polypeptide growth factor influencing endothelial cell migration and proliferation. The ordered activity of these two processes is integral for continued wound healing proliferation. VEGF is a member of the PDGF family and is essential for angiogenesis in health and pathophysiology. Nitric oxide enhances VEGF synthesis in vascular smooth muscle cells. Nitric oxide coupled with modified low-density lipoprotein augments VEGF production in macrophages (2).

Cyr61 is a heparin-binding, ECM-associated protein and participates in the induction of angiogenesis. It mediates cell adhesion and induces adhesive signaling, stimulating cell migration, enhancing cell proliferation, and promoting cell survival in both fibroblasts and endothelial cells. Cyr61 regulates the expression of genes involved in angiogenesis, inflammation, matrix remodeling, and cell-matrix adhesions (2).

FACTORS AFFECTING WOUND HEALING

There are a host of pathophysiologic and metabolic factors that can adversely affect the process of wound healing (Table 6.3). These factors include local edema, ischemia, tissue hypoxia, infection, necrosis, and growth factor imbalance, as well as systemic causes such as metabolic disease like diabetes, nutritional status, and other preexisting illness. In addition, external factors such as previous exposure to radiation can significantly and negatively impact the wound healing process.

Local edema increases wound tension leading to an increase in tissue pressure. This scenario reduces microperfusion within the wound and the availability of oxygen to the wound. Oxygen is essential to the wound healing process. Oxygen prevents wounds from infection; stimulates angiogenesis; increases keratinocyte differentiation, migration, and re-epithelialization; enhances fibroblast proliferation and collagen synthesis; and promotes wound contraction. Oxygen levels, namely, superoxide, are also critically important for the neutrophil function of oxidative phagocytosis of pathogens within a wound during the inflammatory phase of wound healing. Temporary hypoxia after injury stimulates the wound healing process; however, chronic hypoxia delays wound healing (6,7).

Infections also impede the wound healing process. After wounding, microorganisms that usually reside on the skin surface have direct access to the underlying tissue. Wound

TABLE 6.3 FACTORS THAT IMPEDE WOUND HEALING

Disease States	Local Factors
Hereditary	Ischemia
Coagulation disorders	Infection
Ehlers-Danlos/Marfan's	Tissue trauma
Prolidase deficiency	Retained foreign body
Werner syndrome	Desiccation
Vascular disorders	Medications
Congestive heart failure	Glucocorticoids
Atherosclerosis	Anticoagulants
Hypertension	Antineoplastic agents
Vasculitis	Colchicine
Venous stasis	Penicillamine
Lymphedema	Vitamin E
Metabolic	Salicylates (high dose)
Chronic renal failure	Nonsteroidals (high dose)
Diabetes mellitus	Zinc sulfate (high dose)
Malnutrition	Vitamin A (high dose)
Cushing syndrome	
Hyperthyroidism	
Immunologic deficiency states	
Others	
Chronic pulmonary disease	
Liver failure	
Malignancy	

contamination refers to the presence of nonreplicating organisms on a wound surface, while colonization indicates the presence of replicating microorganisms on the wound without causing tissue damage. Invasive infection denotes the presence of replicating microorganisms within a wound that results in host injury. When the inflammatory phase of wound healing is prolonged or ineffective at removing debris and bacteria, prolonged elevation of proinflammatory cytokines such as IL-1 and TNF-α further prolongs inflammation. Increased duration of inflammation leads to augmented levels of matrix metalloproteases (MMPs) that serve to degrade the ECM under production during the proliferative phase. This excess level of proteases also contributes to the degradation of growth factors, and these growth factors are necessary for the process of wound healing (6,7).

In addition, bacteria in chronic infected wounds have the opportunity to form communities of aggregated microorganisms maintained within an extracellular polysaccharide matrix they secrete. The biofilm-protected environment renders the contained organisms resistant to conventional antibiotic therapy. *Pseudomonas* and *Staphylococcus* species may utilize a biofilm environment to shield themselves from the phagocytic activity of invading neutrophils and hence the failure of antibiotics to cure chronic wounds (6).

The systemic factor of older age, that is, patients over the age of 60, also is known to adversely affect wound healing. Healthy older patients experience a temporal delay in wound healing but not an actual quality defect of the healing process. Delayed wound healing in the aged is associated with an alteration of every phase of the wound healing process. Hemostasis is affected by enhanced platelet aggregation. Inflammation is affected by an increase in number of secreted inflammatory mediators, delayed infiltration of macrophages and lymphocytes to the wound site, and impaired macrophage function. The proliferative phase is altered by a decreased amount of secreted growth factors, delayed re-epithelialization and angiogenesis. Remodeling is adversely affected by decreased collagen deposition, a reduction in collagen turnover, and overall decreased wound strength (6).

Studies indicate that estrogen can improve the age-related impairment in healing in both men and women and that aged males experience a delay in the wound healing process in comparison to aged females. Female estrogens estrone and 17β-estradiol regulate a variety of genes associated with regeneration, matrix production, protease inhibition, epidermal function, and the genes primarily associated with inflammation. On the other hand, male androgens testosterone and 5α-dihydrotestosterone and their steroid precursor dehydroepiandrosterone affect wound healing in a negative manner (6).

Many diseases, for example, cardiovascular disease and cancer, are associated with stress. Stress results in the deregulation of the immune system. This is mediated primarily by the hypothalamic–pituitary–adrenal system and the sympathetic–adrenal–medullary axis. Many studies also suggest that psychological stress also results in delayed wound healing. Stress upregulates glucocorticoids and thereby reduces the levels of proinflammatory cytokines IL-1 β, IL-6, and TNF-α at the wound site. Stress also results in decreased amounts of the chemoattractants IL-1α and IL-8 at the wound sites, which are both necessary during this inflammatory phase of wound healing. Glucocorticoids further adversely act on wound healing by suppressing differentiation and proliferation, gene transcription, and reducing the expression of cell adhesion molecules involved in immune cell trafficking (6).

Diabetic patients are documented to have impairment in the healing process of acute wounds. Diabetic wounds are accompanied by hypoxia. As discussed previously in this chapter, hypoxia can amplify and prolong the early inflammatory response resulting in an increased amount of oxygen radicals within the wound. Hyperglycemia can also add to the oxidative wound stress when the production of reactive oxygen species exceeds the antioxidant capacity. In addition, high levels of MMPs increase tissue destruction and inhibit normal repair processes. Diabetic wounds display dysregulated T-cell immunity; defective leukocyte chemotaxis, phagocytosis, and bactericidal capacity; and dysfunctional fibroblast and epidermal cell activity. This results in inadequate bacterial clearance and delayed wound healing. There is also impairment of angiogenesis in the diabetic wound. There is a defect in epithelial cell

mobilization and homing and a decreased level of VEGF, the primary angiogenic factor, in the diabetic wound (6,8).

The neuropathy that occurs in diabetic individuals also affects wound healing. Neuropeptides such as nerve growth factor, substance P, and calcitonin gene-related peptide normally promote cell chemotaxis, induce growth factor production, and stimulate the proliferation of cells. These factors are decreased in diabetic patients with peripheral neuropathy. In addition, sensory nerves play a role in modulating immune defense mechanisms and denervated skin experiences a reduction of leukocyte infiltration (6,8).

Some commonly used medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids may contribute to impaired wound healing. These agents interfere with clot formation, platelet function, the inflammatory phase of wound healing, as well as negatively impact the proliferative phase of wound healing. NSAIDs are widely used for the treatment of inflammation and arthritis as well as for pain management. Low-dose aspirin is also commonly prescribed for its antiplatelet properties for cardiovascular health but not as an anti-inflammatory agent. There is limited data to suggest a negative impact on wound healing with the short-term use of NSAIDs; however, the long-term use of NSAIDs and their negative effect on wound healing is not clearly defined. Some animal models have shown an antiproliferative effect on wound healing, which results in decreased numbers of fibroblasts, weakened wound breaking strength, decreased wound contractility, delayed epithelialization, and impaired angiogenesis. Glucocorticoids cause global anti-inflammatory effects and suppression of cellular wound responses. There is suppression of fibroblast proliferation and collagen synthesis. Wounds heal with incomplete granulation tissue and reduced wound contraction. There is an inhibition of the necessary transcriptional factor hypoxia inducible factor-1 (HIF-1). Glucocorticoids also predispose to wound infection, and its negative impact on wound healing was discussed previously (6).

Obese patients often experience wound complications including skin wound infection, dehiscence, hematoma and seroma formation, pressure ulcers, and venous ulcers. An increased rate of surgical site infection often occurs in obese individuals likely due to a relative hypoperfusion and ischemia in the subcutaneous adipose tissue. Surgical wounds in the obese display increased tension at the wound edges, and this can contribute to wound dehiscence. Wound tension also increases tissue pressure, which in turn reduces the microcirculation and hence oxygen levels of the wound. In addition, obese patients have excessive skin folds that often harbor microorganisms that thrive in moist environments and can contribute to infection and tissue breakdown. The friction generated by skin on skin contact also leads to ulceration. Obesity is also linked to stress, anxiety, and depression, conditions that can impair the host immune response (6).

Alcohol exposure affects wound healing as well, namely, by increasing host susceptibility to infection. Short-term alcohol exposure suppresses proinflammatory cytokine release in response to an inflammatory challenge. The higher incidence of postinjury infection correlates with decreased neutrophil recruitment and phagocytic function in the acute alcohol exposed state. The most significant impairment associated with alcohol exposure is wound angiogenesis. There is a decreased expression of VEGF receptors and a reduced nuclear expression of HIF-1α in endothelial cells that reduces wound angiogenesis by up to 60% after a single alcohol exposure. Connective tissue restoration is also negatively impacted by acute alcohol exposure due to decreased levels of collagen production and an overall increase in wound proteases. Chronic alcohol exposure also negatively affects wound healing; however, the exact mechanisms remain unclear (6).

Likewise, smoking inhibits wound healing. There is a delay in wound healing and a predisposition to the development of postoperative infection, wound dehiscence and rupture, anastomotic leakage, wound and flap necrosis, epidermolysis, and decreased tensile strength of the wound. Cosmetic outcomes are also worse in patients who continue smoking in the perioperative period. Nicotine acts as a vasoconstrictor thereby interfering with wound oxygen supply by inducing tissue ischemia. Nicotine also stimulates sympathetic nervous activity that results in the release of epinephrine into the circulation that also serves as a vasoconstrictor in the peripheral circulation and decreases tissue blood perfusion. Nicotine increases blood viscosity caused by decreased fibrinolytic activity and augmented platelet adhesiveness. Cigarette smoke carbon monoxide binds to hemoglobin with an affinity 200 times greater than that of oxygen resulting in a decreased fraction of oxygenated hemoglobin in the circulation (6,9).

Smoking adversely affects the inflammatory phase by impairing neutrophil migration and reducing the neutrophil bactericidal activity. Lymphocyte function, cytotoxicity of natural killer cells, and the production of IL-1 are all depressed, and macrophage ability to sense gram-negative bacteria is also compromised. The proliferative phase is impaired by a decreased fibroblast migration and proliferation, reduced wound contractility, hindered epithelial regeneration, decreased ECM production, and established unfavorable wound protease balance. Smoking cessation improves repair and reduces the incidence of wound infection even within 7 days of surgery (6,9).

Protein is one of the most important nutrient factors affecting wound healing. A deficiency of protein can impair capillary formation, fibroblast proliferation, proteoglycan synthesis, collagen synthesis, and wound remodeling (3). Protein deficits also negatively impact the immune system evidenced by decreased neutrophil phagocytosis and increased susceptibility to wound infection. Collagen is the major protein component of connective tissue and is primarily comprised of glycine, proline, and hydroxyproline. Collagen synthesis depends upon the hydroxylation of lysine and proline. Ferrous iron and vitamin C are necessary cofactors for this hydroxylation. Arginine also exerts many

effects on the body, including the modulation of immunity, wound healing, hormone secretion, vascular tonicity, and endothelial function. Arginine also serves as a precursor to proline. Deficiency of arginine can therefore lead to inadequate collagen deposition, angiogenesis, and impaired wound contractility. Insufficient levels of glutamine result in an inadequate inflammatory immune response in the early phases of wound healing. It is hypothesized that omega-3 fatty acids are involved in the proinflammatory cytokine production, cell metabolism, gene expression, and angiogenesis at the site of a wound and that deficits of the fatty acid may predispose to host wound infection (6,10,11).

Vitamin C deficiency is well known to result in impaired collagen synthesis and fibroblast proliferation, decreased angiogenesis, and increased capillary fragility. There is also an increased susceptibility to wound infection. Vitamin A deficiency impedes antioxidant activity, fibroblast proliferation, cellular differentiation and proliferation, collagen and hyaluronate synthesis, and MMP-mediated ECM degradation. Vitamin A increases the inflammatory response in wounds through enhanced lysosomal membrane lability, increased macrophage influx, and activation and stimulation of collagen synthesis (6). Inadequate levels of vitamin E also impede antioxidant activity within a wound. The wound also suffers instability of cellular membrane integrity and may lead to excessive scar formation. Zinc deficiency significantly impairs wound healing as this micronutrient is necessary for RNA and DNA polymerase activity, DNA synthesis, protein synthesis, and cellular proliferation (10). The micronutrient iron is required for the hydroxylation of proline and lysine, and severe iron deficiency results in decreased collagen production. A study by Heyman et al. illustrates the importance of vitamins and micronutrients on wound healing. The study demonstrated that a high-energy, protein-enriched supplement containing arginine, vitamin C, vitamin E, and zinc improves the overall healing of chronic pressure ulcers (6,10,11).

It is also incumbent upon the surgeon to preoperatively inquire about patient use of herbal supplements. Dong quai, also known as female ginseng, is notable for coumadin-like properties and interference with the clotting mechanism. Echinacea displays immunosuppressive properties (6).

Similarly, the head and neck surgeon must also respect the previously radiated neck in this era where definitive chemoradiation therapy is commonly employed for our head and neck cancer patients whom may eventually require a salvage surgical procedure. Ionizing radiation results in endothelial cell injury causing endarteritis. This in turn leads to wound atrophy, fibrosis, and delayed tissue repair. Injury of a previously irradiated wound does *not* lead to angiogenesis. Radiotherapy alters the balance between the wound healing promotion local mediators and those mediators that act to inhibit the process. Radiation is employed to cure various cancers due to its greatest effect on cells in the G2 through M phases of the cell cycle. That is, cell populations that are rapidly dividing are those cells most sensitive to the effects of radiation. Such cells include fibroblasts and keratinocytes. Therefore, wounds occurring in a previously irradiated site display impaired formation of granulation tissue as well as dysfunctional epithelialization (12).

DERANGEMENTS OF WOUND HEALING

A spectrum of scar formation ranging from normal scar formation to normotrophic, hypertrophic, and keloid scar formation warrants consideration by the otolaryngologic surgeon as well. Abnormal scar formation can lead to both functional and cosmetic problems such as limitation of mobility and aesthetic disfigurement causing psychosocial repercussions.

There remains controversy regarding the distinction among the various scar types histologic description and etiology largely due to nonstandardization of methods employed to determine histologic characterization. Normotrophic scars are often described with characteristics similar to hypertrophic scars except the height of scar elevation above the normal skin surface is less than 2 mm. Hypertrophic scars are severe excessive scars that are frequently described as histologically containing an abundance of collagenous scar tissue and hypercellularity consisting of mainly myofibroblasts. The scar is phenotypically elevated greater than 2 mm above the normal skin surface. The exact etiology is unknown; however, it is theorized that failure of apoptosis at the conclusion of the proliferative phase of wound healing to eliminate the myofibroblasts leads to this excessive scar formation of a hypertrophic scar (13,14). Keloids are benign skin tumors that occur in patients with genetic predisposition and are thought to arise in part to upregulation of TGF-β. Keloid scars grow outside the confines of the original wound bed in contrast to hypertrophic scars that present as an elevation of the scar maintained within the confines of the original wound bed.

Several reports have suggested histologic differences between scar types with respect to collagen orientation and thickness of the collagen bundles. However, many of these reports contradict each other, and thus, the histopathologic characteristic differences remain unclear. Further investigation is warranted as treatment efficacy is dependent upon elucidation of etiology and behavioral characteristics of these deranged scars (13,15).

METHODS TO IMPROVE WOUND HEALING

Hyperbaric oxygen (HBO) treatment is a therapy employed since the 1960s adjunctively in the management of mandibular osteoradionecrosis (ORN). ORN was theorized by Marx to result from tissue hypoxia, hypocellularity, and hypovascularity. HBO is utilized to increase the blood–tissue oxygen gradient. This in turn enhances the diffusion of oxygen into hypoxic tissue. An increase in oxygen supply stimulates

fibroblast proliferation, angiogenesis, and collagen formation. Increased oxygen tension is also bactericidal and bacteriostatic (16–18). Recently new protocols have emerged for the prevention and treatment of ORN, challenging the utility of HBO therapy. Also employed during the early stages of ORN, pentoxifylline, for example, is one of a few medications recently espoused as efficacious. The mechanism of action of pentoxifylline is to decrease the viscosity of blood and hence improve the peripheral circulation and oxygen supply to the affected area. This too is the ultimate effect of HBO therapy. There remains a role for HBO therapy in the treatment of early stage ORN, whereas this conservative medical treatment modality will not successfully treat patients with pathologic fracture, fistula formation, or chronic infection, which ultimately requires reconstruction, such as free tissue transfer, after composite resection (18,19).

The local wound environment proton gradient, or pH, changes throughout the phases of wound healing. Each phase is dependent upon a particular pH range as enzyme activity fluctuates due to change in pH. The ability to alter wound pH may prove a promising, inexpensive strategy for improving chronic wound healing. For example, the application of a biodegradable polymer that releases certain growth factors, such as FGF, where the release occurs in a pH dependent fashion may optimize the activity of FGF during the inflammatory and proliferative phases of wound healing. In addition, pH changes affect bacterial colonization. For instance, elevated pH encourages *Candida albicans* infection of the wound. The ability to alter the pH of the wound environment can lessen the incidence of candidiasis of chronic wounds (20,21).

Another promising wound healing therapeutic are antimicrobial peptides. Antimicrobial peptides may influence the proliferation and migration of keratinocytes as well as their cytokine and chemokine production. Likewise, the proliferative phase, in particular the re-epithelialization process, is potentially modified by stimulation of such peptides (20).

Also during the proliferative phase, the mammalian target of rapamycin, mTOR, plays a role in re-epithelialization. mTOR is an FK506-binding protein/rapamycin-associated protein kinase that is upregulated in wounded stratified epithelia. Proliferation and protein synthesis of keratinocytes increase as a result. When this process is unchecked or overactive, hypertrophic scarring or keloid scarring may occur. This is evidenced by reports of increased levels of mTOR in keloid scars. Therefore, the ability to locally inhibit mTOR via agents such as rapamycin may help prevent hypertrophic or keloid scarring in the future (20).

A novel topical wound healing aid known as calreticulin induces proliferation of keratinocytes, fibroblasts, and endothelial cells in vitro. These cells play a role in all phases of wound healing. In a porcine model, calreticulin has enhanced macrophage recruitment to the wound bed, improved granulation, and stimulated granulation and re-epithelialization (20).

Other potential wound healing adjuncts include gene transfer, the use of stem cells, and modulation of the peripheral nervous system. Gene transfer via transfected allogenic keratinocyte cell suspensions, for example, could potentially transplant growth factors like epidermal growth factor into a wound bed to enhance the proliferative phase of wound healing (20). A recent study conducted at Stanford University demonstrated regeneration capability of mice skull defects via chemical control of FGF-2 exposure to adipose stem cells. By genetically fusing a protein of interest, FGF-2, to a destabilizing protein domain, the construct permits spatial and temporal control of signaling factor. FGF-2 has previously proven to increase the proliferation of mouse adipose stem cells while maintaining the potential for differentiation. This study thereby illustrates the ability for chemical control of important protein factors in tissue engineering and potentially wound healing (21,22).

Similarly, there exists a newly discovered network between the nervous system and the immune system. Various neuropeptides and cytokines cross talk. For example, substance P acts as an injury-inducible factor early in the wound healing process. Perhaps substance P and other neuropeptides have a potential application in improving the wound healing process (20,21).

These are just a few examples of the ongoing research regarding the molecular mechanisms vital to the wound healing process that may result in improvement of the wound healing process in the future.

HIGHLIGHTS

- Wound healing is a complex process accomplished by four phases that naturally overlap including the coagulative and hemostatic phase, the inflammatory phase, the proliferative phase, and the remodeling phase.
- A variety of cytokines and growth factors play a vital role in the various phases of wound healing including PDGF, TGF-β, TGF-α, EDGF, VEGF, FGF-1, and FGF-2.
- Several adverse conditions may contribute to aberrant wound healing including local edema, tissue hypoxia, infection, metabolic diseases such as diabetes mellitus, malnutrition, nutrition medications, and advanced age to name a few.
- Collagen is a major component of ECM that is initially deposited in a wound primarily as type III, which is largely replaced by type I collagen as wound healing progresses and an equilibrium is established between collagen synthesis and breakdown during the remodeling phase.
- The maximum wound tensile strength attained does not exceed 80% of the previously unwounded tissue strength.
- Ongoing research continues regarding targeted modification of the wound healing process such as inhibition of mTOR, the mammalian target of rapamycin, to prophylax against the formation of hypertrophic or keloid scars.

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7 Understanding Data and Interpreting the Literature

Richard M. Rosenfeld

"It is a capital mistake to theorize before one has data," observed Sherlock Holmes. Physicians are rarely guilty of this offense, because they are inundated with data from clinical observations, journal articles, professional meetings, and governmental agencies. Unfortunately, the theories that result often have little relevance to the data that produced them. This is not unexpected, because physicians rarely devote the same efforts to mastering data that they devote to mastering clinical skills. As a partial remedy, this chapter offers a principle-centered approach to data analysis with emphasis on interpreting the medical literature (1,2).

Nearly all data relevant to clinical care comes from articles in peer-reviewed medical journals, whose content is generally assessed using principles that mirror those in this chapter (3).Unfortunately, the process of editorial peer review is largely untested and its effects are uncertain. Manuscript assessment, like even the most sophisticated diagnostic tests, has a certain sensitivity and specificity; worthy articles may be unappreciated (and unpublished) or worthless ones may pass undetected to the printing press. Peer reviewers may be biased, unqualified, or possess widely discrepant opinions about a study. The bottom line? Caveat lector: beware of what you read even in excellent medical journals.

Of more concern to clinicians than the inadequacies of peer review, however, is that the medical literature generally serves science rather than medical practice. Peer-reviewed publications facilitate communication from scientist to scientist, not necessarily from scientist to clinician. Most published studies are nondefinitive tests of hypotheses and innovations, only a very small percentage of which may warrant routine clinical application. Whereas the science may be sound, the idea has not progressed beyond the laboratory or preliminary field studies. Definitive studies constituting true scientist to clinician communication are rare in medical journals, and must be identified by critical appraisal.

Clinicians can use the medical literature to support clinical decisions in two complimentary ways: regular surveillance (or browsing) and problem-oriented searches. While the latter mode is more effective for learning, both are necessary for continuing clinical competence. Both methods require appreciating the purposes of the medical literature and understanding of the strengths and weaknesses of various study designs for providing valid and clinically applicable information.

HOW TO IDENTIFY ARTICLES WORTH READING

Articles worthy of in-depth analysis have enticing titles and abstracts, which espouse innovative, controversial, or clinically relevant ideas. Reading the abstract alone, however, is a poor substitute for perusing the entire article. Whereas abstracts in otolaryngology journals generally do convey information about study design, sample size, and the source of the data, they infrequently describe adverse events, study limitations, and dropouts or losses (4). Abstracts may also report selective, incomplete, or inaccurate data leading to biased conclusions. Abstracts are a starting point for analysis, not the finish line.

Worthy articles appear as original research in the main section of a peer-reviewed journal. Methods and results sections, which represent the heart and soul of the article, should be appropriately detailed and lengthy. Statistical reporting includes confidence limits and measures of clinical benefit (5). Enough details should be provided for you to reproduce the study on your own, if desired, with a reasonable chance of obtaining the same results. A quick review of the paper in general should disclose many of the signs of grandeur in Table 7.1.

TABLE 7.1 SIGNS OF GRANDEUR AND DECADENCE IN JOURNAL ARTICLES

Section	Signs of Grandeur	Signs of Decadence
Abstract	Structured summary of goals, methods, results, and significance	Unstructured qualitative overview of study; contains more wish than reality
Introduction	Clear, concise, and logical; ends with study rationale or purpose	Rambling, verbose literature review; no critical argument or hypothesis
Methods	Specific enough for the reader to reproduce the study and understand how quantitative results were generated	Vague or incomplete description of subjects, sampling, outcome criteria; no mention of statistical analysis
Results	Logical blend of narrative and numbers, including 95% CIs, with supporting tables and figures	Difficult to read, with overuse or underuse of statistical tests; emphasis on P-values, not clinical importance
Discussion	Puts main results in context; reviews supporting and conflicting literature; discusses strengths and weaknesses	Full of fantasy and speculation; rambling and biased literature review; does not acknowledge weaknesses
References	Demonstrates clearly that work of others has been systematically considered; emphasizes original research from peer-reviewed journals	Key articles are conspicuously absent; excessively brief; emphasizes review articles, book chapters, and lower-quality journals

Articles unworthy of in-depth analysis may have enticing titles and abstracts, but have no ability to support the lofty claims and conclusions therein. The article may appear in a non–peer-reviewed (throwaway) journal or in an industry-funded supplement to the main section (which generally implies lower quality). Signs of decadence (Table 7.1) are readily apparent when perusing the article's main sections. The methods and results sections are vague and sparse, overshadowed by a verbose discussion section with unsupported opinions and creative misinterpretations. Don't waste any time analyzing an unworthy article unless the premise is so novel and important that it overshadows the obvious weaknesses.

FIVE BASIC QUESTIONS FOR INTERPRETING DATA

As expert clinicians consider something abnormal until they examine it and prove otherwise, a connoisseur of medical evidence considers a data set or a journal article to be laden with flaws, distortions, and omissions until proven to the contrary. The five basic questions in Table 7.2 are the key to this analytic process. Each question is discussed below using established principles of data analysis and literature interpretation (1).

Question 1: How Was the Study Performed

Study Design

Medical data arise from a research study, defined as an "organized quest for new knowledge, based on curiosity or perceived needs" (6). Validity of the data is determined in large part by the study design (specific procedures and methods) used by the investigators to produce their data. The study design must fit the research question. Despite the befuddling array of study designs espoused in the epidemiologic literature, the savvy data analyst need only address a few basic considerations (Table 7.3). These relate to (a) how the data were gathered, (b) what degree of control the investigator had over study conditions, (c) whether a control or comparison group was used, and (d) what direction of inquiry was followed.

Data collected specifically for research (Table 7.3) are likely to be unbiased—they reflect the true value of the attribute being measured. In contrast, data collected during routine clinical care will vary in quality. *Experimental* studies, such as randomized trials, are likely to produce high-quality data because they are performed under carefully controlled conditions. In *observational* studies, however, the investigator is simply a bystander who records the natural course of health events during clinical care. Regardless of data quality bias may be introduced at any stage of the research process, which includes reviewing literature, defining baseline states, performing interventions, measuring outcomes, analyzing data, and publishing results (7).

The presence or absence of a *control group* has a profound influence on data interpretation. An uncontrolled study—no matter how elegant—is purely descriptive (2). Case series, which appear frequently in the otolaryngology literature, *cannot* assess efficacy or effectiveness, but they *can* convey feasibility, experience, technical details of an intervention, and predictive factors associated with good outcomes or adverse events (8). The best case series use a consecutive sample of patients, adjust for interfering

TABLE 7.2 FIVE BASIC QUESTIONS FOR INTERPRETING MEDICAL DATA

Question	Why It Is Important	Underlying Principles
1. What type of study produced the data?	Study design has a profound impact on interpretation; scrutinize the data collection, degree of investigator control, use of control groups, and direction of inquiry	Bias, research design, placebo effect, control groups, causality
2. What are the results?	Results should be summarized with appropriate descriptive statistics; positive results must be qualified by the chance of being wrong, and negative results by the chance of having missed a true difference	Measurement scale, association, *P* value, power, effect size, clinical importance
3. Are the results valid within the study?	Proper statistical analysis and data collection ensures valid results for the subjects studied; measurements must be accurate and reproducible	Internal validity, accuracy, statistical tests
4. Are the results valid outside the study?	Results can be generalized when the sampling method is sound, subjects are representative of the target population, and sample size is large enough for adequate precision	External validity, sampling, CIs, precision
5. Are the results strong and consistent?	A single study is rarely definitive; results must be viewed relative to their plausibility, consistency with past efforts, and by the strength of the study methodology	Research integration, level of evidence, systematic review

TABLE 7.3 EFFECT OF STUDY DESIGN ON DATA INTERPRETATION

Aspect of Study Design	Effect on Data Interpretation
How were the data originally collected?	
Specifically for research	Interpretation is facilitated by quality data collected according to an a priori protocol
During routine clinical care	Interpretation is limited by the consistency, accuracy, availability, and completeness of the source records
Database or data registry	Interpretation is limited by representativeness of the sample and the quality and completeness of data fields
Is the study experimental or observational?	
Experimental study with conditions under direct control of the investigator	Low potential for systematic error (bias); bias can be reduced further by randomization and masking (blinding)
Observational study without intervention other than to record, classify, analyze	High potential for bias in sample selection, treatment assignment, measurement of exposures, and outcomes
Is there a comparison or control group?	
Comparative or controlled study with two or more groups	Permits analytic statements concerning efficacy, effectiveness, and association
No comparison group present	Permits descriptive statements only, because of improvements from natural history and placebo effect
What is the direction of study inquiry?	
Subjects identified prior to an outcome or disease; future events recorded	Prospective design measures incidence (new events) and causality (if comparison group included)
Subjects identified after an outcome or disease; past histories are examined	Retrospective design measures prevalence (existing events) and causality (if comparison group included)
Subjects are identified at a single time point, regardless of outcome or disease	Cross-sectional design measures prevalence (existing events) and association (if comparison group included)

TABLE 7.4 EXPLANATIONS FOR FAVORABLE OUTCOMES IN TREATMENT STUDIES

Explanation	Definition	Solution
Bias	Systematic variation of measurements from their true values; may be intentional or unintentional	Accurate, protocol-driven data collection
Chance	Random variation without apparent relation to other measurements or variables (e.g., getting lucky)	Control or comparison group
Natural history	Course of a disease from onset to resolution; may include relapse, remission, and spontaneous recovery	Control or comparison group
Regression to the mean	Symptom improvement independent of therapy, as sick patients return to a mean level after seeking care	Control or comparison group
Placebo effect	Beneficial effect caused by the expectation that the regimen will have an effect (e.g., power of suggestion)	Control or comparison group with placebo
Halo effect	Beneficial effect caused by the manner, attention, and caring of a provider during a medical encounter	Control or comparison group treated similarly
Confounding	Distortion of an effect by other prognostic factors or variables for which adjustments have not been made	Randomization or multivariate analysis
Allocation (susceptibility) bias	Beneficial effect caused by allocating subjects with less severe disease or better prognosis to treatment group	Randomization or comorbidity analysis
Ascertainment (detection) bias	Favoring the treatment group during outcome analysis (e.g., rounding up for treated subjects, down for controls)	Masked (blinded) outcome assessment

variables, plan in advance for systematic data collection, and are humble and cautious when interpreting results.

Without a control or comparison group, treatment effects cannot be distinguished from other causes of clinical change (Table 7.4) (9). Some of these causes are found in Figure 7.1, which depicts change in health status after a healing encounter as a complex interaction of three primary factors:

1. *What was actually done*. Specific effect(s) of therapy, including medications, surgery, physical manipulations, and alternative or integrative approaches.
2. *What would have happened anyway*. Spontaneous resolution, including natural history, random fluctuations in disease status, and regression to a mean symptom state.
3. *What was imagined to be done*. Placebo response, defined as a change in health status resulting from the symbolic significance attributed by the patient (or proxy) to the encounter itself (10).

A placebo response is most likely to occur when the patient receives a meaningful and personalized explanation, feels care and concern expressed by the healer, and achieves control and mastery over illness (or believes that the healer can control the illness).The placebo response differs from the traditional definition of placebo as an inactive medical substance. Unlike the "placebo pills" in randomized trials, a placebo response can be elicited by touch, words, gestures, local ambiance, and social interactions. A valid and reliable 12-item survey, the PR-12, is available to measure aspects of the placebo response in office encounters (11).

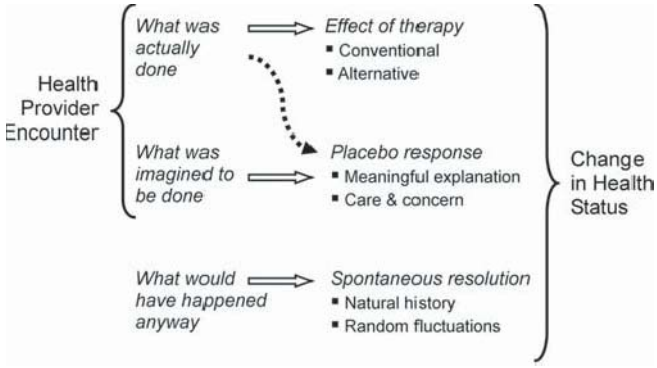


Figure 7.1 Model depicting change in health status after a healing encounter. *Dashed arrow* shows that a placebo response may occur from symbolic significance of the specific therapy given or from interpersonal aspects of the encounter.

Assessing Causality

When data from a comparison or control group are available, statistics may be used to test hypotheses and measure associations. Causality may also be assessed when the study has a time-span component, either retrospective or prospective (Table 7.3). Prospective studies measure *incidence* (new events) whereas retrospective studies measure *prevalence* (existing events). Unlike time-span studies, cross-sectional inquiries (surveys, screening programs, evaluations of diagnostic tests) measure association, not causality.

Efficacy and causality are best assessed by randomized controlled trials, because nonrandom treatment assignment is prone to innate distortions caused by individual judgments and other selective decisions (allocation bias). A dangerous habit, however, is to label all randomized trials as high quality and all observational studies (e.g., outcomes research) as substandard. Randomization cannot compensate for imprecise selection criteria, poorly defined endpoints, inadequate follow-up, or low compliance with treatment. Moreover, randomized trials with inadequate methodology tend to exaggerate treatment effects compared with trials that are properly designed and executed (12).

The best randomized trials ensure adequate randomization, conceal treatment allocation (blinding), and analyze results by intention-to-treat. The intention-to-treat analysis maintains treatment groups that are similar apart from random variation, which may not occur if only subjects who complied with treatment (on-treatment analysis) are included (13). A blinded (masked) trial is always superior to a nonblinded (open, open-label, or unmasked) trial in which everyone involved knows who received which interventions (14). In a double-blind trial the participants, investigators, and assessors all remain unaware of the intervention assignments. A triple-blind trial also maintains a blind data analysis, but some use this simply to indicate that the investigators and assessors are distinct.

Randomized controlled trials comprise only about 4% of articles in leading otolaryngology journals, with about 25% supported by industry funding (15). The presence of industry support, however, is unrelated to conclusions favoring intervention. Nearly 60% of articles use intention-to-treat analysis, but only a minority specify randomization schemes, employ a double-blind protocol, include confidence intervals (CIs), or explicitly discuss adverse events. The earlier advice of "caveat lector," therefore, also applies to randomized trials, not just observational research.

Question 2: What Are the Results?

Describing Central Tendency and Dispersion

Describing results begins by defining the *measurement scale* that best suits the observations. Categorical (qualitative) observations fall into one or more categories, and include dichotomous, nominal, and ordinal scales (Table 7.5). Numerical (quantitative) observations are measured on a continuous scale, and are further classified with a graphic display to assess distribution (histogram, stem-leaf plot, or frequency distribution curve) (16). Numerical data with a symmetric (normal or Gaussian) distribution are evenly placed around a central crest or trough (bell-shaped curve). Numerical data with an asymmetric distribution are skewed (shifted) to one side of the center or contain unusually high or low outlier values. Skewed data can sometimes be normalized with a transformation (e.g., logarithmic).

When summarizing numerical data, the descriptive method varies according to the underlying distribution. Numerical data with a symmetric distribution are best summarized with the mean (Table 7.6) and standard deviation (SD), because 68.3% of the observations fall within the mean ±1 SD, 95.4% within the mean ±2 SD, and 99.7% within the mean ±3 SD. In contrast, asymmetric numerical data are best summarized with the median, because even a single outlier can strongly influence the mean.

TABLE 7.5 MEASUREMENT SCALES FOR DESCRIBING AND ANALYZING DATA

Scale	Definition	Examples
Dichotomous	Classification into either of two mutually exclusive categories	Breast feeding (yes/no), sex (male/female)
Nominal	Classification into unordered qualitative categories	Race, religion, country of origin
Ordinal	Classification into ordered qualitative categories, but with no natural (numerical) distance between their possible values	hearing loss (none, mild, moderate), patient satisfaction (low, medium, high), age group
Numerical	Measurements with a continuous scale, or a large number of discrete ordered values	Temperature, age in years, hearing level in decibels
Numerical (censored)	Measurements on subjects lost to follow-up or in whom a specified event has not yet occurred at the end of a study	Survival rate, recurrence rate, or any time-to-event outcome in a prospective study

For example, if five patients are followed after sinus surgery for 10, 12, 15, 16, and 48 months, the mean duration of follow-up is 20 months, but the median is only 15 months. In this case a single outlier, 48 months, distorts the mean.

A special form of numerical data is called *censored* (Table 7.5). Data are censored when (a) the study direction is prospective, (b) the outcome is time related, and (c) some subjects die, are lost, or have not yet had the outcome when the study ends. Interpreting censored data is called *survival analysis*, because of its use in cancer studies where survival is the outcome of interest (17). For example, a study might report median survival time (by groups, if applicable) and the percent surviving at fixed time periods (e.g., 1, 5, 10 years). Survival analysis permits full utilization of censored observations (e.g., patients with less than 1 year of follow-up), by including them in the analysis up to the time the censoring occurred. Results of cancer studies are often reported with *Kaplan-Meier curves*, which may describe overall survival, disease-free survival, disease-specific survival, or progression-free survival (18). Survival data at the far right of the curves should be interpreted cautiously because fewer patients remain yielding less precise estimates.

Nominal and dichotomous data (Table 7.5) are best described using ratios, proportions, and rates. A ratio is the value obtained by dividing one quantity by another, both of which are separate and distinct. In a tonsillitis treatment study, for example, the ratio of children with clinical resolution after 10 days to those remaining symptomatic might be 80/20 or 4:1. In contrast, a proportion is a type of ratio in which the numerator is included in the denominator. In the previously mentioned study, the proportion with clinical resolution would be 80/100 or 0.80. Alternatively, this could be multiplied by 100 and expressed as a percentage (80%). Rates are similar to proportions except that a multiplier is used (e.g., 1,000 or 100,000) and they are computed over time. For example, a study might report a rate of 110 physician office visits per 100 children per year for upper respiratory infections.

Describing Associations

The odds ratio, relative risk, and rate difference (Table 7.6) are useful for comparing two groups of dichotomous data (19). A study of otitis media and day care might report an *odds ratio* of 1.6, indicating that a child who developed otitis media was 1.6 times more likely to have attended day care than a child with healthy ears. In contrast, a *relative risk* of 1.6 means the incidence of otitis media was 1.6 times higher in children who attended day

TABLE 7.6 DESCRIPTIVE STATISTICS

Descriptive Measure	Definition	When to Use It
Central tendency		
Mean	Arithmetic average	Numerical data that are symmetric
Median	Middle observation; half the values are smaller and half are larger	Ordinal data; numerical data with an asymmetric distribution
Mode(s)	Most frequent value(s)	Nominal data; bimodal distribution
Dispersion		
Range	Largest value minus smallest value	Numerical data without outliers
SD	Spread of data about their mean	Numerical data that are symmetric
95% reference range	Mean ± 1.96 SD	Numerical data that are symmetric
Percentile	Percentage of values that are equal to or below that number	Ordinal data; numerical data with an asymmetric distribution
Interquartile range	Difference between the 25th and 75th percentiles; contains 50% of data	Ordinal data; numerical data with an asymmetric distribution
Outcome		
Survival rate	Proportion of subjects surviving, or with some other outcome, after a time interval (1, 5 y, etc.)	Numerical (censored) data in a prospective study; can be overall, cause specific, or progression free
Odds ratio	Odds of a disease or outcome in subjects with a risk factor divided by odds in controls	Dichotomous data in a retrospective or prospective controlled study
Relative risk	Incidence of a disease or outcome in subjects with a risk factor divided by incidence in controls	Dichotomous data in a prospective controlled study
Rate difference[a]	Event rate in treatment group minus event rate in control group	Compares success or failure rates in clinical trial groups
Correlation coefficient	Degree to which two variables have a linear relationship	Numerical or ordinal data

[a]Also called the absolute risk reduction.

care versus controls who did not. Because the relative risk measures incidence, it should be used only in prospective (cohort) studies. When the frequency of events is low, however, the relative risk and odds ratio are nearly equivalent. An odds ratio or relative risk approaching unity (1.0) would suggest no association between day care and otitis media.

The *rate difference* (also called risk reduction or risk difference) may be expressed in absolute or relative terms. Suppose that initial treatment failures for acute otitis media (AOM) occur in 20% (A) of children managed expectantly but in only 10% (B) of those who receive antibiotics. The *absolute* rate difference, A – B, between groups is only 10% but the *relative* rate difference, (A – B)/B, is 100%. As a measure of clinical importance the absolute rate difference is preferred, because it is easier to interpret and takes into account the baseline risk. Relative rate differences can be deceptive, especially when event rates are low. A new antibiotic may be touted as causing 75% less gastric upset than an established standard (relative rate difference), but we are less likely to be impressed if incidence decreased from 1.00% to 0.25% (absolute rate difference of only 0.75%).

Two groups of ordinal or numerical data are compared with a *correlation coefficient* (Table 7.6). A coefficient (r) from 0 to 0.25 indicates little or no relationship, from 0.26 to 0.50 a fair relationship, from 0.51 to 0.75 a moderate to good relationship, and greater than 0.75 a good to excellent relationship. A perfect linear relationship would yield a coefficient of 1.00. When one variable varies directly with the other, the coefficient is positive; a negative coefficient implies an inverse association. Sometimes the correlation coefficient is squared (R^2) to form the *coefficient of determination*, which estimates the percentage of variability in one measure that is predicted by the other. For example, if hearing levels show an excellent correlation with duration of middle ear fluid ($r = 0.80$), then we could predict 64% (R^2) of the variability in hearing levels by knowing the fluid duration.

A final aspect of descriptive statistics concerns the reporting and interpretation of data from diagnostic tests. Important concepts in reporting test characteristics are defined in Table 7.7. Note that the sensitivity (true positive rate) and specificity (true negative rate) are fixed properties of the test. In contrast, predictive values (positive and negative) vary according to the baseline prevalence of the condition in the population where the test is applied. Last, clinicians should note that likelihood ratios are being used with increasing frequency in the medical literature. Because of space limitations, readers are referred to other sources for additional details about data from diagnostic tests (2).

Analytic Statistics

A single medical study with several groups treated differently will almost always show some difference in group outcomes. If we conclude the groups are different, we may be mistaking chance variations for treatment effects. If we conclude the groups are equivalent, we may have missed

TABLE 7.7 STATISTICAL TERMS ENCOUNTERED WITH DIAGNOSTIC TESTS

Term	Definition
Sensitivity	Ability of the test to correctly identify patients with a condition; calculated as TP/(TP + FN)
Specificity	Ability of the test to correctly identify patients without a condition; calculated as TN/(TN + FP)
Criterion (gold) standard	A method, procedure, or measurement that is widely accepted as being the best available; used as a comparison for new methods
Predictive value of a positive test	Likelihood that a patient with a positive test will actually have a condition; calculated as TP/(TP + FP)
Predictive value of a negative test	Likelihood that a patient with a negative test will actually not have a condition; calculated as TN/(TN + FN)
Likelihood ratio for a positive test	Odds of a positive test in patients with the condition vs. a positive test in patients without the condition; calculated as sensitivity/FP
Receiver operating characteristic curve	Graphic display of how well a test with a continuous outcome can discriminate among patients with and without a condition; the *y*-axis plots the TP rate and the *x*-axis plots the FP rate

FN, false negative; FP, false positive; TN, true negative; TP, true positive.

TABLE 7.8 STATISTICAL TERMS ENCOUNTERED WHEN TESTING HYPOTHESES

Term	Definition
Hypothesis	A supposition, arrived at from observation or reflection, that leads to predictions which can be tested and refuted
Null hypothesis	Results observed in a study, experiment, or test are no different from what might have occurred due to chance alone
Statistical test	Procedure used to reject or accept a null hypothesis; statistical tests may be parametric or nonparametric (distribution free)
P value	Probability of seeing the observed difference (association) or greater, just by chance, if the null hypothesis is true
Type I (alpha) error	Rejecting a true null hypothesis; declaring that a difference exists when in fact it does not; probability of a type I error is the *P* value
Type II (beta) error	Accepting a false null hypothesis; declaring that a difference does not exist when in fact it does
Power	Probability that the null hypothesis will be rejected if it is indeed false; mathematically, power is 1.00 minus type II error

a true difference. In statistical lingo (Table 7.8), we begin with some testable *hypothesis* about the groups under study, such as "Gibberish levels in Group A differ from those in Group B." Rather than keep it simple, we now invert this to form a *null hypothesis*: "Gibberish levels in Group A are equal to those in Group B." Next we fire up a computer, enter the gibberish levels for the subjects in both groups, choose an appropriate statistical test, and wait for the omnipotent *P* value to emerge.

The *P value* tells us the probability making a *type I error*: rejecting a true null hypothesis. In other words, if $P = 0.10$ we have a 10% chance of being wrong (false positive) when we declare Group A differs from Group B. Alternatively, there is a 10% probability that the difference in gibberish levels is explainable by random error—we can't be certain that uncertainty isn't the cause. Uncertainty is present in all data, because of the inherent variability in biologic systems and our ability to assess them in a reproducible fashion (20). Since we can never avoid uncertainty entirely in measurements and observations, we instead estimate the probability (*P* value) that observed results are consistent with unavoidable random variations or fluctuations.

In medicine, $P < 0.05$ is generally considered low enough to safely reject the null hypothesis. Recall, however, that when P approaches 0.05 a researcher who accepts a "significant" result as real will be wrong 5% of the time (type I error) (21). Only *P* values *much smaller than 0.05* provide strong evidence against the null hypothesis. Conversely, when $P > 0.05$ we accept the null hypothesis of equivalent gibberish levels. Nonetheless, we may be making a *type II error* (false negative) because we studied too few subjects to overcome the random fluctuations that inevitably exist. Type II error rates of up to 20% are generally acceptable, which is equal to statistical power of 80% or higher (Table 7.8).

As an example of statistical inference, consider a prospective study to see if ice cream causes sneezing. Suppose that 80% of ice cream eaters (16/20) begin sneezing but only 50% of controls (10/20). If we infer that, based on these results in 40 specific patients, ice cream causes sneezing *in general*, what is our probability of being wrong (type I error)? Because $P = 0.10$ (Fisher's exact test) there is a 10% chance of type I error, so we are reluctant to associate ice cream with sneezing based on this single study: the strength of evidence *against* the null hypothesis is simply too much to ignore.

Intuitively, however, a rate difference (absolute) of 30% seems meaningful, so what is our chance of being wrong when concluding it is not? The probability of a type II error is 48% (same as saying 52% power), which means we may indeed be wrong in accepting the null hypothesis. Now suppose we repeat this study with twice as many subjects, and 80% of ice cream eaters (32/40) start sneezing compared with 50% of controls (20/40). The rate difference is still 30%, but now $P = 0.01$. Increasing the sample size allowed us to exclude chance variations as responsible for the observed findings; the strength of evidence against the null hypothesis is now much higher.

Studies with "negative" findings should be interpreted by their statistical power, not by *P* values. There is a big difference between *observing* nothing in a study and *proving* that nothing really happened. Most often, not enough patients were studied to offer a reasonable chance of not missing differences of up to 50% between groups. Even randomized trials in otolaryngology journals, with a median samples size of only about 50 patients, suffer from low statistical power and potential "false negative" results (15). An ideal study has high power, making it likely to detect differences that exist. If no differences are detected, then the researcher can conclude with reasonable confidence that none exists in reality.

Higher power is generally achieved by increasing sample size. Calculating sample size before beginning a study ensures that the planned number of observations will offer a reasonable chance (power) of obtaining a clear answer at the end (22). The basic ingredients needed to calculate sample size include the smallest difference that must be detected between the groups (minimal clinically important difference), the variability (SD) of this difference (if the measurement scale is numerical), the limit of tolerance for a type I error (typically 5% or 1%), and the limit of tolerance for a type II error (typically 20% or 10%) (23).

Statistical Significance versus Clinical Importance

The next logical question after "Is there a difference?" (statistical significance) is "How big a difference is there?" (*clinical importance*). For example, a randomized trial of nonsevere AOM found amoxicillin superior to placebo as initial treatment ($P = 0.009$). Before we accept the authors' recommendation for routine amoxicillin therapy, let's look more closely at the magnitude of clinical effect. Initial treatment success occurred in 96% of amoxicillin-treated children versus 92% of controls, yielding a 4% rate difference (96% minus 92%) favoring drug therapy. Is this clinically important? Although statistically significant, the rate difference seems small; intuitively we suspect that many children will need treatment to benefit only a few. The next few paragraphs reveal exactly how many.

Statistically significant results must be accompanied by a measure of *effect size*, which reflects the magnitude of difference between groups (2,19). Otherwise, findings with minimal clinical importance may become statistically significant when a large number of subjects are studied. In the above example, the 4% difference in success rates was highly statistically significant because over 1,000 episodes of otitis media were analyzed. Large numbers provide high precision (repeatability), which in turn reduces the likelihood of a type I error. The final result is a hypnotically tiny *P* value, which may reflect a clinical difference of trivial importance. A *P* value of 0.000001 with a rate difference of 5% is much less clinically relevant than a *P* value of 0.01 with an absolute rate difference of 25%.

A useful measure of effect size is the *number needed to treat* (NNT), which is simply the reciprocal of the absolute rate difference (or risk reduction) (2). The NNT reflects the amount of clinical effort that must be expended to achieve one additional treatment success, and is easily calculated by dividing 100 by the absolute rate difference. For example, in the study cited above, the NNT would be 25 (100% divided by 4%). Consequently, we must treat 25 children on average with amoxicillin to increase the resolution rate of nonsevere AOM by one child above what would occur from placebo alone. What constitutes an important NNT magnitude depends on disease severity and treatment side effects. An NNT of 25 might be unimpressive for AOM, but headline news for cancer survival.

Similar to the NNT, we can also calculate the *number needed to harm* (NNH). For example, if a new antibiotic causes diarrhea in 20% of patients, the NNH is 5 (100/20). Although this drug may have other beneficial effects, they would need to be significant to justify one new case of diarrhea for every five people who use it. For example, oral antibiotics and steroids have short-term benefits for otitis media with effusion (NNTs of 4 to 7), but are not recommended in national guidelines because of adverse effects. Unfortunately, only about 40% of randomized trials adequately report clinical adverse events (12).

Relative measures of effect size (relative risk, odds ratio, relative rate difference) provide limited information in clinical trials because they do not reflect changes in baseline risk. For example, a relative risk of 50% may mean that the treatment decreases the chance of an unfavorable outcome from 4% to 2% or from 60% to 30%. Conversely, the absolute rate difference and NNT reflect both the baseline risk and degree of relative risk reduction. In the AOM trial above, the absolute decrease in treatment failures because of amoxicillin therapy was only 4% using the rate difference but an impressive 50% using the relative risk! Not surprisingly, most clinicians rate the effectiveness of an intervention lower when presented in absolute terms rather than using relative measures. Since published trials rarely provide an NNT or rate difference, readers will often have to calculate it on their own based on the absolute difference in group outcomes (24).

Question 3: Are the Results Valid within the Study?

Internal Validity

A critical aspect of understanding data is determining the validity of the research, which is a two-step process: deciding if (a) the results are and conclusions are credible for the study sample (e.g., within the study) and (b) the results and conclusions can be generalized and applied to others (e.g., outside the study sample) (3). These two questions are the topics of this and the following section, and address the issues of internal and external validity, respectively.

When a study is internally valid we conclude that the results obtained are due only (or at least, primarily) to the effect under study and are free of substantial distortions caused by improper study design, measurement errors, sloppy data collection, flawed outcome assessment, or inappropriate statistical analysis, Principles of study design, describing data, and determining significance (statistical and clinical) are covered in earlier sections and are not discussed again. Instead, we focus on bias and selecting the right statistical test for analyzing data.

Valid measurements are unbiased (free of systematic error) and reflect what they intend to measure. If a faulty audiometer consistently gives readings that are off by 15 decibels, the readings are precise (repeatable), but inaccurate (biased). Bias is not limited to faulty

instruments but may also be introduced unconsciously by study investigators (Table 7.4) through the power of suggestion (placebo effect), by using fancy equipment in impressive settings (halo effect), preferentially assigning patients with the best prognosis to the treatment group (allocation bias), or by favoring the treatment group when assessing outcomes and analyzing the data (ascertainment bias).

Questionnaires and quality of life surveys are particularly prone to bias if they have not been assessed for reliability, validity, and responsiveness (25). Unless the authors used a "validated" measure the results are suspect, but problems may also arise if a validated instrument is used in an intended way. For example, some surveys are developed specifically to compare individuals at a point in time (discriminative surveys) and may or may not be valid when used to measure change in status within individuals before and after intervention (evaluative surveys). Additional bias may arise in survey research related to sampling the population, administering the questionnaire, and managing the resultant data (26).

Bias affects not only data measurements but can creep into a study at any stage of design, conduct, analysis, or publication (7). For example, patients often have illnesses or comorbid conditions unrelated to the disease under study that can impact diagnosis, treatment, or outcomes. When these factors are significant, adjustments for comorbidity are needed to avoid confounding.

Choosing the Right Statistical Test

All statistical tests have a common purpose (to measure error), which cannot be fulfilled unless the right test is used for the data being analyzed. To determine if the right statistical test was used you must first check (a) whether the observations come from independent or related samples, (b) whether the purpose is to compare groups or to associate an outcome with one or more predictor variables, and (c) the measurement scale of the variables. Tables 7.9 and 7.10 can then be used to find the right statistical test for valid analysis.

Two events are independent if the occurrence of one is in no way predictable from the occurrence of the other. A common example of *independent samples* is two or more parallel (concurrent) groups in a clinical trial or observational study. Conversely, *related samples* include paired organ studies, subjects matched by age and sex, and repeated measures on the same subjects (e.g., before and after treatment). Sometimes, the situation is unclear, as when ears (not patients) are the unit of analysis. There are often large differences in left versus right Eustachian tube function, which is more related to a given ear than a specific child. Therefore, to analyze ears as independent samples (which often occurs to inflate sample size) may bias results.

The tests in Tables 7.9 and 7.10 labeled as "parametric" assume an underlying symmetric distribution for the data or a relatively large sample size (about 20 or more observations per group). A statistical test, the Kolmogorov-Smirnov

TABLE 7.9 STATISTICAL TESTS FOR INDEPENDENT SAMPLES

Situation	Parametric Test	Nonparametric Test
Comparing two groups of data		
Numerical scale	*t*-Test	Mann Whitney *U* test,[a] median test
Numerical (censored) scale	Mantel-Haenszel life table	Wilcoxon, Logrank, Mantel-Cox
Ordinal scale	—	Mann Whitney *U* test,[a] median test, chi-squared test for trend
Nominal scale	—	Chi-squared, log-likelihood ratio
Dichotomous scale	—	Chi-squared, Fisher's exact test, odds ratio, relative risk
Comparing three or more groups of data		
Numerical scale	One-way ANOVA	Kruskal-Wallis ANOVA
Ordinal scale	—	Kruskal-Wallis ANOVA, chi-squared test for trend
Dichotomous or nominal scale	—	Chi-squared, log-likelihood ratio
Associating an outcome with predictor variables		
Numerical outcome, one predictor	Pearson correlation	Spearman rank correlation
Numerical outcome, two or more predictor variables	Multiple linear regression, two-way ANOVA	—
Numerical (censored) outcome	Proportional hazards (Cox) regression	—
Dichotomous outcome	Discriminant analysis	Multiple logistic regression
Nominal or ordinal outcome	Discriminant analysis	Log-linear model

ANOVA, analysis of variance.
[a]The Mann Whitney *U* test is equivalent to the Wilcoxon rank-sum test.

TABLE 7.10 STATISTICAL TESTS FOR RELATED (MATCHED, PAIRED, OR REPEATED) SAMPLES

Situation	Parametric Test	Nonparametric Test
Comparing two groups of data		
Dichotomous scale	—	McNemar's test
Ordinal scale	—	Sign test, Wilcoxon signed rank test
Numerical scale	Paired *t*-test	Sign test, Wilcoxon signed rank test
Comparing three or more groups of data		
Dichotomous scale	—	Cochran *Q* test, Mantel-Haenszel chi-squared
Ordinal scale	—	Friedman ANOVA
Numerical scale	Repeated measures ANOVA	Friedman ANOVA

ANOVA, analysis of variance.

test, can be used to measure the "normalcy" of numerical data ($P > 0.05$ indicates that parametric methods are appropriate) (16). If the data are sparse, asymmetric, or ordinal, then a *nonparametric test* must be used. Nonparametric tests rank the observations in order of magnitude, and then compare the ranks not the measurements themselves. Compared with traditional tests, however, nonparametric tests lack power and offer less meaningful estimates of effect size (27).

Another feature of Tables 7.9 and 7.10 is that special tests are required to compare three or more groups of data. Recall that every "significant" statistical test has some possibility of type I error (false positive) defined by the *P* value. If we study three groups and analyze the data with three pairwise comparisons (A vs. B, B vs. C, A vs. C) the combined type I error rate is 14% assuming a 5% rate for each individual comparison. Studying four groups yields six possible pairwise comparisons with a combined error rate of 27%. Analysis of variance avoids this problem by providing a single overall test of differences between groups or treatments (28). Special techniques allow multiple comparisons between groups.

Here are some brief examples to illustrate statistical test selection. Assume we are comparing patient satisfaction for two different treatments using a 5-point outcome scale (poor, fair, good, very good, excellent). According to Table 7.9, the correct test for two groups of independent ordinal data is the Mann Whitney *U* test (Wilcoxon rank-sum is equivalent). If the investigators instead used a *t*-test, results might be invalid. Now suppose we wish to compare hearing levels (numerical scale) before and after stapedectomy for 50 patients. Using Table 7.10 (we are dealing with a matched sample) we note a paired *t*-test or Wilcoxon signed-rank test could be used. Finally, if we wanted to associate survival after tumor resection (a censored outcome) with several predictor variables (e.g., age, type of surgery, comorbidity, TMN stage) we would use proportional hazards (Cox) regression (Table 7.9).

Proper selection of statistical tests can never compensate for flaws in study design. Suppose we measure intelligence quotient (IQ) in 200 children before and after tympanostomy tubes, and find a mean IQ increase of 10 points per child. We *can* conclude that the improvement is unlikely to be fortuitous ($P = 0.01$, matched *t*-test), but we *cannot* be certain what caused it. Stated differently, improvement *after* surgery (or any intervention) does not necessarily imply improvement *because* of surgery. More likely the change in IQ was not a real increase, but bias caused by learning from the first test. Without a control group, we cannot determine what part of the change (if any) was caused by tubes.

A fundamental assumption underlying all statistical tests is that the hypothesis under study was fully developed before the data were examined in any way. Consider the Texas sharpshooter who shoots an arrow at a barn wall, then meticulously draws a bulls eye around it. When hypotheses (or bulls eyes) are formulated *post hoc*—after even the briefest glance at the data—the basis for probability statements (or shooting accuracy) is invalidated. All statistical tests are based on assumptions about the distribution, variability, and relationships of the underlying data that invalidate results if violated. Specific assumptions apply to comparing means, correlation, and regression.

Last, an internally valid study not only uses the right statistical test for the data but also reports the results in a clear, coherent, and complete manner. Since proper reporting varies according to the data format (Table 7.5) and specific test used (Tables 7.9 and 7.10) the reader is referred elsewhere for details (29), which should generally appear in one or more well-constructed tables in the research manuscript.

Question 4: Are the Results Valid Outside the Study?

Having first determined that the investigator's conclusions correctly describe what happened *inside* the study (Question 3), the next task is to determine if they can

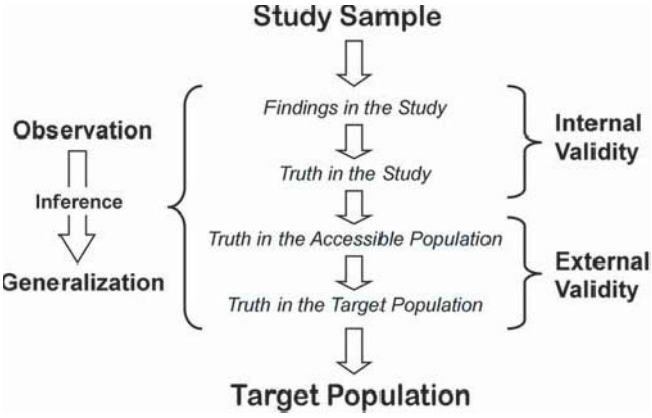


Figure 7.2 Flow chart showing the relationships of validity, sampling, and inference. Not all internally valid studies are externally valid and vice versa. See Table 7.11 for definitions of individual terms.

be applied (generalized) to the universe *outside* the study (Fig. 7.2). Unfortunately, not all well-conducted, internally valid studies have *external validity* (generalizability or applicability). This distinction is nontrivial, because the key question from the clinician's viewpoint is "Can I apply the results of this study to the patients I see in my practice?" For the answer to be "yes," the sampling method must be sound, the subjects studied must be representative of the target population, and the sample size must be large enough to instill confidence in the results.

Sampling a Population

When we interpret medical data, we ultimately seek to make *inferences* about some target population based on results in a smaller study sample (Table 7.11). Rarely is it possible to study every subject with the condition of interest. Nor is it necessary—statistics allow us to generalize from the few to the many, provided that the few are *representative* of the many. However, representative samples rarely arise from divine providence. Review carefully the inclusion and exclusion criteria (check the article's methods section) to be sure that the subjects studied are representative of those in whom you wish to apply the results. A study with vague subject selection criteria may yield fascinating results, but we have no way of knowing to whom they apply.

Consider, for example, a randomized trial of early versus delayed tympanostomy tubes for persistent otitis media that concluded early tube insertion did not improve developmental outcomes at 3 years of age. To whom do these results apply? The 429 randomized children with persistent effusion were culled from a birth cohort of 6,350 healthy infants examined at least monthly for 3 years; if not in the study many of these children would never have received tubes because their middle-ear effusion was transient, asymptomatic, or unilateral. In contrast, study participants received tubes based solely on cumulative effusion prevalence (identified with regular, intensive screening), not based on hearing levels or other otitis media signs and symptoms. Therefore, the ability to generalize these results beyond asymptomatic, otherwise healthy infants identified with aggressive screening is unknown.

Having determined that the target population and subject selection criteria are meaningful, the next step in judging external validity is to assess how the study sample was selected. Investigators typically have access to only a small subset of the target population because of geographic, temporal, or demographic constraints. When they choose an even smaller subset of this *accessible population* to study (Table 7.11; Fig. 7.2), the method of choosing (sampling method) affects their ability to make inferences about the

TABLE 7.11 STATISTICAL TERMS RELATED TO SAMPLING AND VALIDITY

Term	Definition
Target population	Entire collection of items, subjects, patients, observations, etc., about which we want to make inferences; defined by the selection criteria (inclusion and exclusion criteria) for the study
Accessible population	Subset of the target population that is accessible for study, generally because of geographic or temporal considerations
Study sample	Subset of the accessible population that is chosen for study
Sampling method	Process of choosing the study sample from the larger accessible population
Selection bias	Error caused by systematic differences between a study sample and target population; examples include studies on volunteers and those conducted in clinics or tertiary care settings
Inference	Developing a generalization based on data from a study sample, usually with calculated degrees of uncertainty
Internal study validity	Degree to which conclusions drawn from a study are valid for the study sample; results from proper study design, unbiased measurements, and sound statistical analysis
External study validity (generalizability)	Degree to which conclusions drawn from a study are valid for a target population (beyond the subjects in the study); results from representative sampling and appropriate selection criteria

original target population. Unless an appropriate sampling method is used, the study sample may differ systematically from the intended target population (selection bias).

The best sampling method is to randomly select members of the accessible population. Bias is minimized because all subjects have a known (and equal) probability of selection, but random sampling is rarely feasible in most clinical research studies. Fortunately, a consecutive or systematic sample offers a relatively good approximation. Consecutive samples are common, and include all subjects over a specified time interval or until a specified sample size is reached. Systematic samples are obtained using some simple, systematic rule, such as day of week, date of birth, or first letter of last name. The worst sampling method occurs when subjects are chosen based on convenience or subjective judgments about eligibility by the investigators. Convenience (grab) sampling should be assumed when no other method is specified.

Random allocation of patients to treatment groups differs from random sampling of a population. Randomization improves internal validity by reducing allocation bias (Table 7.4), but has no impact on external validity. Most randomized trials, however, have rigid and restrictive subject selection criteria that tend to limit generalizability compared to less restrictive outcomes-type studies.

Precision and Confidence Intervals

Another component of external validity is *precision*, which reflects the degree of variability in the observations. Variability (precision) must be dealt with when interpreting data, unless the results are meant to apply only to the particular group of patients, animals, cell cultures, DNA strands, etc., in which the observations were initially made. Recognizing this limitation, we call each of the descriptive measures in Table 7.6 a *point estimate*, specific to the data that generated it. In medicine, however, we seek to pass from observations to generalizations, from point estimates to estimates about other populations. When this process occurs with calculated degrees of uncertainty, we call it *inference*.

Here's a brief example of clinical inference. After administering Echinacea to five patients with Ménière disease you remark to a colleague that four had excellent relief. She asks, "How confident are you of your results?" "Quite confident," you reply, "there were 5 patients, 4 got better, and that's 80%." "Maybe I wasn't clear," she interjects, "how confident are you that 80% of patients with Ménière disease you see in the next few months will respond favorably, or that 80% of similar patients in my practice will do well with Echinacea?" "In other words," she continues, "what can you *infer* about the *real* effect of Echinacea from experience with only 5 patients?" Hesitatingly you retort "I'm pretty confident about that number 80%, but maybe I'll have to see a few more patients to be sure."

The real issue, of course, is that a sample of only five patients offers low *precision* (repeatability). How likely is it that the same results would be found if five new patients were studied? Actually, we can state with 95% confidence that four successes out of five in a *single* sample is consistent with a success rate of 28% to 99% in *other* samples of five patients from the accessible Ménière population. This *95% confidence interval* (CI) may be calculated manually, with a statistical program or with numerous applications and calculators accessible on the internet (23).

What is the best way to conceptualize and understand confidence intervals? Simply stated, a CI offers a *zone of compatibility* with the data (30). In the Ménière example above, a 95% CI of 28% to 99% tells us that we do not know much about the real outcome of therapy, because a single study with four patients is compatible with a very broad range of results. Stated differently, the results lack precision; the range of values that are considered plausible for the population is too large to really know what to expect in the future (31). In statistical terms, a CI tells us the range of *sample means* consistent with the observed data, but this type of explanation rarely helps clinicians in understanding, or communicating, the concept (32).

Precision may be increased (uncertainty may be decreased) by using a more reproducible measure, by increasing the number of observations (sample size), or by decreasing the variability among the observations. The most common method is to increase the sample size, because we can rarely reduce the variability inherent in the subjects we study. If 50 patients (instead of 5) received Echinacea and 40 had symptomatic relief, the 95% CI for success narrows to between 66% and 90%. The point estimate, however, remains 80% (40/50). Although we are more confident in our results following this larger trial (e.g., the zone of compatibility is tighter), we cannot say anything about the *efficacy* of Echinacea without an untreated control group for comparison.

Realizing that uncertainty can never completely be avoided, we use statistics to estimate precision. Thus, when data are described using the summary measures listed in Table 7.6, a corresponding 95% CI should accompany each point estimate. When the study reports "positive" findings ($P < 0.05$), the *lower* limit of the interval should be scrutinized; if it is less than what you consider to be a clinically important effect size then precision is inadequate. When the study reports "negative" findings ($P > 0.05$), the *upper* limit of the interval should be checked; if it is consistent with a clinically important effect size then statistical power is inadequate.

As an example of CI interpretation, consider an evidence report on AOM that found an absolute rate difference of 12.3% (95% CI: 2.8% to 21.8%) favoring amoxicillin over placebo. Since the lower limit of the CI is 2.8%, which may not be clinically important, the precision is less than optimal. The 95% CI for the NNT is easily calculated (see above) as 4.6 to 35.7, which again shows the results are consistent with a need to treat up to 36 children to benefit one. The findings suggest a significant benefit of antibiotics

for some children with AOM (95% CI does not contain zero), but the imprecision and modest NNT argue for selective and judicious therapy.

When a study reports "no significant difference" the CI can help determine if something might have been missed (low power). For example, a meta-analysis of streptococcal pharyngitis concludes that short-course antibiotic (5 to 7 days) is equivalent to full-course (10 days) because the odds ratio for treatment failure is 1.00 (95% CI: 0.50 to 1.50). Whereas the point estimate of 1.0 suggests equivalency, the 95% CI is consistent with sample means from 0.50 (half as many failures with short-course therapy) up to 1.50 (twice as many failures with short-course therapy). Thus, we have insufficient data to conclude with reasonable certainty that short-course therapy is comparable to full course.

The examples above clarify why describing study results as simply statistically "significant" or "nonsignificant" is unacceptable (33). A *P* value measures strength of evidence against the null hypothesis, but offers no information on effect size. A *P* value approaching 0.05 often has precision that is too low to exclude a trivial effect and a "nonsignificant" *P* value often has an associated 95% CI that contains clinically important sample means. Studies with narrow CIs have high precision, and are most meaningful regardless of the *P* values. Conversely, studies with broad CIs require careful scrutiny.

Question 5: Are the Results Strong and Consistent?

The first step in assessing strength and consistency is asking "Do the results make sense?" Significant findings that are biologically implausible, or that are inconsistent with other known studies, can often be explained by hidden biases or design flaws, which were initially unsuspected. Improbable results can become statistically significant through biased data collection, natural history, placebo effects, unidentified confounding variables, or improper statistical analysis. A study with design flaws or improper statistical analysis has low internal validity and should be reanalyzed or discarded.

At the next level of integration, we compare the study design that produced the current data with the design of other published studies. The *level of evidence* generally increases as we progress from observational studies to controlled experiments (randomized trials) (2). For example, if several randomized efficacy trials have already been published about the topic of interest, an uncontrolled study is unlikely to provide any new insights. Conversely, for populations in which randomization is unethical, a well-designed cohort study may be the best attainable evidence. When a certain level of evidence has been accumulated, causation may be inferred. *Causation* is an epidemiologic concept based on the consistency, strength, specificity, and temporal relationship of the association between a factor and a particular disease or outcome (34).

When assessing the level of evidence, readers must realize that certain study designs are more suited than others to answer specific clinical questions (Table 7.12) (35). *Therapy* questions, which seek to determine the effect of different treatments on outcomes, are best answered with randomized controlled trials, which ideally have been synthesized using systematic review. Questions about *diagnostic tests* are best answered using cross-sectional designs in which patients with and without the condition of interest undergo both the new diagnostic test and an established, consistently applied, gold (criterion) standard. *Prognosis* questions are addressed by observing groups of patients with and without baseline risk factors over time in a prospective cohort design. Last, if the study focus is about *prevalence* or *incidence*, a local or current random sample survey (or census) is best.

A single study—no matter how elegant or seductive—is rarely definitive. Science is a cumulative process that requires a large body of consistent and reproducible evidence before conclusions can be formed. For this reason, achieving the highest level of evidence (Table 7.12) often requires a *systematic* review of available evidence, using explicit and reproducible criteria to assemble, appraise, and combine articles with a minimum of bias (36). Meta-analysis is a form of systematic review that uses statistical techniques to derive quantitative estimates of the magnitude of treatment effects and their associate precision (37). Valid systematic reviews (and meta-analyses) address focused questions, assess the quality and combinability of articles, provide graphic and numeric summaries, and can be generalized to a meaningful target population. They also contain a flow diagram showing the fate of articles as they pass through different phases of the review process, including identification, screening, eligibility, and inclusion (38).

Clinical practice guidelines are encountered with increasing frequency in the otolaryngology literature and may be defined as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" (39). Guidelines, therefore, build upon systematic reviews by incorporating values, preferences, and recommendation strengths, ideally based upon explicit and transparent processes that represent all stakeholders, including consumers (40). The best guidelines contain a limited number of actionable recommendations supported by distinct evidence profiles, such as the tonsillectomy guideline released by the American Academy of Otolaryngology—Head and Neck Surgery in 2011 (41).

In summary, all scientific data are plagued by errors, biases, and uncertainties. Statistical analysis minimizes sampling error and appropriate study design minimizes bias. Uncertainty is a more difficult problem, but can be partially reduced with humility and 95% CIs. Glimpses of association and causation emerge as the level of evidence increases and a critical mass of high-quality, combinable studies is achieved. A sufficient evidence base facilitates clinical practice guidelines that enable optimal patient care

TABLE 7.12 LEVELS OF EVIDENCE[a]

Level[b]	Treatment Benefits	Prevalence or Incidence	Prognosis	Diagnostic Test Assessment
1	Systematic review of randomized trials or *n*-of-1 trials	Local and current random sample surveys (or censuses)	Systematic review of inception cohort studies[c]	Systematic review of cross-sectional studies with consistently applied reference standard and blinding
2	Randomized trial or observational study with dramatic effect	Systematic review of surveys that allow matching to local circumstances	Inception cohort studies[c]	Individual cross-sectional studies with consistently applied reference standard and blinding
3	Nonrandomized controlled cohort or follow-up study	Local nonrandom sample	Cohort study or control arm of randomized trial	Nonconsecutive studies, or studies without consistently applied reference standards
4	Case-series, case–control studies, or historically controlled studies	Case-series	Case-series or case–control studies, or poor quality prognostic study	Case–control studies, or studies with a poor or nonindependent reference standard
5	Mechanism-based reasoning from physiology, bench research, first principles, or expert opinion			

[a]Adapted from Howick J, Chalmers I, Glasziou P, et al. Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence. Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653. Accessed August 1, 2011.
[b]Level may be graded down based on study quality, imprecision, indirectness, inconsistency between studies, or because the absolute effect size is very small; level may be graded up if there is a large or very large effect size.
[c]Inception cohort: group of individuals identified for subsequent study at an early, uniform point in the course of the specified health condition, or before the condition develops.

by making recommendations based on levels of evidence and harm–benefit ratios. Clinicians can best understand and benefit from this dynamic flow of ideas through an enlightened approach to understanding data and interpreting the medical literature.

HIGHLIGHTS

- The peer-reviewed medical literature generally serves science, not medical practice; critical appraisal is needed to locate clinically relevant and valid evidence
- Critical appraisal begins with the principles outlined in Tables 7.1 and 7.2, with emphasis on the magnitude, clinical relevance, and generalizability of the main results
- Study design has a profound impact on validity; answer the questions in Table 7.3 before attempting to interpret or apply results
- Improvement after therapy does not always equate with improvement because of therapy; unless the study is controlled and randomized, bias, chance, or natural history (Table 7.4) may account for apparent "efficacy" of the intervention
- Statistical analysis involves describing results, selecting the right test based on the nature of the variables and questions being asked, and addressing clinical importance (Tables 7.5 to 7.10)
- A properly performed and analyzed study has internal validity, but the ability to generalize results beyond the study (external validity) depends on sampling and subject selection criteria
- No amount of statistical wizardry can compensate for flawed study design, poorly collected data, and biased outcome assessment; *P* values and CIs deal with sampling error, not bias

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8 Outcomes Research and Evidence-Based Medicine

Michael G. Stewart

INTRODUCTION AND HISTORY

Outcomes research can be defined as the scientific study of the outcomes of disease therapies used for a particular disease, condition, or illness (1). While all clinical research measures some type of outcome, such as mortality, morbidity, or some other objective measure, in "outcomes research," the patient's perception of their outcome is assessed.

Historically, the movement toward outcomes-based research was started by Dr. Paul Ellwood, who in the 1980s suggested that in the future physicians would assess outcomes by measuring what the patient experienced (2). Subsequently, tools to assess these outcomes were developed and applied across many diseases. However, outcomes research also includes other types of studies in addition to patient-based outcomes studies. Today, outcomes researchers study all aspects of the health care system—from the status of the patient or population at entry, to the organization, delivery, regulation and financing of the health care system, to the status of the patient or population after treatment.

To be inclusive of other aspects of health services research, some have divided outcomes research into *record-based* outcomes research and *patient-based* outcomes research. Examples of these different types of studies are shown in Table 8.1.

DEFINITION OF OUTCOME

Traditional clinical outcomes, such as survival and complication rate, are still assessed in outcomes research. However, emphasis is placed on *expanded* measures of outcome, which primarily are assessed from the patient's perspective. These expanded outcomes include quality of life, global health status, and disease-specific health status. In addition, assessment of other factors that might impact outcome, such as comorbid disease, should also be assessed. Outcomes assessment is discussed in more detail later in the chapter.

Another significant difference between traditional clinical research and outcomes research is that outcomes studies are often performed in "real-world" settings using larger groups of patients versus traditional clinical research where typically smaller groups of patients are studied under very controlled environments.

TYPES OF STUDIES

Prospective, retrospective, or cross-sectional study designs can be used in outcomes research. However, many outcomes studies use an *observational* prospective design, where outcomes are assessed after diverse treatments—rather than an *experimental* prospective design, where treatments are carefully controlled or randomized. The differences between these study designs are an important point for discussion.

In experimental or controlled trials, particularly randomized trials, the ideal design uses two groups of patients that are nearly identical in every aspect—except the treatment received. So therefore, any difference in outcome between groups must be due only to the different treatments, since otherwise the groups were the same. Of course, acquiring patient groups that are actually identical is rarely achieved, but nevertheless, that is the basis behind the rigorous design and methodology of controlled trials. In addition, to account for the inherent differences between treatment groups, the randomization process should theoretically distribute those differences (say, in demographics or disease severity) equally between the two groups. Carefully controlled experimental studies can be said to measure the *efficacy* of treatment, under ideal circumstances. These studies usually yield very reliable results concerning the effects of treatment—in the group that was studied.

TABLE 8.1 TYPES OF OUTCOMES RESEARCH

Record-based outcomes research

- Meta-analysis
- Appropriateness research
- Reviews of administrative databases
- Population-based studies

Patient-based outcomes research

- Development of quality of life and health status instruments
- Development of disease severity stratification systems
- Longitudinal outcomes studies
  - Prospective
  - Retrospective
  - Observational

Modified from Rosenfeld RM, Bluestone C, eds. *Evidence-based otitis media*. Hamilton, ON: BC Decker, Inc., 1999:51–60, with permission.

However, there are questions about the generalizability of results from rigorously controlled trials to larger populations of patients with a disease because the larger group of patients will not be so carefully controlled and homogeneous. In addition, patient compliance and other factors may lead to different results than in tightly controlled trials. Furthermore, clinical trials are very expensive to perform, especially when considered from the standpoint of cost per patient studied.

Observational study designs are commonly used in outcomes research. All patients with a disease are included, and they are studied in the actual setting in which they receive their health care. This naturally introduces many other factors, which may impact outcome after treatment, including potential selection bias for different treatments. However, many would argue that results from large-scale outcome studies are more applicable to the general population because of their setting and scope. Studies that assess the actual ("real world") results of treatment are said to measure the *effectiveness* of treatment versus *efficacy* measured from controlled trials (3). Furthermore, in addition to their "real-world" setting, the expanded outcome measured (quality of life, etc.) might be more relevant and important to patients than other clinical or biologic outcomes.

STEPS IN PERFORMING OUTCOMES RESEARCH

There are several basic steps involved in performing patient-based outcomes research (3–5). The fundamental steps are as follows: (a) identify and define the disease of interest, (b) create a staging system (clinical-severity index) for disease severity, (c) identify comorbid conditions, and (d) establish the outcomes to be measured (4). Studies can perform only one of those steps or some or all. Therefore, development and validation of an outcomes instrument is one type of outcomes research, and identification of comorbid conditions is another type. Each step is discussed in more detail below.

Define the Disease of Interest

This may be a straightforward step if the disease has clear and widely agreed upon diagnostic criteria. However, many diseases are difficult to rigorously define, such as gastroesophageal reflux or chronic rhinosinusitis, and research may be needed to develop clear reproducible diagnostic criteria.

Create a Staging System or Clinical-Severity Index

Grouping or stratification by disease severity is important in all types of clinical research. However, it is particularly important in outcomes research. This is because large numbers of patients may be studied without strict entry or exclusion criteria. Patients with more severe disease may receive more (or less) aggressive treatment, so it is therefore important to statistically adjust for disease severity when evaluating outcomes.

Staging systems already exist for many diseases, for example, the TNM staging system for cancer. It is important to distinguish between staging systems that are descriptive and systems that are prognostic. Descriptive staging systems simply group together patients who have similar characteristics. Prognostic systems are designed to predict an outcome; for example, the TNM staging system is designed to predict 5-year survival. In general, staging systems used for outcomes research should be prognostic (3). However, even if a prognostic staging system already exists, it may not contain all the important variables that predict outcome (5).

To develop a prognostic staging system, the researcher should first define the outcome of interest to be predicted by the staging system, which is defined as the dependent variable. Next, identify a group of variables that might predict outcome—those are the independent variables. Potential independent variables can be identified from prior literature, a prospective study, or expert opinion. Then next, perform a prospective study, identifying a heterogeneous group of subjects that is likely to contain patients with mild, moderate, and severe disease. In that group, measure the presence of all potential predictor variables and the outcomes after treatment.

Then, using data on both the outcome of interest and the presence of predictor variables, perform a multivariate analysis to identify which predictor variables actually impact outcome. Multivariate analysis is important in clinical studies because several different variables usually exert effects on each other, so it is preferable to study the effects of a large group of variables at the same time while controlling for the effects of the other potentially important variables.

Multivariate regression (linear or logistic) is one option for analysis; however, there are other options such as conjunctive consolidation (3,6,7). If regression is used, predictive factors are identified, and each can create a category with different outcomes. However, if multiple predictor variables are identified, the process of developing a single staging system can be difficult and at best requires multiple iterations of trial and analysis. The technique of conjunctive consolidation allows new clinical factors to be added to a staging system without necessarily increasing the number of groups or categories. Also, for development of a staging system, the data collection can be performed retrospectively, particularly if the outcome requires a significant time interval.

There are several potential "models" of staging systems from which to choose. Under any circumstances, developing a staging system is an iterative process in which patients are grouped by predictor variables, and the outcomes, by group, are assessed. If the groups are not sufficiently distinct, then another arrangement of predictor variables is used and outcomes by group are again compared. Ideally, the staging system should be organized so that patients are easily grouped into distinct strata, with clearly different outcomes, and such that all patients should be classifiable.

Identify Comorbid Conditions

The concept of a "comorbid" condition that seriously affected treatment outcome was first described by Dr. Alvan Feinstein. A comorbid condition is defined as a condition—distinct from the condition of interest—that affects the outcome being measured. For example, when measuring mortality from laryngeal cancer, if the patient has another serious condition causing potential mortality (i.e., unstable angina), then that condition is defined as a comorbid condition. Since the initial description, researchers in multiple specialties have identified the impact of comorbid disease on several different outcomes (6,7). Therefore, in any outcomes study, it is important to identify all potentially important comorbid conditions and to measure their presence and severity as part of the data collection process. Of course, that only applies if the comorbid condition actually affects the condition under study. Using the same example of unstable angina, if one were performing an outcomes study of hearing satisfaction 1 month after receiving different types of hearing aids, the presence of unstable angina would not necessarily be an important comorbid condition to consider.

Define the Outcomes to be Measured

The expanded, patient-based outcomes usually measured in outcomes research are quality of life, health status, and functional status. There are multiple potential definitions for each of those terms; however, "quality of life" has three key aspects: (a) it is more than the absence of disease, (b) it is subjective (assessed from the patient's perspective), and (c) it is multidimensional. In addition, the overall quality of life depends on multiple aspects of life not directly related to disease, so most researchers studying treatment outcomes are actually assessing the "health-related quality of life." Most outcomes instruments designed for use in patient care are designed to assess health-related quality of life. The term "health status" is self-explanatory, but again, it must be measured from the patient's perspective. Functional status refers to the patient's ability to perform daily activities. In most circumstances, researchers are only interested in the effect of a particular disease, so disease-specific functional status is typically assessed.

To measure functional status or quality of life, the patient must answer several questions that have been validated for the purpose of measurement. Although these data can be gathered using interviews or other interactive techniques, under most circumstances patients complete a written questionnaire. In outcomes research, the questions are called "items" and the questionnaires are called "instruments." Instruments must be validated, and the validation process uses the scientific principles of psychometrics. A full discussion of the process of instrument validation would require more than one chapter, although the basic concepts are reviewed.

A health status or quality of life instrument should be reliable, valid, and sensitive (8). Two types of reliability are usually assessed—test–retest reliability and internal consistency reliability. Test–retest reliability means that the results will be similar if the status of the patient has not changed, and internal consistency reliability means that responses on similar items will be correlated.

Validity means that the instrument is measuring what it is supposed to measure. Validity is confirmed by a combination of evidence: content validity, criterion validity (if scores on the instrument correlate with objective measurable external criteria), and construct validity (if scores on the instrument correlate with scores on other instruments measuring similar concepts).

Sensitivity (or responsiveness) means that the instrument is responsive to change in status. In other words, if the patient's clinical status changes, then their score should also change. Sensitivity is assessed using statistical techniques measuring the degree of change against known standards, such as the standardized response mean and the effect size.

Another aspect of assessing sensitivity or change in status using an instrument has been called the "minimal significant difference" in score (3). For example, average scores on a health status instrument may change from 40 to 50 (on a scale of 0 to 100), and the difference might have a p-value less than 0.05. The question arises—is that 10-point difference a *clinically* significant change? If studies have indicated that the minimal clinically significant difference for the instrument is 15 points (out of 100), then the score change does not reach a level of minimal

significant difference. Therefore, although *p*-value indicates that the 10-point difference is likely not due to chance, it is probably too small a change to be noticed clinically by a patient.

Fortunately, it is seldom necessary to develop your own instrument. There are already hundreds of quality of life and health status instruments available in the literature. Some examples of validated quality of life instruments to assess global quality of life include the Medical Outcomes Study SF-36 and SF-12, the Quality of Well-Being Scale, the London Handicap Scale, the Sickness Impact Profile, and the Child Health Questionnaire. Some disease-specific quality of life instruments for Otolaryngology include the Chronic Sinusitis Survey, the Sinonasal Outcome Test-20 items, the University of Washington Quality of Life Index, and the Voice Handicap Index.

Assuming that a validated instrument exists, the main question for a researcher becomes: which instrument to choose? This choice is usually based on the content of the instrument, and the potential respondent burden. To discuss the assessment of content, a good example is hearing loss where several validated instruments are available. Review of the design and content of those instruments indicates that some are intended to assess satisfaction with a hearing aid, one is for elderly patients only, one is designed for conductive hearing loss in the otherwise healthy patient, etc. Therefore, content can guide instrument selection.

Respondent burden deals with the length of time and effort required to complete an instrument. Particularly when multiple questionnaires are used, selecting instruments with lower respondent burden should improve patient compliance and follow-up. In addition, researchers have found that shorter instruments are usually very sensitive to change, so little is lost from the standpoint of responsiveness by using a briefer instrument.

Another important issue is whether to choose a general ("global" or "generic") quality of life/health status instrument or a disease-specific instrument. Both have advantages and disadvantages (3). Global instruments have the advantage of being comparable across disease states, and their use allows comparisons between the relative impacts of certain diseases. However, many global health status instruments are relatively insensitive to the impact of more limited disease states, which nevertheless may cause significant worsening of patients' quality of life. This might not be true for all global instruments, but this finding has been replicated in several diseases. Therefore, if a global quality of life instrument is not sensitive enough, then use of a disease-specific instrument is appropriate.

Disease-specific instruments are much more sensitive to the impact of a particular disease, and they allow meaningful comparisons between treatments or groups of patients. However, disease-specific instruments do not allow comparisons across disease states, which can be a disadvantage if the goal is to demonstrate the overall impact of a given disease. Therefore, in many circumstances, it is wise to use both a global and a disease-specific instrument (3).

Finally, as discussed previously, traditional clinical outcomes such as disease-free survival remain important outcomes for assessment. In some cases in which the traditional outcomes are well-known and only the expanded, patient-based outcomes are of interest, then perhaps only quality of life/health status might be assessed. However, if there is a minimal added burden to the patient and researcher to assess "traditional" clinical outcomes (such as disease-free survival), under most circumstances, those outcomes should also be assessed.

RESULTS FROM OUTCOMES RESEARCH IN OTOLARYNGOLOGY

Outcomes studies in Otolaryngology have yielded many important results, and some brief examples are listed here. There are now validated outcomes instruments for use in chronic sinusitis, nasal obstruction, hearing loss, chronic ear disease, tinnitus, dizziness, head and neck cancer, voice, gastroesophageal reflux, tonsil and adenoid disease, pediatric otitis media, and pediatric sleep apnea, among other diseases. In addition, there is a comprehensive prognostic staging system for obstructive sleep apnea in adults. Studies have shown that global quality of life is significantly worsened in adults with chronic rhinosinusitis and improves to near normal after endoscopic sinus surgery. Similarly, global quality of life is significantly worsened in children with tonsil and adenoid disease. We have learned that comorbid conditions have significant impact on survival and outcome in patients with laryngeal cancer and other head and neck cancers. Disease-specific quality of life has been shown to improve significantly after surgical treatment for the following conditions: chronic rhinosinusitis, pediatric otitis media, vocal cord paralysis, conductive hearing loss, nasal septal deformity, and pediatric sleep apnea, among others. In addition, cochlear implantation has been demonstrated to be very cost-effective relative to other health care interventions.

OTHER TYPES OF OUTCOMES RESEARCH

In addition to patient-based studies, other types of outcomes research have made important contributions, for example, appropriateness studies. In an appropriateness study, records from a large population are reviewed to test the hypothesis that treatment (medical or surgical) was based on appropriate indications. These studies often yield controversial results for two primary reasons. One reason is that it is difficult to achieve consensus on what is an appropriate versus equivocal versus inappropriate indication. An appropriateness study might find that a large percentage of procedures were performed for "equivocal" indications, when there is legitimate contradicting evidence

showing that those indications could have been classified as "appropriate." The second reason is that those studies rely heavily on medical record documentation, which is often insufficient. So although the patient's chart might indicate that appropriate indications were not met, in fact that particular patient might have actually met all the criteria. Despite the controversy, these studies are important because they generate discussion and can act as an impetus for further research, collaborative guideline development, etc.

Another type of outcomes research is population studies. Many important findings have been identified from studies of rates of medical care received by different populations. Of particular interest are studies that compare the rates of procedures with controversial indications. Some early examples were studies of population rates of tonsillectomy, hysterectomy, lumbar disk surgery, and carotid endarterectomy: researchers found that populations that seemed remarkably similar in demographics, economics, and health status had markedly different rates of elective procedures performed. The only apparent differences seemed to be where they lived, and the number of specialty physicians per capita in their region. Other studies have shown remarkable differences in rates of hospital admission for the same admitting diagnoses in different cities, even after controlling for many health status and demographic factors that might influence admission rate. While these studies sometimes generate more questions than answers, they give important insight into the delivery of health care.

One important example of a database/population-based study was one that compared overall survival between patients with obstructive sleep apnea who were treated with continuous positive airway pressure (CPAP) versus patients who underwent uvulopalatopharyngoplasty (9). This study was performed in the Veterans Affairs (VA) system, which has had a national computerized medical record for many years and has a consistent population of patients who receive all their care at the VA. The authors reviewed the database and identified more than 15,000 patients eligible for study. They found that—controlling for a variety of variables including severity and comorbidity—survival was better in the surgery group than the CPAP group. This seemed surprising since in head-to-head comparisons CPAP is more effective than uvulopalatopharyngoplasty. The reason for the population finding seemed to be that many people prescribed CPAP were actually not using it, whereas everyone who had surgery did receive the benefit of surgery. A subanalysis seemed to indicate that regular CPAP users actually had better survival than surgery patients, but again the total group of CPAP patients (including many nonusers) did worse. This sort of population-based outcomes study is very important in determining treatments that actually work in populations. This is also an example of the difference between effectiveness research (in a real-world population) and efficacy research (in a controlled trial).

Meta-analysis is another type of outcomes research. In meta-analysis, the results from several individual studies are combined and a new statistical analysis is performed using the raw data from individual studies. Meta-analysis is more than just a detailed review of the literature, and to perform the analysis, each study must have used very similar methods and report data in a similar format. Despite some methodologic complexity, meta-analysis is a very helpful tool to help achieve an adequate sample power to answer some questions that individual small studies cannot, and also to help resolve conflicting results from individual studies.

EVIDENCE-BASED MEDICINE

Evidence-based medicine (EBM) is an important topic in contemporary medicine. While in fact there is some type of evidence behind many aspects of medical treatment, the explicit techniques of "EBM" have only been recently described and popularized. Dr. David Sackett has been a key developer and leader in EBM and is the lead author on an excellent textbook in the field (10).

More medical schools are teaching their students the techniques of EBM, and articles, books, lectures, and courses on EBM are popular in many fields. Two contemporary disease-related textbooks cover surgical fields: *Evidence-based otitis media*, by Rosenfeld and Bluestone, and *Evidence-based otolaryngology*, by Shin, Hartnick and Randolph.

EBM has been defined as the conscientious, explicit, and judicious use of the current best evidence in making decisions about the care of individual patients (11). Furthermore, the practice of EBM has been described as integrating individual clinical expertise with the best available external clinical evidence from systematic research (11,12). Several points—and misconceptions—are worth emphasizing.

First, EBM does *not* mean only the use of randomized clinical trials. The definition states that it requires the use of the "best available" evidence, not "only the best" evidence. If findings from a randomized clinical trial are available, then that is strong, high-quality evidence and should be used. If, however, randomized trials have not been performed and therefore that type of evidence is not available, you can still practice EBM by using the best available evidence.

Next, EBM does *not* eliminate the physician's own experience or knowledge base. The physician should integrate their own clinical experience with the patient's desire and with the current best clinical evidence when deciding on the best treatment for an individual patient.

The practice of EBM has been likened to a three-legged stool—which would be unstable if one leg were missing (13). The three "legs" of the stool are best evidence, clinical experience, and patient wishes. Along those lines, it would not be practical or reasonable for a physician to rely

only on results from high-quality evidence to make clinical decisions—since there are many questions and issues that have not been addressed with experimental studies. On the other hand, if a physician relies only on personal experience, their practice could become out of date or inappropriate. So the thoughtful and appropriate combination of experience and evidence is a goal to emulate.

There are five steps in practicing EBM (10,12), and we cover each step individually. Those steps are as follows:

1. Ask an answerable clinical question.
2. Search for the best available external evidence.
3. Critically appraise the quality of the evidence.
4. Understand the findings from the best evidence and create a summary/recommendation.
5. Integrate the best evidence with clinical expertise and unique patient factors (desires, values, unique circumstances).

Ask an Answerable Clinical Question

This step might seem simple but in fact can be challenging. Many questions that clinicians might pose are quite general—for example, "is endoscopic sinus surgery effective?"—and there will be limited or no evidence that directly addresses such a question. When developing a specific and answerable question, there are several aspects of the question that should be considered: a helpful tool is to remember "PICO": Patient, Intervention, Comparison, Outcome. Good clinical questions will usually define each of those four components. An example of a good question is the following: "In a 5-year-old child with acute Group A streptococcal pharyngitis (patient), does treatment with antibiotics and anti-inflammatories (intervention) reduce symptoms and fever duration (outcomes), compared to anti-inflammatories alone (comparison)?" That is a potentially answerable clinical question.

While it is *possible* to practice EBM when starting with very general questions, experts in the field have found that focusing the question makes all the subsequent steps easier—particularly the search for evidence.

Search for the Best Available Evidence

The evidence used in EBM is from clinical studies on humans, not from laboratory or animal studies. The evidence search should be a rigorous process for the most contemporary evidence using available technology—not merely identifying a textbook chapter or other handy reference. There are some available databases, for example, the Cochrane Library, that identify and grade pertinent literature on many clinical topics. These are usually compiled by experts, and updated regularly. In addition, there are journals devoted to EBM. Furthermore, evidence-based reviews for many clinical questions have been completed and disseminated. These might be published in the peer-reviewed literature, or as monographs, or placed on Web sites, among other locations. So on occasion, it is possible to identify the best evidence without actually performing the search yourself.

If, however, you need to perform your own search, then using MEDLINE over the internet is another option. This topic is explored in more detail elsewhere (14). But briefly, MEDLINE is a database of the published biomedical literature from around the world. It is maintained by the National Library of Medicine and is available on the internet free of charge. Journal articles are referenced into MEDLINE by trained librarians using index terms called Medical Subject Heading terms, or "MeSH terms." Once the user becomes familiarized with the techniques of searching using MEDLINE, comprehensive lists of articles that cover a particular topic can be identified. The search should be organized and planned to identify articles that address the answerable question.

MEDLINE is quite comprehensive, so in fact, many times a search will yield a very large number of articles—many of which might not be pertinent to the search of interest. In addition, not *all* medical journals are indexed into MEDLINE, and very old articles are not included (although MEDLINE is systematically adding references from before 1966). So there is some published literature that will not be found using MEDLINE. However, MEDLINE is overall an extraordinarily powerful tool for searching the biomedical literature.

Once the search is completed, the list of articles identified should be perused, and articles pertinent to the specific question pulled for further review.

Critically Appraise the Quality of the Evidence

In EBM, there is a fundamental principle at work: not all evidence is equal. Studies are evaluated based on their methodology, and studies using superior methodology are given more "weight" and evidence from those studies is considered more strongly. The basic rules of study quality are as follows: randomized studies are better than nonrandomized, prospective studies are better than retrospective, and controlled studies are better than noncontrolled. By definition, in EBM, only clinical studies using human subjects are considered. While basic laboratory research is an essential part of discovery in medicine, until studies have been performed in humans, their results are not included in the practice of EBM.

Individual studies are rated and given a *level*, based on the quality of the methodology. The standard hierarchy of levels proposed by Sackett is shown in Table 8.2. There are different levels depending on the type of question or study. For example, in a study on active therapy, the best methodology would be a randomized controlled trial (RCT); therefore, that represents level 1 evidence. However, in a study of the prognosis of some disease, randomization is not an option, and the best possible methodology would be a prospective cohort study; therefore, that is level 1 evidence for that type of question.

TABLE 8.2 EVIDENCE LEVELS FOR THERAPY/ETIOLOGY STUDIES AND PROGNOSIS STUDIES

Evidence Level	Therapy/Etiology	Prognosis
1a	Systematic review (SR) of RCTs	SR of inception cohort studies
1b	Single RCT	Individual cohort study
1c	"All or none" study	"All or none" case series
2a	SR of cohort studies	SR of either retrospective cohort studies or untreated control groups in randomized trials
2b	Individual cohort study	Retrospective cohort studies or untreated control groups in randomized trials
2c	Outcomes research	Outcomes research
3a	SR of case–control studies	
3b	Individual case–control study	
4	Case series	Case series
5	Expert opinion	Expert opinion

Modified Sackett DL, Straus SE, et al. *Evidence-based medicine: how to practice and teach EBM*, 2nd ed. London: Wolfe Pub Ltd., 2000, used with permission.

Study ratings are based on methodology, but if there are other problems with the study, the reviewer has options. If the study has major flaws, such an inappropriate entry criteria or obvious bias, the reviewer may exclude the study and not give it any grade. If problems are more minor, such as no power analysis or incomplete data reporting, then the study can be given a "minus" grade, such as level 2–. It is not appropriate to move the evidence level down a level, such as from 2 to 3, because a different level of evidence means a different methodology was used.

Studies should be organized, from highest level to lowest. Often, creating a table is the best way to organize the studies. If there are multiple studies of the same level, then studies showing similar findings can be organized together.

With the effort involved in creating a question, searching, finding, and grading the literature, it may be wise to maintain a record of search results, particularly for frequently asked questions. These organized search results have been called critically appraised topics, or "CATs" (10). When practicing EBM, the clinician can refer back to CATs whenever needed, and when new evidence is reported, it can be added to an existing CAT.

Understand the Results and Create a Recommendation

Once individual studies have been rated, then the overall results and findings are reviewed for evidence quality and the consistency of results. While individual studies are given *levels*, the overall evidence is given a *grade*. Grades of evidence are summarized in Table 8.3. This final compilation can be called a grade of recommendation or grade of overall evidence.

There is some judgment required in assigning a grade to the overall evidence. The grade is based on the best quality evidence, and the consistency of evidence and results—not just the level of evidence with the most papers. For example, there will often be multiple case series (level 4 evidence) reported, but if there are a large number of RCTs with consistent results, that would considered grade A evidence—even if there are numerically more level 4 studies than level 1. On the other hand, just because there are one or two RCTs (level 1 studies), that does not automatically mean there is grade A evidence. If the few studies show conflicting results or have methodologic problems, and the rest of the studies are case series, then the overall evidence might actually be grade C. Again, this requires some interpretation and judgment by the reviewer.

Integrate Best Evidence with Clinical Experience and Patient's Circumstances

This is the key last step in practicing EBM. After the best external evidence has been identified, graded and summarized, and an overall grade of recommendation created, that recommendation is then integrated with the patient's unique circumstances and the clinician's experience and judgment. The physician practicing EBM should keep in mind the "three legs" of EBM and the importance of each.

TABLE 8.3 GRADES OF OVERALL EVIDENCE

Evidence Grade	Levels of Evidence
Grade A	Consistent level 1 studies
Grade B	Consistent level 2 or 3 studies
Grade C	Level 4 studies
Grade D	Level 5 studies

Modified from Sackett DL, Straus SE, et al. *Evidence-based medicine: how to practice and teach EBM*, 2nd ed. London: Wolfe Pub Ltd., 2000, used with permission.

Evidence-Based Medicine Summary

The techniques of EBM are useful in identifying the best care for an unusual disease or condition, as well as for summarizing and incorporating the results from contemporary research into routine treatment of common disorders. EBM allows for clinical experience and for innovation, but stresses rigor and the scientific method in identifying the best treatment for each patient.

EVIDENCE-BASED GUIDELINES

Evidence-based guidelines are a product of EBM, where treatment recommendations are formulated into guidelines for the practitioner—with recommendations given different strength, based on the quality of the underlying evidence (15,16). The development of consensus evidence-based guidelines is a detailed and lengthy process, which often requires external funding and significant time contribution by experts. In many diseases, inclusion of content and clinical specialists from multiple disciplines is recommended to ensure that all evidence is included and reviewed with minimal bias. For example, an early guideline developed in otitis media with effusion included pediatricians, otolaryngologists, and audiologists in the review panels. The American Academy of Otolaryngology–Head and Neck Surgery Foundation has undertaken the development of multiple evidence-based guidelines and has detailed the steps involved in guideline development in a comprehensive and helpful publication (16). The Academy Foundation completes each guideline over several months.

The Cochrane Collaboration also reports evidence-based reviews, again using a rigorous iterative process of literature retrieval and review, with recommendations made based on the strength of evidence (17). There are Cochrane working groups in most specialties including Otolaryngology, and that group has published a variety of reviews. Cochrane groups generally take the view that they will only perform a review or create a guideline when there is sufficient level 1 evidence on the question. Their view is "top down" in that they start with only the best evidence, and therefore, they will not expend the time and energy to create a guideline if the best evidence happens to be low-level.

Some articles are also reported as "evidence-based reviews" or reports because they use the same steps in identification, review, and compilation of evidence but without the large panel and multiple iterations. In some cases, particularly when the question is straightforward and the evidence is manageable, these published reviews will likely be equivalent to a more formal one developed using the more extensive process.

Guidelines are organized around statements of action, for example, what a clinician should do or what test they should perform. These actions are given different levels of recommendation, depending on the strength of the underlying evidence and also the probability of benefit or harm associated with a treatment or test. The "final product" of the evidence review is a *recommendation*, which is given one of the following levels: Strong Recommendation, Recommendation, Option, or No Recommendation.

These levels can be summarized as follows (16). "Strong recommendation" means the benefits clearly exceed the harms, and the supporting evidence is strong. Therefore, clinicians should follow this recommendation, unless there is strong reason not to. "Recommendation" means that the benefits exceed the harms, although the evidence is not as strong, and clinicians should generally follow this recommendation, subject to additional information or patient preference. "Option" means that either the evidence is not strong or that strong evidence shows conflicting results, and in this case, clinicians have flexibility in treatment decisions, and patient preference can play a more significant role. "No recommendation" means that supporting evidence and benefit/risk data are insufficient to allow any recommendation to be made.

The organization of potential recommendations is shown in Table 8.4, but in the process of making a guideline

TABLE 8.4 RECOMMENDATIONS USED IN PRACTICE GUIDELINES

Evidence Grade	Levels of Evidence	Preponderance of Benefit or Harm	Balance of Benefit or Harm
Grade A	Consistent level 1 studies	Strong recommendation	Option
Grade B	Consistent level 2 or 3 studies	Strong recommendation or recommendation	Option
Grade C	Level 4 studies	Recommendation	Option
Grade D	Level 5 studies	Option	No recommendation
Grade X	Exceptional situation: no studies, but clear evidence of benefit or harm	Strong recommendation or recommendation	

Adapted from Rosenfeld RM, Shiffman RN. Clinical practice guidelines: a manual for developing evidence-based guidelines to facilitate performance measurement and quality improvement. *Otolaryngol Head Neck Surg* 2006;135(4 Suppl):S1–S28.

recommendation, the lines between levels of recommendation are not always absolute. However, you would usually not make a strong recommendation if the best evidence was grade C, for example.

So in summary, evidence-based guidelines are an extension of EBM, where the best evidence is systematically reviewed by a multidisciplinary panel of experts and treatment decisions are organized into a series of recommendations to guide the clinician during treatment. These are recommendations and should always be balanced with clinical experience, and potential unique circumstances of a particular patient.

HIGHLIGHTS

- Outcomes research can be divided into patient-based research and record-based research.
- Patient-based outcomes research is characterized by the assessment of expanded measures of outcome, such as quality of life and patient-based disease-specific health status, as well as new research methodologies such as observational studies.
- The steps in patient-based outcomes research are as follows: identify and define the disease of interest, create a disease severity staging system, identify comorbid conditions, and establish the outcomes to be measured.
- There are multiple available validated instruments to assess global and disease-specific quality of life.
- Patient-based outcome studies in otolaryngology have demonstrated the effectiveness of many common surgical treatments.
- Some examples of record-based outcomes research are appropriateness research and population studies.
- EBM can be defined as the conscientious, explicit, and judicious use of the current best evidence in making decisions about the care of individual patients.
- In the practice of EBM, there are five steps: ask an answerable clinical question, search for the best available external evidence, critically appraise the quality of the evidence, understand the findings and create a summary/recommendation, and integrate the best evidence with clinical expertise and unique patient factors.

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Introduction to Otolaryngic Genetics

9

Selena E. Heman-Ackah *Anil K. Lalwani*

Human genetics forms the foundation of existence and the backbone of basic human formation and function. Since the turn of the century, the body of knowledge and understanding of human genetics has grown tremendously. The decoding of the human genome has unlocked the door to understanding gene function. Further investigation and unveiling of the genetic code will facilitate the identification of fundamental genes, critical genetic pathways, and deleterious genetic disorders. Current studies are now aiming to decipher the complex interaction between environmental factors and genetics in the manifestation and evolution of genetic disorders. As the body of knowledge continues to grow, human genetics will increasingly be an integral component in the diagnosis, prevention, and ultimately treatment of genetic disorders. This will further aid in identifying disease susceptibility to treatments and targeted therapies to improve individualized drug response. The utilization of genetics in diagnosis and treatment planning may dramatically revolutionize the management of chronic diseases that have plagued mankind for centuries.

Consequently, a keen understanding of human genetics, both the current triumphs and future endeavors, is essential to the practice of otolaryngology—head and neck surgery. Numerous genetic disorders are encountered in otolaryngology and its subspecialties. These genetic disorders may occur as a result of sporadic chromosomal anomalies and mutations or may be transmitted from generation to generation. The purpose of this chapter is to review the basic principles of human genetics and to review genetics as it pertains to the practice of otolaryngology. This chapter provides an overview of normal human genetics, patterns of genetic transmission, genetic disorders in otolaryngology, and molecular therapies in genetics.

MOLECULAR BASIS OF INHERITANCE

The human genetic code provides the basis upon which information encoded within genetic material is translated into proteins vital to cellular function and the sustenance of life. This process starts with deoxyribonucleic acid (DNA), which is transcribed as ribonucleic acid (RNA) and ultimately translated into proteins and polypeptides (Fig. 9.1). This is a highly specific and regulated process by which the building blocks of life are created.

DNA and Chromosomes

DNA provides the basis for all genetic material and is the cornerstone of the human genomic code. DNA provides the code from which all human proteins are derived. The majority of DNA is housed within the cell's nucleus with a relative minor proportion being contained within the mitochondria. Nuclear DNA is referred to as autosomal DNA, whereas DNA derived from the mitochondria is referred to as mitochondrial DNA. Roughly half of all autosomal DNA is derived from each parent respectively. All mitochondrial DNA is maternally derived. The structure of autosomal and mitochondrial DNA differs substantially.

DNA is a double-stranded helix comprised of two paired nucleotides with a phosphate-deoxyribose backbone joined by ester bonds. Within DNA, there are four nucleotides with specific binding patterns: adenine (A) pairs with thymine (T) and cytosine (C) pairs with guanine (G). The entire human autosomal DNA genome is comprised of 3×10^9 base pairs measuring approximately 2 m in length, all of which is condensed and housed within a nucleus that is only 0.06 μm in diameter. Less than 5% of the entire human genome codes for the fewer than 30,000 genes that are translated into proteins. A trinucleotide sequence,

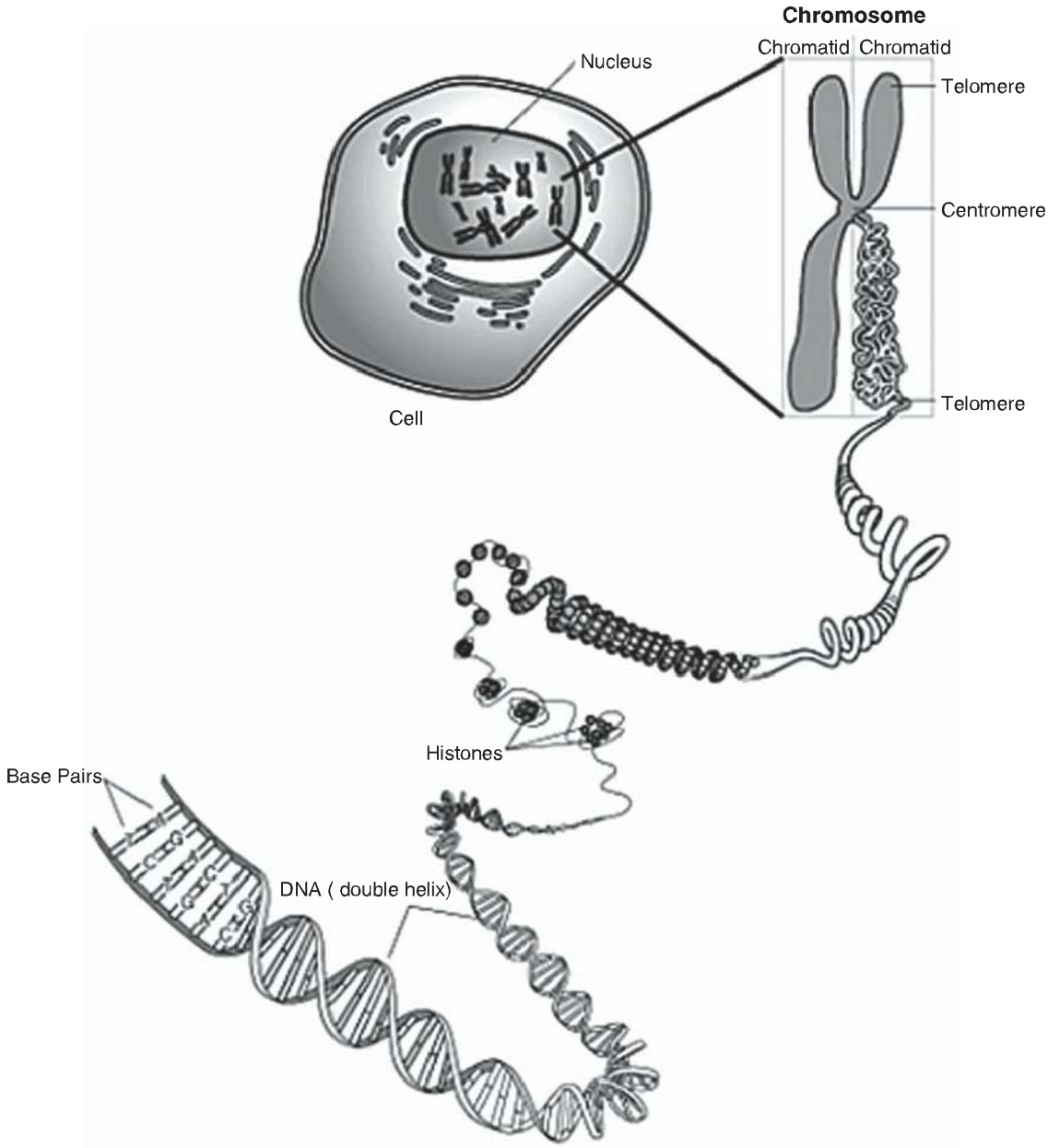


Figure 9.1 Structure and components of the chromosome.

a codon, corresponds to a specific amino acid. Each DNA molecule is comprised of a sense or coding strand (5′ to 3′) that is paired with a complementary antisense or template strand (3′ to 5′). Segments of the DNA containing genetic information that is transcribed into corresponding RNA, proteins, and polypeptides are called genes.

Within the nucleus, DNA is organized into chromosomes following DNA replication and preceding cellular division. Chromosomes are comprised of dense DNA-protein complexes known as chromatin. The human genome contains 23 paired chromosomes of maternal and paternal origin for a total of 46 chromosomes: female (46, XX) and male (46, XY) (Fig. 9.2).

Mitochondrial DNA is also comprised of a double-stranded helix. However, instead of the linear organization, mitochondrial DNA is a circular molecule with 16,569 base pairs (Fig. 9.3). Each mitochondrion contains multiple copies—from 100 to 10,000—of this circular DNA (1). The mitochondrial genome consists of 37 genes coding for 2 rRNAs, 22 tRNAs, and 13 polypeptides. Mitochondrial DNA is essential in its contribution to enzyme complexes critical for oxidative phosphorylation (2). During fertilization, the nucleus of the sperm and oocyte fuse, allowing for transmission of both maternal and paternal autosomal DNA into the developing offspring. Interestingly, shortly following fertilization, the mitochondria derived from the

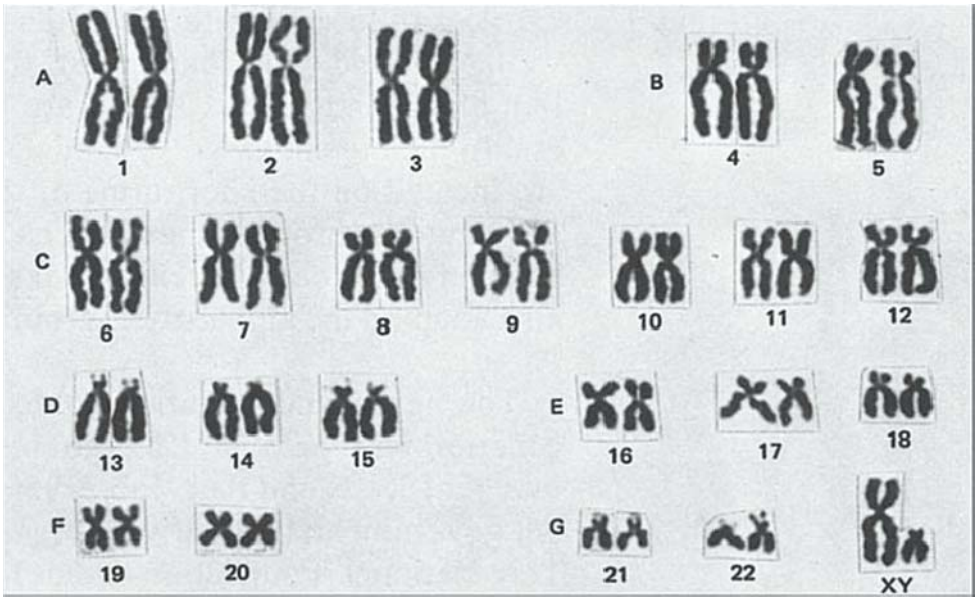


Figure 9.2 Human karyotype.

sperm undergo programmed destruction, leaving only the maternally mitochondria within the developing offspring (3). For this reason, mitochondrial DNA is solely of maternal origin.

RNA and Proteins

Information coded within the genome is translated into the vital proteins by RNAs. Similar to DNA, RNA is comprised of a sugar-phosphate backbone with a nucleotide base. However, unlike the double-stranded configuration of the DNA molecule, RNA is configured as a single-stranded molecule. RNA is comprised of three of the same nucleotide base pairs encountered in DNA: adenine (A), guanine (G), and cytosine (C). The thymine (T) base associated with DNA is replaced by uracil (U) in the RNA molecule. Similarly, during the transcription process, adenine pairs with guanine, and uracil replaces thymine in pairing with cytosine. There are multiple types of RNA, which are critical to the cellular function (Table 9.1).

RNA functions to aid in the transcription of the DNA code and the translation of the genetic code into protein

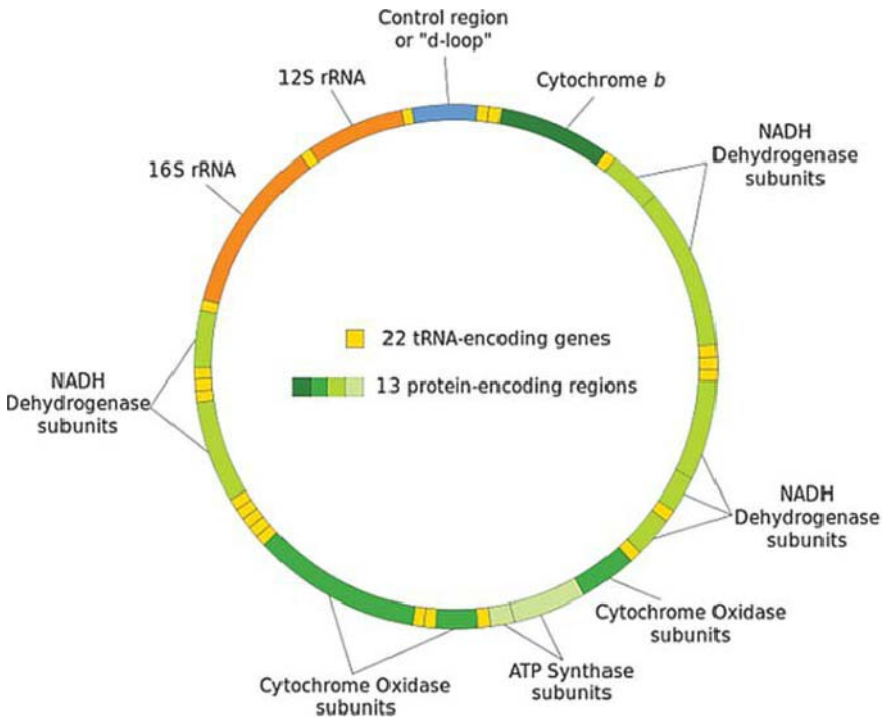


Figure 9.3 The mitochondrial genome.

TABLE 9.1 TYPES OF RIBONUCLEIC ACIDS

Types of RNA	Abbreviation	Function
Messenger RNA	mRNA	Codes for protein sequence Essential to transcription
Micro RNA	miRNA	Posttranscriptional regulators Translational repression and gene silencing
Ribosomal RNA	rRNA	Decoding mRNA Interact with tRNA during translation
Small interfering RNA (inhibitory RNA, silencing RNA, short interfering RNA)	siRNA	Interferes with specific gene expression Antiviral mechanism Shaping chromatin structure of the genome
Small nuclear RNA	snRNA	RNA splicing Regulation of transcription factors Maintenance of telomeres
Signal recognition particle RNA	SRP RNA	Translational translocation Membrane integration Posttranslational transport
Transfer RNA	tRNA	Translation

and polypeptide products (Fig. 9.4). In short, during the process of transcription, messenger RNA (mRNA) pairs with DNA, utilizing the sense strand as a template. Therefore, mRNA is configured in a 3′ to 5′ orientation and is identical to the antisense strand of DNA with the exception of the thymine to uracil substitutions. Transcription takes place completely within the cell nucleus. Once this process is complete, the mRNA exits the nucleus where, with the assistance of transfer RNA (tRNA) and ribosomal RNA (rRNA), the code is translated on a ribosome (a complex of protein and rRNA) into protein. Because the mRNA is similar to the antisense DNA strand, the nucleotide bases of the tRNA correspond directly to that of the sense DNA strand. For translation to occur, tRNAs specific for individual amino acid, with the amino acid covalently attached to it, are required. Each nucleotide triplet represents a codon, of which there are 64, corresponding to a specific amino acid or a stop signal (Fig. 9.5). The peptide produced by the tRNA ultimately forms proteins and polypeptides, which are critical to virtually every cellular function.

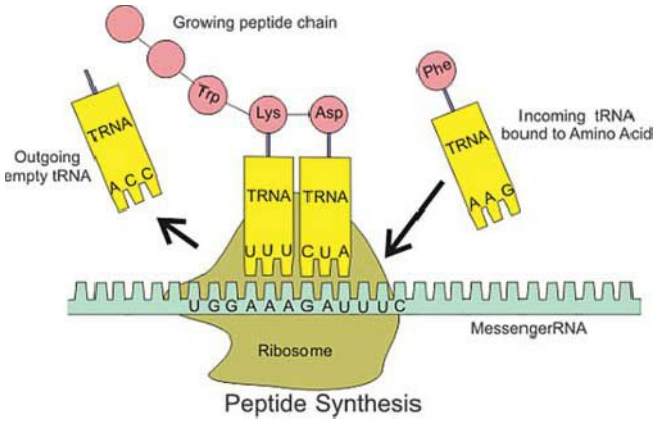


Figure 9.4 RNA translation.

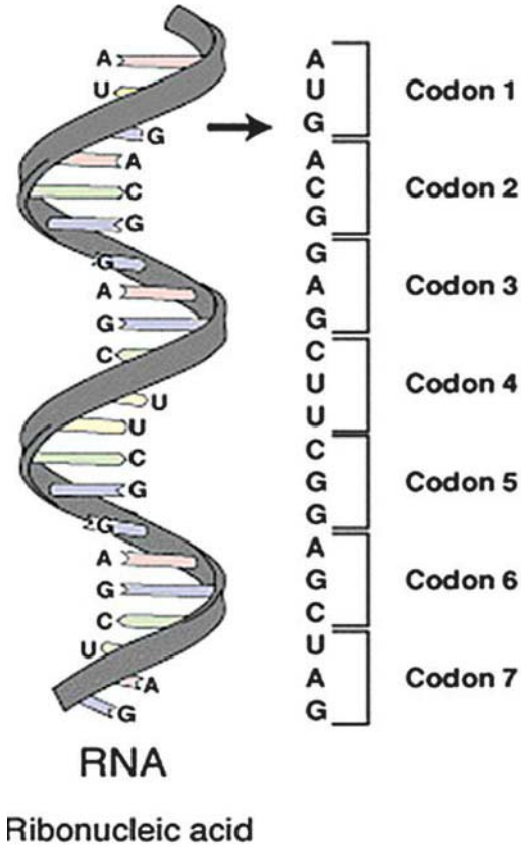


Figure 9.5 Nucleotide triplets.

Proteins are essential for cellular structure and life function. Proteins form the structural components of cells, the foundational material of tissue, and the enzymes that catalyze chemical reactions. Although every cell contains the entire genome, only specific genes are expressed to enable the production of the precise proteins required for that specific cell's function. The entire process of gene expression to protein production, therefore, requires precise timing and orderly expression of genes specific to carry out functions within divergent cells and organ systems.

MENDELIAN GENETICS

The concepts of Mendelian genetics were first introduced by Gregor Mendel in his work *Experiments in Plant Hybridization* in 1865 presented on February 8 and March 8 before the *Naturforschender Verein* (Natural Science Association) in Brunn (4,5). Using the pea plant for artificial insemination studies, he was able to identify various patterns of inheritance based upon transmission of specific physical characteristics in the plant's offspring such as color variations and seed form. The works of Mendel were largely ignored for a period of 35 years until their rediscovery in 1900 independently by Correns et al. (6). Since then, Mendel's model of inheritance has become the cornerstone of human genetics. The main forms of Mendelian inheritance include autosomal dominant, autosomal recessive, and sex-linked inheritance, all of which are discussed in detail below. Table 9.2 provides definitions of basic terminology upon which Mendelian genetics is based.

Autosomal Dominant Inheritance

Each individual possesses two copies or alleles of a specific gene, one maternally derived and the other paternally derived. Autosomal dominant inheritance is a form of inheritance wherein only a single mutated allele is required for the transmission of disease. Therefore, an individual with the disease phenotype need only inherit the mutated allele from one parent while inheriting a normal allele from the other parent. Figure 9.6 depicts a prototypical pedigree of a family with autosomal dominant inheritance. If one parent possesses one diseased allele (heterozygous dominant) and the other parent possesses two normal alleles, their offspring have a 50% chance of inheriting the disorder. Alternatively, in extremely rare cases, if one parent possesses two diseased alleles (homozygous dominant) and the other parent possess two normal alleles, the offspring have a 100% chance of inheriting the disorder. There is no sexual predilection in the pattern of inheritance with autosomal dominant disorders. Additionally, there is no carrier state with autosomal dominant disorders. Therefore, inheritance of one disease allele confers the phenotype of disease unless there is "incomplete penetrance." Inherited diseases may demonstrate complete penetrance (every individual with the disease allele has the disease phenotype) or incomplete penetrance (not all individuals with the disease allele have the disease phenotype). Because of the nature of transmission, autosomal dominant disorders are rarely associated with fatal mutations. This is because the presentation of fatal mutations with autosomal dominant inheritance would preclude its transmission.

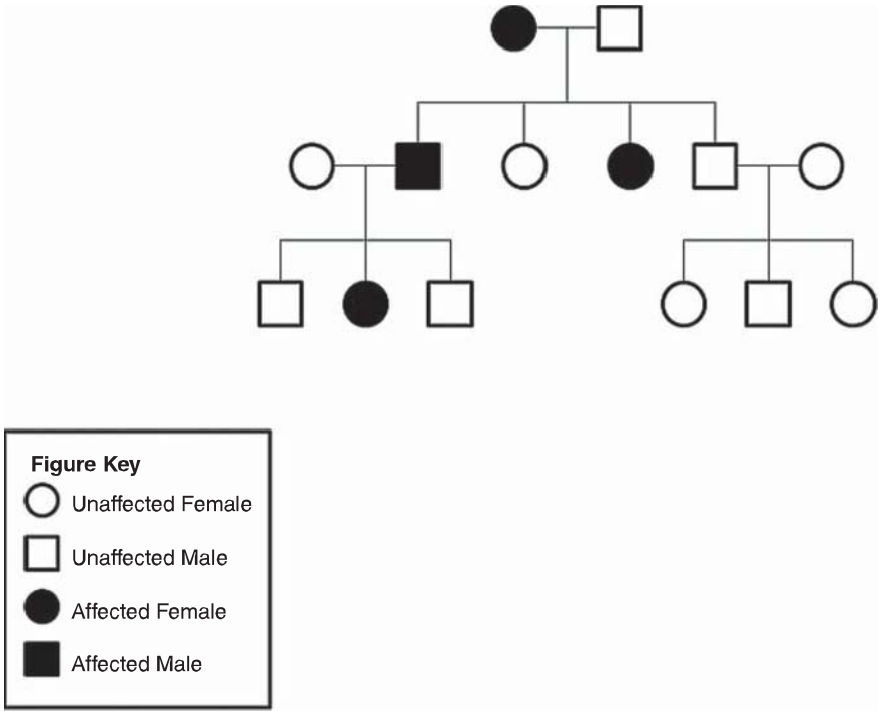
There are a number disease in otolaryngology with known autosomal dominant inheritance including achondroplasia, Charcot-Marie-Tooth, Ehlers-Danlos syndrome, Marfan syndrome, neurofibromatosis type I, neurofibromatosis type II, osteogenesis imperfecta, Pfeiffer syndrome, von Hippel-Lindau syndrome, Treacher-Collins syndrome, Noonan syndrome, Osler-Weber-Rendu syndrome, Gorlin syndrome, branchio-oto-renal (BOR) syndrome, DiGeorge syndrome, Gardner syndrome, Pallister-Hall syndrome, Stickler syndrome, van der Woude syndrome, and otosclerosis. These disorders are discussed later in the chapter.

TABLE 9.2 BASIC GENETIC TERMINOLOGY

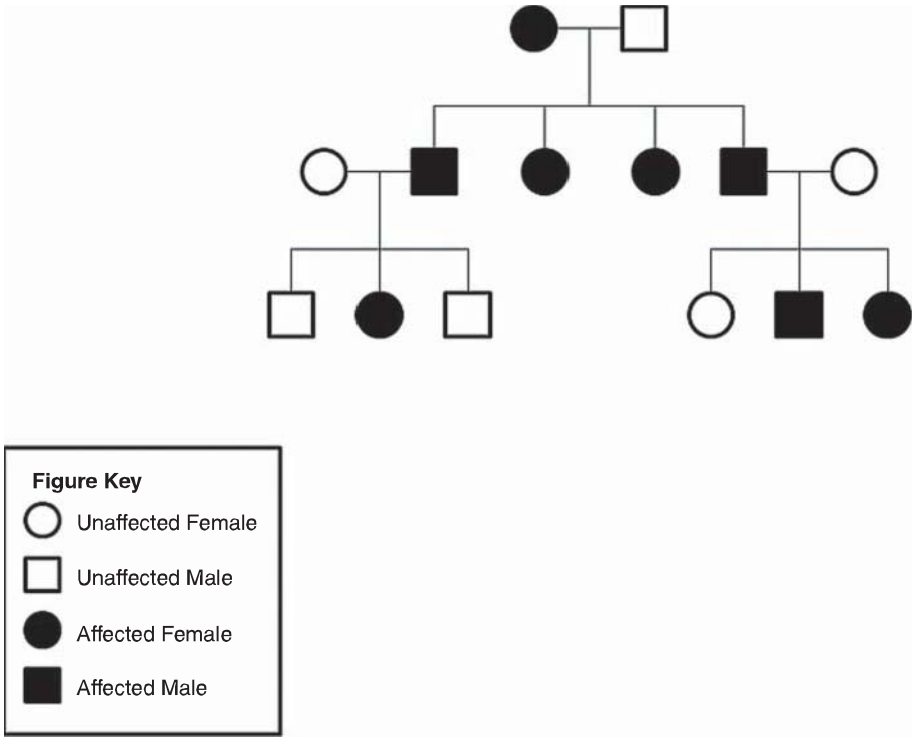
Terminology	Definition
Genotype	Genetic constitution of a particular genetic locus
Phenotype	Observable characteristics of a cell or organism that are coded by a particular genetic locus
Alleles	The particular form of a gene on each chromosome
Homozygous	Individual who carries two identical alleles of a specific gene loci
Heterozygous	Individual who carries two different alleles of a specific gene loci

Autosomal Recessive Inheritance

With autosomal recessive inheritance, two diseased alleles are required for the phenotypical presentation of disease. Figure 9.7 depicts a prototypical pedigree of a family with cystic fibrosis, an autosomal recessive disorder. Cystic fibrosis is caused by various mutations within the CFTR gene (7). If an individual possesses two mutated CFTR genes (homozygous recessive), they phenotypically present with cystic fibrosis. However, if an individual possesses only one mutated CFTR gene and possesses one normal copy (heterozygous recessive), this individual is considered a carrier. Carriers typically do not phenotypically present with the disease process, but possess the ability to pass the abnormal gene to their offspring. If two carriers procreate, 25% of their offspring will have the disease process (homozygous recessive), 25% of their offspring will have two normal alleles, and 50% of their offspring will be carriers (heterozygous recessive). Additionally, if one parent is a carrier and one parent is normal, half of their children will be carriers and half will be normal.



A



B

Figure 9.6 **A**: Pedigree of family with neurofibromatosis (heterozygous dominant parent inheritance). **B**: Pedigree of family with neurofibromatosis (homozygous dominant parent inheritance).

Like autosomal dominant disorders, there are numerous examples of autosomal recessive diseases within otolaryngology. These disorders include Usher syndrome, Refsum disease, Pendred syndrome, Jervell Lange-Nielsen syndrome, xeroderma pigmentosa, Fanconi anemia, Friedreich ataxia, and Letterer-Siwe disease. Unlike autosomal dominant disorders, genetic disorders with lethal phenotypes are more likely to be autosomal recessive in

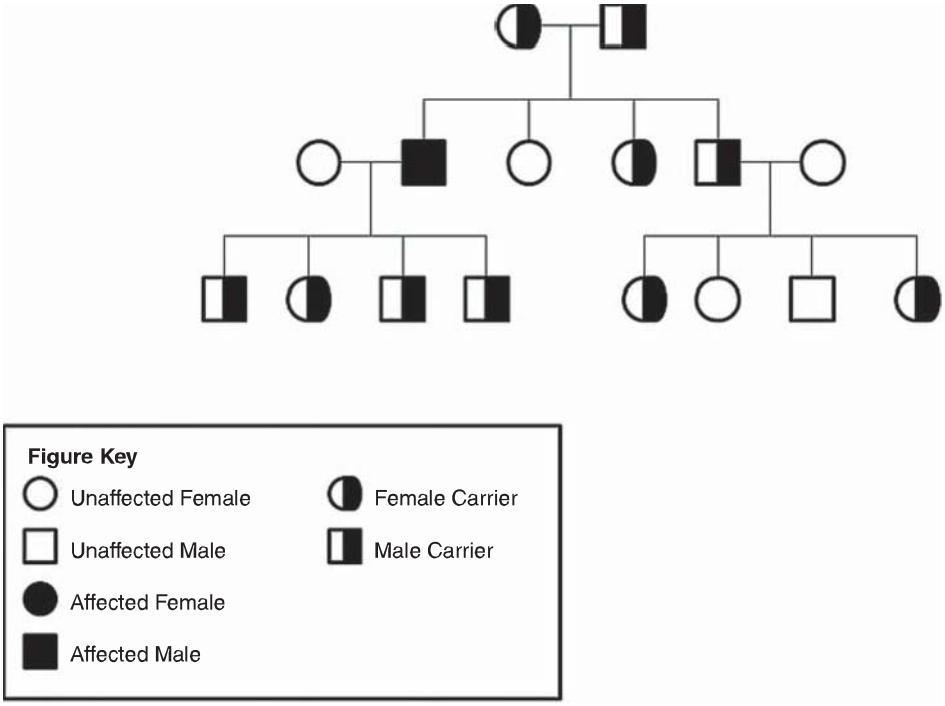


Figure 9.7 Pedigree of family with cystic fibrosis (autosomal recessive inheritance).

nature owing to the normal phenotypical presentation of the carrier individuals at childbearing age. Autosomal recessive disorders with lethal phenotypes, such as Tay-Sachs disease and Bowen-Conradi syndrome, most often occur in patient with no prior family history of disease. The lethal phenotypes tend to occur more frequently among consanguineous families in which the parents are genetically related. Many autosomal recessive disorders tend to have a racial or ethnic predilection (i.e., sickle cell anemia, β-thalassemia, and Gaucher disease) believed to be a function of the founder effect. The founder effect describes the expression of a mutation initially occurring in one or few founding members of a group that has been propagated by the tendency for marriages to occur within the same group. As with autosomal dominant disorders, there is no sexual predilection associated with autosomal recessive disorders.

Sex-Linked Inheritance

Sex-linked inheritance refers to genes expressed on the X or Y chromosome. Among humans, most sex-linked genetic disorders are carried on the X chromosome. As the daughter inherits an X chromosome from the mother and the father, therefore, with X-linked disorders, a female may inherit a mutated gene allele from either the mother or the father. However, as the male inherits the X chromosome from the mother and the Y chromosome from the father, thus, sons can only inherit the diseased allele from the mother. X-linked disorders are further subdivided into X-linked dominant and X-linked recessive disorders.

X-linked dominant disorders are exceedingly rare. As with autosomal dominant disorder, X-linked dominant disorders only require one diseased allele for the phenotypical expression of disease. Therefore, both males and females may be affected. Figure 9.8 depicts a pedigree of a family with Aicardi syndrome, an X-linked dominant disorder characterized by partial or complete absence of the corpus callosum, retinal abnormalities, and seizures (8). All females born to a male with an X-linked dominant disorder will possess the disease mutation and express the disease phenotype as the father has only the single affected X chromosome. Paternal possession of X-linked dominant disorders has no influence on the genotype or phenotype of male offspring as the father only passes the Y chromosome to the son. Half of males born to a female with an X-linked dominant disorder will inherit the disease genotype and phenotype. In certain X-linked dominant disorders (i.e., focal dermal hypoplasia), expression of the genetic mutation within males is highly or uniformly fatal. There are few examples of X-linked dominant disorders including X-linked hypophosphatemia, CHILD syndrome, Lujan-Fryns syndrome, and incontinentia pigmenti.

The vast majority of X-linked disorders are recessive in nature, meaning that one functional form of the gene precludes the phenotypical presentation of disease. Figure 9.9 depicts a pedigree of a family with Kallmann syndrome, an X-linked disorder. With X-linked recessive disorders, females possessing one copy of the disease allele are carriers and typically do not have the disease. Females must possess two copies of the diseased allele for expression of disease, which is extremely uncommon. Females may inherit this diseased X-linked allele from either or both parents. However, because male offspring inherit their only X chromosome from their mother, males may only

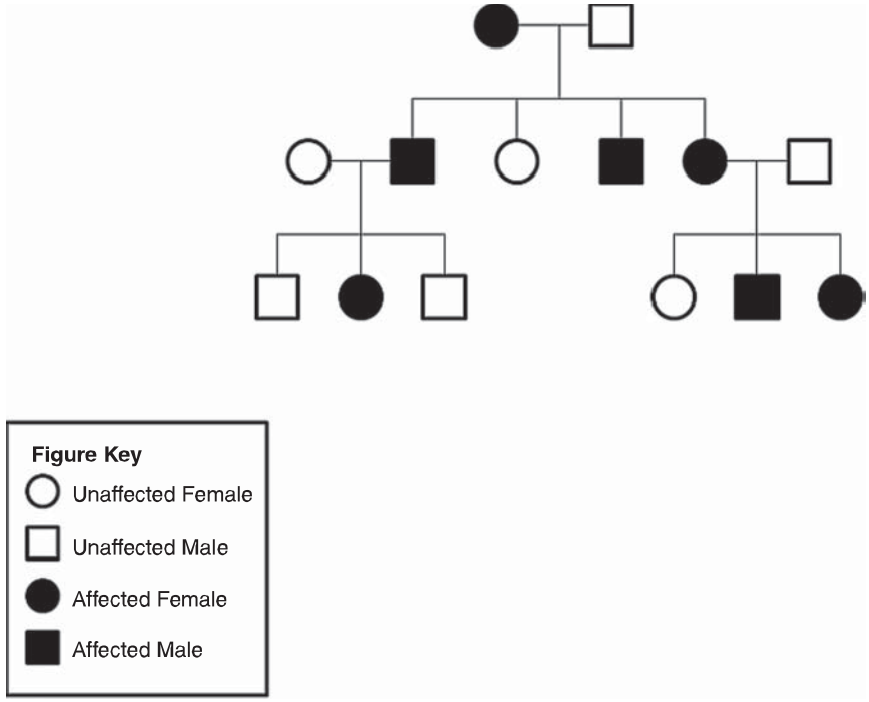


Figure 9.8 Pedigree of family with Aicardi syndrome (X-linked dominant inheritance).

inherit X-linked recessive disorders from their mother. Also, because males lack a second X chromosome, the disease allele represents the only functional X chromosome allele leading to the phenotypical expression of disease. There are a number of X-linked recessive diseases encountered in otolaryngology including X-linked stapes gusher syndrome, X-linked Alport syndrome, idiopathic hypoparathyroidism, X-linked agammaglobulinemia of Bruton, Lesch-Nyhan syndrome, severe combined immunodeficiency disease, Wiskott-Aldrich syndrome, Norrie disease, X-linked ichthyosis, Keipert syndrome (nasodigitoacoustic syndrome), and fragile X syndrome.

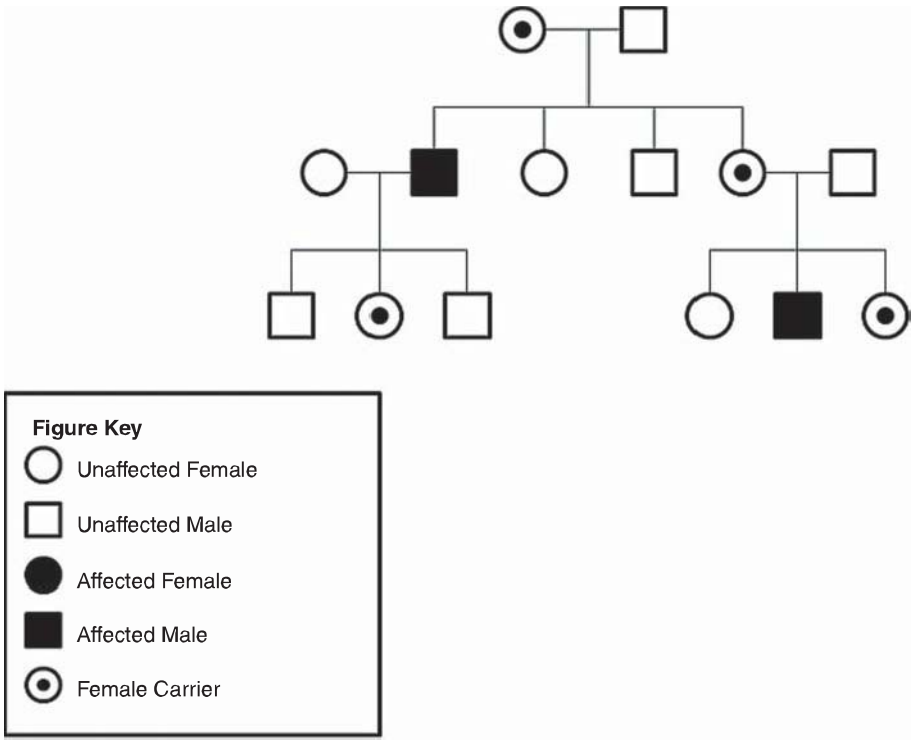


Figure 9.9 Pedigree of family with Kallmann syndrome (X-linked recessive inheritance).

Penetrance and Expressivity

When discussing Mendelian genetics, it is also important to understand the concepts of penetrance and expressivity. Penetrance describes whether individuals carrying a particular gene mutation also express an associated trait or phenotype. Penetrance may be complete or incomplete, that is, among individuals harboring a mutated gene, all or some have the disease, respectively. Expressivity describes the variation in phenotype among individuals carrying a particular genotype. For example, a mutation may be associated five different findings; in patients with a disease characterized by variable expression, they may have one to all five of the features.

Neurofibromatosis type I (NF1), an autosomal dominant disorder, is an excellent example to illustrate the concepts of penetrance and expressivity as it is a genetic disorder characterized by incomplete penetrance with variable expressivity. Individuals with the NF1 genotype may phenotypically appear normal representing the phenomenon of nonpenetrance. Nonpenetrance describes the lack of phenotypical presentation of a genetic disorder in an individual known to possess the genotype associated with disease. Additionally, the expression of NF1 varies greatly among affected individuals. Approximately, 97% of patients with the NF1 genotype have five or more café-au-lait spots, 60% cutaneous neurofibromas by age 20 years, 17% scoliosis, and 13% optic gliomas. The variability in presentation of these components of the disease process is a reflection of the variable expressivity associated with NF1.

NON-MENDELIAN GENETICS

Mendel's description of patterns of inheritance formed the foundation upon which the current level of knowledge and understanding of genetics was built. In addition to the Mendelian forms of genetic inheritance, further investigation has revealed a number of non-Mendelian processes by which genetic mutations can be inherited conferring the phenotype of a disease. These include mitochondrial inheritance, genetic imprinting, epigenetic influences, digenic inheritance, complex genetics, and chromosomal anomalies.

Mitochondrial Inheritance and Mutations

As described above, mitochondrial DNA is instrumental in the production of proteins and enzymes fundamental to oxidative phosphorylation. Mitochondrial DNA is solely maternally inherited. As with autosomal DNA, mutations within the mitochondrial genome can produce the phenotype of disease. These mutations may be inherited or acquired.

Because the mitochondrial genome in maternally transmitted, all inherited mitochondrial genetic disorders are maternally derived (9). Figure 9.10 depicts two pedigrees of families with mitochondrially inherited nonsyndromic hearing loss (MINSHL). The first family depicts the case of a family derived from the maternal unit with MINSHL, and the second depicts the case of a family derived from the paternal unit with MINSHL. Mitochondrially inherited disorders are more rarely encountered in otolaryngology than autosomal inherited disorders and range in severity from asymptomatic to fatal. Because the mitochondrial genome is essential to cellular energy production, tissues with high energy demand are preferentially affected including the nervous system, muscle, heart, and endocrine systems (10). Examples of mitochondrially inherited genetic disorders include aminoglycoside induce ototoxicity, NARP (neuropathy, ataxia, and retinitis pigmentosa), Leber hereditary neuropathy, MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes), and MINSHL. Certain forms of male infertility are also proposed to be secondary to inherited mitochondrial genomic mutations.

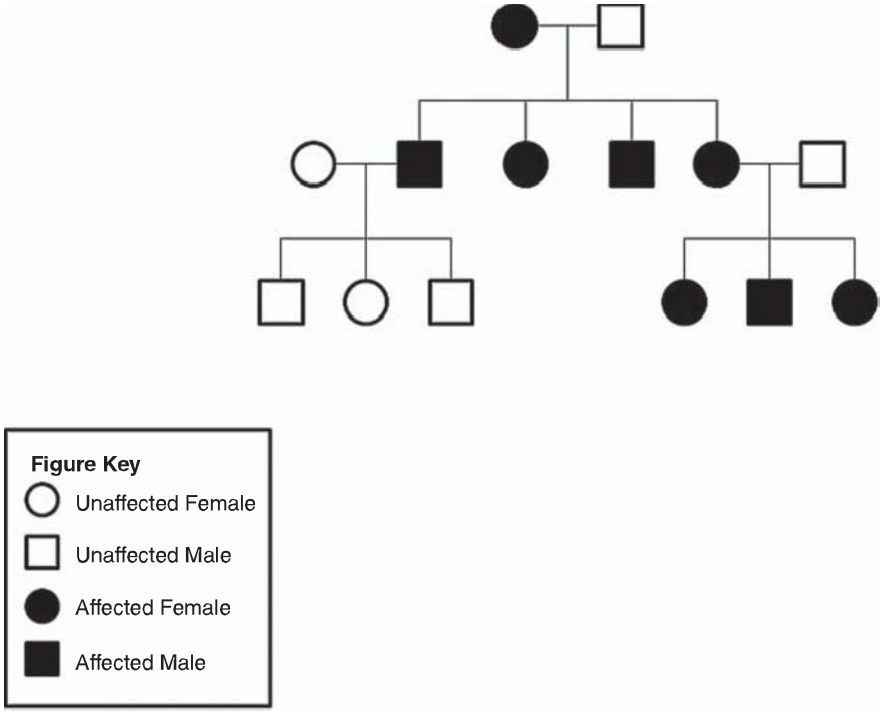
Mutations within the mitochondrial genome may also be acquired. Acquired mitochondrial mutations are proposed to be associated with aging in many organ systems including the inner ear, skin, and retina. Oxidative damage due to increased reactive oxygen species and a decrease in endogenous antioxidants has been identified as a major contributor to acquired mitochondrial genomic mutations (11,12).

Various cancers have also been associated with mitochondrial genomic mutations. These mutations have been found to be germline related and *de novo*. In addition to head and neck tumors, renal adenocarcinoma, colon cancer, astrocytic tumors, thyroid tumors, breast tumors, and prostate tumors have been associated with mitochondrial genomic mutations (13,14).

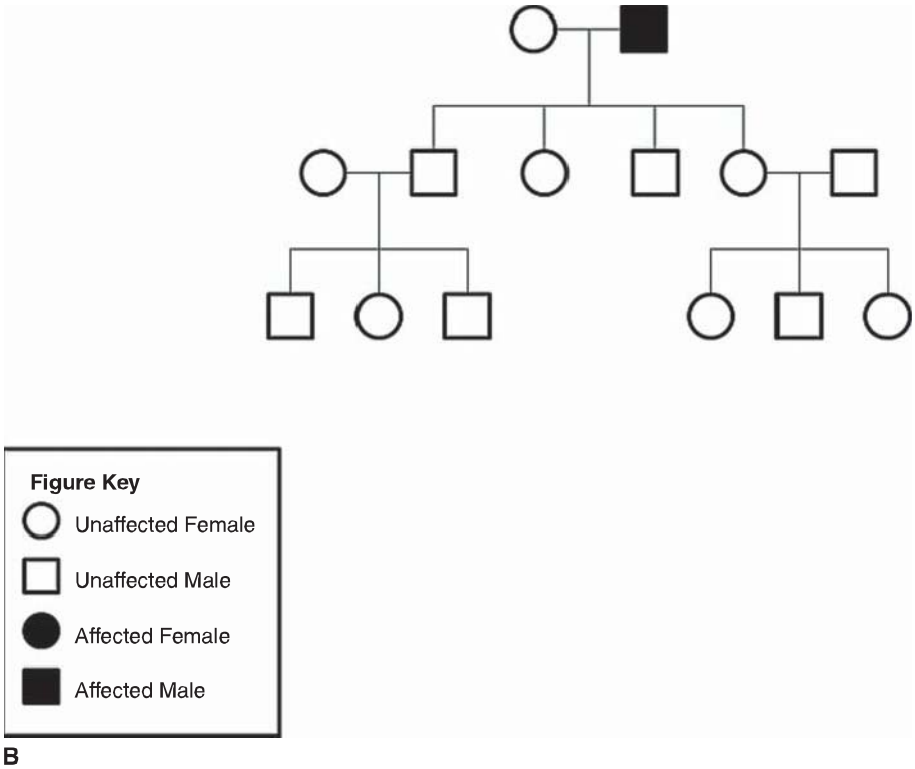
Genetic Imprinting

Genetic or genomic imprinting is an epigenetic process not described or explained by the traditional Mendelian patterns of inheritance. It describes a genetic process by which certain genes are expressed in a parent-of-origin specific manner. The process of genetic imprinting silences an allele derived from a specific parent such that only the genes from the nonimprinted allele are expressed. Imprinting may occur on either the maternally derived or paternally derived allele. Genetic imprinting is accomplished via methylation of cytosine within DNA and histone acetylation, which produces monoallelic gene expression without alteration of the genetic sequence. The markers for genetic imprinting are established through the germline and are maintained throughout all somatic cells. Imprinted genes are typically grouped within clusters, which allow them to share common regulatory units including noncoding RNA and differentially methylated regions, which together comprise the imprinting control regions (15).

There are a number of genes that have been identified that lead the disease phenotype as a function of genetic



A



B

Figure 9.10 **A:** Pedigree of family with MINSHL (maternal inheritance). **B:** Pedigree of family with MINSHL (paternal inheritance).

imprinting. Beckwith-Wiedemann syndrome is a disorder of genetic imprinting coincidentally described by Hans-Rudolf Wiedemann in Germany and J. Bruce Beckwith of Loma Linda University, California in the 1960s. Beckwith-Wiedemann syndrome is the most common overgrowth syndrome. It is characterized by gigantism, macroglossia, anterior abdominal wall defects (most commonly congenital exomphalos), neonatal hypoglycemia,

organomegaly, and the development of multiple tumors during childhood, most commonly Wilms tumors (16–18). *H19*, also known as *BWS*, has been found to be associated with Beckwith-Wiedemann syndrome. The paternal allele of the *H19* gene is always silenced, and only the maternal allele is expressed. Interestingly, variability in *H19* or *BWS* has been associated with tumorigenicity and variable degree of aggressive behavior of certain tumors (19–21). Similarly, the cyclin-dependent kinase inhibitor 1C gene, also known as *CDKN1C* or *p57KIP2*, has been implicated in Beckwith-Wiedemann syndrome (22). *CDKN1C*, like *H19* undergoes the process of imprinting and only the maternal allele is expressed. *CDKN1C* is proposed to be a tumor suppressor gene that, when mutated, leads to the formation of various tumors (22,23). *Insulin-like growth factor 2 gene* (*IF2*) has also been implicated in the presentation of Beckwith-Wiedemann syndrome (24). In the case of *IF2*, in the normal situation, only the paternal copy of the allele is expressed. In tumors derived from patients with Beckwith-Wiedemann syndrome, a lack of imprinting has been demonstrated with both alleles being expressed in association with the disease.

Additional syndromes associated with genetic imprinting include Angelman syndrome, Prader-Willi syndrome, and Silver-Russell syndrome. Angelman syndrome is characterized by developmental delay, sleep disturbance, seizures, movement and balance disorders, microcephaly, and an unusually happy demeanor. Aberrations in *UBE3A* expression that codes for ubiquitin ligase have been implicated in Angelman syndrome. Angelman syndrome is caused by paternal imprinting of a normal *UBE3A* gene located on chromosome 15q11–13 with associated maternally inherited deletion or inactivation of the same genes (25). Converse to Angelman syndrome, Prader-Willi syndrome is caused by maternal imprinting of a normal *UBE3A* gene located on chromosome 15q11–13 with associated paternally inherited deletion or inactivation of the same genes (26). Prader-Willi syndrome is characterized by hypotonia, short stature, hyperphagia, obesity, behavioral issues, hypogonadism, and mental retardation. Silver-Russell syndrome is characterized by intrauterine growth restriction, dwarfism, hypoglycemia, failure to thrive, blue sclera, hemihypertrophy, craniofacial dysostoses, clinodactyly, hypotonia, precocious puberty, and cardiac defects (27,28). Silver-Russell syndrome has been associated with anomalies in chromosome 7 and 11 (29). Hypomethylation of the imprinting control region 1 (ICR1) in 11p15.5 has been demonstrated to affect the expression of *IGF2* and *H19* in association with Silver-Russell syndrome (24,29,30).

Additional Epigenetic Influences

Inheritable changes in phenotype or gene expression caused by mechanisms other than changes in the underlying DNA sequence refers to epigenetics. Gene silencing is a major component of epigenetic phenomenon. Gene silencing is a regulatory process by which certain genes are inactivated by mechanisms other than genetic modifications. This process typically involves DNA methylation or histone acetylation. Genetic imprinting as described above is an example of gene silencing. Genetic imprinting as described above is one of the most common forms of epigenetics by which DNA methylation and histone acetylation lead to the silencing of a specific gene allele based upon it pattern of inheritance. Additional forms of genetic silencing include transposon silencing, transgene silencing, transcriptional gene silencing, and RNA-directed DNA methylation.

Bookmarking is an epigenetic mechanism by which cellular memory is passed to subsequent cellular generations. Patterns of gene expression in the cell are transmitted through cellular memory by bookmarking though mitosis (31–33). This process is critical in the maintenance of cellular phenotype in the cellular lineage. This is accomplished by noncompaction of gene promoters, which are marked for expression during mitosis. Bookmarking may occur via gene silencing by DNA methylation, transcriptional regulation by histone modifications, regulation of gene expression by noncoding small RNA molecules, and retention of regulatory machinery on target gene loci for activation and repression (31–33).

X chromosome inactivation describe the process by one of the two inherited copies of the X chromosome in females is inactivated. In X chromosome inactivation, one copy of the X chromosome is silenced by packaging into heterochromatin, which prevents active transcription. This inactivation occurs in a random fashion in which either the maternal or paternal copy of the X chromosome may be inactivated. Similar to gene silencing, X chromosome inactivation may be associated with high levels of DNA methylation and histone acetylation (34).

Additional forms of epigenetic influence include paramutation, reprogramming, and position effect. Paramutation refers to the interaction between two alleles of a single locus, which results in a heritable change of one allele that is induced by the other allele. Reprogramming describes the process by which epigenetic markers are erased and remodeled. Position effect describes the effect of change in chromosome location on the expression of a gene.

Digenic Inheritance

Digenic inheritance or diallelic inheritance refers to coinheritance of mutation at two distinct genes or genetic loci that produce the phenotype of disease. There are a number of otolaryngologic disorders and syndromes that have been implicated to have a digenic mode of inheritance. There is evidence that certain forms of Usher type 1 syndrome may be transmitted via a digenic pattern of inheritance. Familial studies have implicated mutations in the *CDH23*

and *PCDH15* genes, which code for cadherin 23 and protocadherin 15, respectively, in the etiology of Usher type 1 syndrome (35). Bardet-Biedl syndrome, characterized by obesity, retinal dystrophy, polydactyly, renal malformation, mental retardation, and hypogenitalism, has been demonstrated to have a diallelic mode of inheritance and, in some cases, triallelic inheritance (36). Certain forms of nonsyndromic hearing loss have been demonstrated to be associated with digenic inheritance of mutation in gap junction proteins genes *GJB2* and *GJB6* (37). Digenic inheritance has also been demonstrated in Waardenburg syndrome type II with ocular albinism (38,39). Additionally, certain forms of hypertrichosis have been associated with digenic mutation at the 12q21.2–q22 and 16q21–q23 loci (40).

Complex Genetics

Complex genetics or polygenic inheritance refers to the pattern of inheritance by which multiple genes in combination lead to the phenotype of disorders or disease. Additional factors including lifestyle and environment often influence the phenotype of disease presentation in polygenic inheritance. The vast majority of inherited traits are transmitted via polygenic inheritance. Because of the multifactorial etiology associated with polygenic disorders, it can sometimes be difficult to quantify the probability by which inheritance may be conferred. Common disorders such as hypertension and obesity are frequently encountered examples of disorders with polygenic inheritance. Within otolaryngology, the most commonly cited disorders with polygenic inheritance are cleft lip and cleft palate. The etiology of cleft lip and cleft palate is thought to be complex involving both major and minor genetic influences with variable interactions from environmental factors (41).

Chromosomal Anomalies

In addition to the patterns of genetic transmission described above, chromosomal anomalies are responsible for a number of disorders. Chromosomal anomalies may occur sporadically, or they may be transmitted from generation to generation. Sporadically occurring chromosomal anomalies are more likely to be genetically lethal that inherited anomalies. Chromosomal anomalies take many forms.

Aneuploidy is one of the most common classes of chromosomal anomalies. Aneuploidy refers to an abnormal number of chromosomes. This typically occurs sporadically. The most commonly encountered example of aneuploidy is of trisomy 21 or Down syndrome. In Down syndrome, individuals possess an extra copy of chromosome 21. Patients typically present with a constellation of symptoms and characteristics including impairment in cognitive ability, microgenia, macroglossia, epicanthic folds, upslanting palpebral fissures, short limbs, single transverse palmar crease, high arched palate, short stature, hypotonia, Eustachian tube dysfunction, otologic anomalies, and cardiac anomalies. Down syndrome has also been associated with increased risk of developing certain malignancies including leukemia, retinoblastoma, and germ-cell tumors (42). The presentation of trisomy is often incompatible with life. Forms of trisomy that are compatible with live births include trisomies 9, 13, 18, and 16. Trisomy 9 is characterized by micrognathia, low-set ears, upslanting palpebral fissures, high arched palate, webbed neck, microcephaly, cranial dysostosis, cleft palate, short sternum, rocker bottom feet, cardiac anomalies, mental retardation, and renal anomalies (43). Infants with trisomy 9 often succumb within the first few months of life secondary to feeding difficulties, respiratory deficits, and major organ system dysmorphisms. Trisomy 13, also known as Patau syndrome, is associated with craniosynostosis, upslanting palpebral fissures, broad nose, cleft lip, cleft palate, anteverted nares, micrognathia, small, dysplastic and low-set ears, severe mental retardation, intrauterine growth restriction, cardiac anomalies, and postaxial polydactyly (44,45). Intrauterine growth restriction, clenched hands, rocker bottom feet, low-set or malformed ears, facial clefts, esophageal atresia, renal anomalies, cardiac defects, scalp anomalies, and central nervous system deformities are characteristic of trisomy 18 (46,47). The lifespan for the majority of patients with trisomy 18 is less than 1 year (46,47).

Aneuploidy may also occur in association with the sex-linked chromosomes. This may occur in the form of trisomy X, XYY, XXY, and XXYY. Trisomy X has been associated with hypertelorism, broad nasal dorsum, and recurrent infection, but otherwise, these patients are generally physically and developmentally indistinct from siblings without trisomy presentation (48). Related to trisomy X is the aneuploidy 47 XYY. Similar to trisomy X, 47 XYY syndrome patients typically present with a normal phenotype and are often unaware of their chromosomal anomaly. Reports have, however, linked 47 XYY with infertility (49,50). Klinefelter syndrome (47, XXY) is the second most common aneuploidy and the most commonly encountered sex-linked chromosomal disorder in males (51,52). Klinefelter syndrome is associated with tall stature, palatal cleft, clinodactyly, hypergonadotropic hypogonadism, speech and motor delays, and learning disabilities (52). Rarely, additional sex-linked aneuploidy syndromes, including 48, XXYY, 48, XXXY, and 49, XXXXY, have been described (52).

Chromosomal anomalies may also take the form of chromosomal loss. Chromosomal losses are typically not well tolerated and most commonly precipitate death *in utero*. The most commonly encountered example of chromosomal loss is Turner syndrome (45, X) in which one copy of sex chromosome is lost. However, even in the case of Turner syndrome, the vast majority of fetuses succumb prior to term birth. Those who survive present with characteristic findings of short stature, webbed neck, broad chest,

low frontal hairline, low-set ears, gonadal dysfunction, amenorrhea, infertility, cardiac anomalies, renal anomalies, hypothyroidism, hearing loss, visual disturbance, diabetes, and cognitive deficits.

Chromosomal anomalies may also take the form of rearrangement. Chromosomal rearrangements may take the form of deletions, duplications, translocations, or inversions. Deletions and duplications are more likely to be associated with the phenotype of mental retardation, growth restriction, and multiple congenital malformations, all of which is dependent upon the affected gene. In most cases, a loss of greater than 0.5% or loss of greater than 1% of genetic material is required to produce the phenotypic effect. Translocations and inversions most commonly produce a normal phenotype.

Microdeletion is a common etiology of various syndromes. In microdeletions, duplication or deletion occurs within a small chromosomal segment containing a limited number of linked but functionally unrelated genes. Microdeletion syndromes typically occur sporadically; however, inheritance of microdeletions may occur if the microdeletion results in a balanced chromosomal rearrangement. There are various microdeletion syndromes that are encountered within otolaryngology practice.

Of particular interest is microdeletion within the short are of chromosome 22, the 22q11.2 deletion. Deletions within this region of chromosome 22 have been linked to numerous syndromes including DiGeorge syndrome, velocardiofacial syndrome, CHARGE, and Shprintzen syndrome as well as certain forms of craniocerebellocardiac syndrome, Bernard-Soulier syndrome, Opitz-Frias syndrome, and Cayler cardiofacial syndrome (53–58). The presence of various syndromes associated with a deletion within the chromosomal region is secondary to variability in breakpoints and degree of involvement of the microdeletion. Additional examples of microdeletion syndromes encountered in otolaryngology practice include Williams syndrome (deletion within the q11.23 region of chromosome 7) and Smith-Magenis syndrome (17p11.2 deletion) (59,60).

GENETIC DISORDERS IN OTOLARYNGOLOGY: HEAD AND NECK SURGERY

There are a number of genetic disorders that are encountered within otolaryngology practice. This section is designated to highlight the genetic disorders encountered within the various subspecialties of otolaryngology. The list of disorders presented below is by no means meant to be all inclusive.

Genetic Disorders in Otology and Neurotology

As discussed previous within of this chapter, there are various otologic disorders that are associated with genetic etiology. The most commonly encountered genetic disorders in otology are associated with the phenotype of hearing loss. Approximately half of all congenital sensorineural hearing loss is of hereditary etiology. Among the patients with hereditary sensorineural hearing loss, approximately 70% to 80% of cases are associated with nonsyndromic hearing loss. Autosomal recessive inheritance accounts for approximately 75% to 85% of all nonsyndromic hearing loss. Autosomal dominant inheritance accounts for approximately 15% to 20% of nonsyndromic hearing loss, and approximately 1% to 3% of nonsyndromic hearing loss represents an X-linked pattern of inheritance. Mutations within connexin 26 (*GJB2*) account for up to 50% of all congenital recessive nonsyndromic hearing loss (called DFN1). There are multiple mutations within this gene that have been identified in association with nonsyndromic hearing loss, and several are common; four of the most common are 35delG (deletion of guanine at the 35th position in the gene sequence), 167delT, 235delC, and W24X (substitution of tryptophan by another amino acid at the 24th position in the protein). 35delG and W24X are common in many populations, while 167delT and 235delC are common in individual of Ashkenazi Jewish and Asian descent, respectively.

There are various forms of inherited syndromic sensorineural hearing loss. There are over 400 syndromes with associated hearing loss. Autosomal recessive forms of syndromic hearing loss include Usher syndrome, Refsum disease, Jervall Lange-Nielsen syndrome, Goldenhar syndrome, and Pendred syndrome.

Usher syndrome is associated with the phenotype of congenital sensorineural hearing loss, progressive retinitis pigmentosa, vestibular dysfunction, mental retardation, cataracts, and decreased cardiac conduction. Usher syndrome may be transmitted by an autosomal dominant or X-linked pattern of inheritance, but the primary mode of inheritance is autosomal recessive. Mutations within the *CDH23*, *CLRN1*, *GPR98*, *MYO7A*, *USH1C*, *USH1G*, and *USH2A* gene have been identified as causes of Usher syndrome (61–64). There are three identified types of Usher syndrome: (a) Usher type I, which is characterized by profound congenital sensorineural hearing loss, no vestibular response, and legal blindness by early adulthood; (b) Usher type II, which is characterized by moderate to severe congenital sensorineural hearing loss, legal blindness by mid-adulthood, and normal vestibular function; and (c) Usher type III, which is characterized by progressive sensorineural hearing loss, varied progressive blindness, and progressive vestibular dysfunction. Digenetic or polygenetic inheritance has been proposed in the pathogenesis of Usher type III.

Refsum disease is an autosomal recessive neurocutaneous syndrome characterized by peripheral polyneuropathy, cerebellar ataxia, retinitis pigmentosa, sensorineural hearing loss, and ichthyosis. Two genes have been identified in association with Refsum disease. Ninety percent

of all cases of Refsum disease are caused by mutations within the *PHYH* gene with the remainder of cases being linked to mutations within the *PEX7* gene (65–67). Both genetic mutations lead to deficient activity of the peroxisomal enzyme, phytanoyl-CoA hydroxylase, a peroxisomal enzyme leading to disruption in phytanic acid breakdown.

Jervell Lange-Nielsen syndrome is an autosomal recessive disorder associated with the phenotype of sensorineural hearing loss with associated cardiac dysfunction, namely, prolonged Q-T interval. In association with the presentation of a prolonged QT interval, patients with Jervell Lange-Nielsen syndrome have the propensity for cardiac arrhythmia, cardiac syncope, and sudden death. Mutations within two genes have been associated with the phenotypical presentation of Jervell Lange-Nielsen syndrome, *KCNE1* and *KCNQ1* (68,69). Both genes code for proteins that are critical in potassium channel function.

Goldenhar syndrome is characterized by various otologic findings associated with the phenotype of conductive hearing loss. These include preauricular appendages, pinna abnormalities, aural atresia, ossicular malformation, abnormal development of the facial nerve, anomalies of the stapedius muscle, abnormalities of the semicircular canals and anomalous oval window. Additionally, patients with Goldenhar syndrome may present with the phenotype of hemifacial microsomia, epibulbar dermoids, colobomas of the upper eyelid, vertebral abnormalities, and mild mental retardation. The mode of transmission for Goldenhar syndrome is of an autosomal recessive mode of transmission. The genetic basis for Goldenhar syndrome, however, has not yet been identified.

Alterations within the pendrin protein have been identified as the etiologic factor in the development of Pendred syndrome. The pendrin protein is a transporter protein; dysfunction of the pendrin protein leads to dysfunction of chloride, iodide, and bicarbonate ion transport. The pendrin protein is encoded by the *SLC26A4* gene; this gene has been found to be mutated in patients with Pendred syndrome (70). Pendred syndrome is inherited via an autosomal recessive pattern of inheritance and is associated with the phenotype of enlarge vestibular aqueduct, severe to profound sensorineural hearing loss, Mondini malformation, and euthyroid goiter.

There are a number of autosomal dominant syndromes associated with the phenotype of hearing loss. A sample list of these disorders include Stickler syndrome, BOR syndrome, Treacher-Collins syndrome, Waardenburg syndrome, Apert syndrome, Crouzon syndrome, Bjornstad syndrome, Keipert syndrome, NF1, and neurofibromatosis type 2 (NF2). This list represents the most frequently encountered autosomal dominant disorders of hearing loss in otolaryngology.

Stickler syndrome presents with the phenotype of progressive sensorineural hearing loss, marfanoid habitus, ocular abnormalities (retinal detachment, cataracts, and myopia), arthritic abnormalities (precocious arthritis and joint hypermobility), and Pierre Robin sequence. Mutations within genes responsible collagen production, processing and assembly have been associated with Stickler syndrome. These genes include *COL2A1*, *COL9A1*, *COL11A1*, and *COL11A2* (71,72). *COL2A1* is most commonly associated with Stickler type 1. Mutations within the *COL9A1* gene are more commonly associated with an autosomal recessive pattern of inheritance.

BOR syndrome, also known as Melnick-Fraser syndrome, is characterized by the phenotype of renal anomalies ranging from mild anomalies to agenesis, pinna deformities, preauricular pits, preauricular fistulas, preauricular tags, mixed hearing loss, and Mondini malformation. Mutation within the *EYA1* gene is most commonly associated with BOR syndrome. However, mutations within the *SIX1 and SIX5* genes have also been associated with BOR syndrome demonstrating genetic heterogeneity (more than one gene causing the same phenotype).

Treacher-Collins syndrome is associated with the phenotype of sensorineural, conductive or mixed hearing loss secondary to auricular deformities, aural atresia, external auditory canal stenosis, preauricular fistulas, ossicular malformation, and enlarged vestibular aqueduct. Treacher-Collins syndrome patients have normal intelligence and may present with aberrant facial nerve, Mondini malformation, zygomatic hypoplasia, mandibular hypoplasia, downward slanting palpebral fissures, coloboma of the lower eyelid, and palatal defects. Mutations within the *TCOF1* gene encoding for the treacle protein, critical to prenatal bone and soft tissue development, have been identified in association with Treacher-Collins syndromes (73–75).

Waardenburg syndrome is an autosomal dominant disorder characterized by pigmentary anomalies (i.e., heterochromia iridis, skin depigmentation, white forelock) craniofacial anomalies (i.e., dystopia canthorum, synophrys, and broad nasal dorsum), and sensorineural hearing loss. The genetic mutation most commonly cited in association Waardenburg syndrome is *PAX3*, which is responsible for type I and III Waardenburg syndrome (76–78). Additionally *MITF* and *SNAI2* mutations have been associated with Waardenburg type II; mutations within the *SOX10*, *EDN3*, and *EDNRB* genes have been associated with Waardenburg type IV, which presents with an autosomal recessive mode of inheritance (76–78).

Additional syndromes with otologic manifestations presenting with an autosomal dominant mode of inheritance include Apert syndrome, Crouzon syndrome, NF1, and NF2. Apert syndrome is caused by mutation within the *FGFR2* gene; similarly, Crouzon syndrome is caused by mutations within the *FGFR* gene. NF1 is associated with mutations in the neurofibromin gene on chromosome 17. Mutations within the merlin gene on chromosome 22 are associated with NF2.

A number of X-linked syndromes have been identified with otologic manifestations as well. Keipert syndrome,

or nasodigitoacoustic syndrome, which is characterized by misshaped nose, broad thumbs and halluces, brachydactyly, sensorineural hearing loss, and facial dysmorphisms, has been found to be caused by mutations within the q22.2–q28 positions on the X chromosome (79–81). Alport syndrome, characterized by ocular, renal and otologic anomalies, is associated with mutations within the type IV collagen genes on the X chromosome. Norrie syndrome (SNHL and blindness) is associated with mutations in the NDP gene on chromosome X. Otopalatodigital syndrome is caused by mutations within the *FLNA* gene on the X chromosome. Wildervanck syndrome (abducens palsy, cervical fusion, and SNHL or mixed hearing loss) is attributed to an X-linked dominant mode of inheritance.

Mitochondrial genomic deletions have been associated with the phenotype of sensorineural hearing loss. Acquired mitochondrial genomic deletions have been associated with the phenotype of age-related hearing loss (82). Certain forms of nonsyndromic and aminoglycoside-induced hearing loss have been found to be inherited through mitochondrial genomic deletions (83,84).

Genetic Disorders in Head and Neck Cancer

Genetics plays a critical role in head and neck cancer. Mutations within proto-oncogenes and tumor suppressor genes have been found to be key etiologic factors in various forms of sporadic head and neck cancer. Additionally, various genetic syndromes and disorders have been associated with inherited forms of head and neck cancer.

A number of proto-oncogenes and tumor suppressor genes have been identified in conjunction with squamous cell carcinoma of the head and neck. *p53* is a commonly encountered tumor suppressor gene located at 17p13.1, which is involved in cell cycle regulation and apoptosis. Mutations within *p53* have been identified in on average 40% to 70% of head and neck squamous cell carcinoma (85–89). *Cyclin D1* is an oncogene whose products accelerate cell cycle progression. Normal gene products of *p16* and *p21* are essential in the suppression of cyclin and cyclin-dependent kinase pathways. The *bcl-2* is an oncogene that functions to inhibit apoptosis and counteract p53. The *RET* gene is a proto-oncogene that is a cell surface tyrosine kinase receptor that is involved in the signal transduction pathway for cell growth. Alterations in the expression of each have been implicated in the phenotypical presentation of head and neck squamous cell carcinoma (90–93).

Additionally, genetic inheritance has been found to play a critical role in the development of various head and neck cancers including esophageal cancer, thyroid cancer, and cutaneous malignancies. Both Plummer-Vinson syndrome and tylosis are disorders associated with an increased incidence of esophageal cancer. Plummer-Vinson syndrome is a disorder of complex genetics with both genetic predisposition and environmental factors lead to the phenotypical presentation of disease (94). It is characterized by dysphagia, esophageal strictures, glossitis, iron deficiency anemia, cheilosis, koilonychias, splenomegaly, and squamous cell carcinoma of the postcricoid region or cervical esophagus. Tylosis is an autosomal dominantly inherited disorder characterized by esophageal cancer and hyperkeratosis of the palms and soles. Mutations within the *TOC* gene located on chromosome 17q25 have been implicated in the phenotype of tylosis (95).

Thyroid cancer has been found to be associated with a variety of syndromes including Cowden syndrome, Gardner syndrome, Werner syndrome, and the multiple endocrine neoplasia (MEN) type II syndromes. Cowden syndrome is an autosomal dominant disorder characterized by multiple trichilemmomas; gingival fibromatosis; hamartomas of the breast, thyroid, and gastrointestinal tract; and an increased risk for breast cancer, thyroid adenomas, and thyroid cancer. Mutations within the tumor suppressor gene *PTEN* have been implicated in the inheritance of Cowden syndrome (96). Gardner syndrome is an autosomal dominantly inherited disorder with the phenotypical presentation of multiple epidermal cysts, thyroid carcinoma, facial bone osteomas, cutaneous fibromas, lipomas, leiomyomas of the gastrointestinal tract, and adenomatous polyps of the colon. Mutations within the *APC* gene located at the q21 loci of chromosome 5 are causative in Gardner syndrome (97). Mutations within the *WRN* gene, which encodes the Werner protein, are associated with Werner syndrome (98). The Werner protein is believed to function in DNA maintenance and repair. Werner syndrome is inherited by an autosomal recessive pattern of inheritance and is characterized by the phenotype of accelerated aging, short stature, and increased incidence of thyroid cancer and other malignancies. MEN type II is characterized by the phenotype of medullary thyroid carcinoma and is subdivided into two subgroups: MEN IIA (medullary thyroid carcinoma, pheochromocytoma, parathyroid adenoma/hyperplasia, and hyperparathyroidism) and MEN IIB (medullary thyroid carcinoma, pheochromocytoma, marfanoid habitus, multiple mucosal neuromas, hyperplastic corneal nerves). Mutations within the *RET* gene are associated with the MEN II syndromes (99).

Various cutaneous malignancies manifesting within the head and neck are associated with a genetic mode of transmission, namely, Gorlin syndrome and xeroderma pigmentosa. Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome, is an autosomal dominant disorder caused by mutations within the tumor suppressor gene *PTCH1* (100). Gorlin syndrome presents with the phenotype of multiple basal cell carcinomas, odontogenic keratocyst, bifid ribs, scoliosis, fontal bossing, and mental retardation. Xeroderma pigmentosa is an autosomal recessive disorder characterized by sun sensitivity, ocular disorders and a greatly increased risk of cutaneous neoplasms including basal cell carcinoma, squamous cell carcinoma, and melanoma. Diallelic mutation in the *XPA*, *ERCC3*, *XPC*, *ERCC2*, *DDB2*, *ERCC4*, and *ERCC5* genes as well as

monoallelic mutation within the *ERCC1* and *POLH* gene have been associated with xeroderma pigmentosa (101).

Genetic Disorders in Rhinology

Osler-Weber-Rendu syndrome, also known as hereditary hemorrhagic telangiectasia, is an autosomal dominant disorder caused by defects within the contractile elements in vessels cause in most instances by mutations within the *ENG* or *ALK-1* gene (102). This results in telangiectasias and arteriovenous malformations within various organ systems, including the nose, lung, liver, gastrointestinal tract, and brain. One of the earliest manifestations of Osler-Weber-Rendu syndrome is recurrent, recalcitrant epistaxis and cutaneous telangiectasias.

Cystic fibrosis is an autosomal recessive disorder commonly encountered in the otolaryngology practice. Cystic fibrosis is caused by a mutation within the CF transmembrane conductance regulator (*CFTR*) gene housed within chromosome 7, which encodes a chloride channel protein. Mutations within this gene results in dysfunction in exocrine gland function including decreased chloride secretion and increased sodium and water reabsorption. The phenotypical presentation of cystic fibrosis includes chronic sinusitis, respiratory dysfunction, pancreatic insufficiency, and infertility.

Kartagener syndrome or primary ciliary dyskinesia is an autosomal recessive disorder characterized by ciliary dyskinesia resulting from deficiency in the ciliary outer dynein arm. The phenotype of Kartagener syndrome typically includes abnormal ciliary motion, impaired mucociliary clearance, otitis media, sinusitis, situs inversus, bronchiectasis, chronic cough, and male infertility. Because Kartagener syndrome is a genetically heterogeneous disorder, it has been a challenge to identify all of the genetic mutations in association with this disease process. To date, eight genes have been identified in association with Kartagener syndrome: *DNAI1*, *DNAH5*, *DNAH11*, *DNAI2*, *KTU*, *RSH9*, *RSPH4A*, and TXNDC3 (103).

Genetic etiologies for various inherited immunodeficiency syndromes have been elucidated. Common variable immunodeficiency is the most common form of hypogammaglobulinemia characterized by failure of B-cell maturation. The majority of cases are acquired in nature; however, 15% of patients possess the inherited form of disease. Numerous mutations have been identified in association with common variable immunodeficiency: an autosomal dominantly inherited mutation in the tumor necrosis factor receptor superfamily member 13B gene (*TNFRSF13B*) located at 17p11.2, an autosomal recessively inherited mutation in the inducible T-cell costimulator gene (*ICOS*) located at 2q33, and an autosomal recessively inherited mutation in the B-lymphocyte antigen CD 19 gene (*CD19*) located at 16p11.2. X-linked agammaglobulinemia is associated with mutation in the Bruton tyrosine kinase gene (*BTK*), which results in marked reduction in all classes of serum immunoglobulin and absent B cells. X-linked lymphoproliferative disorder, which is characterized by inappropriate immune response to EBV infection, severe or fatal infectious mononucleosis, dysgammaglobulinemia, and lymphoproliferative disorders typically B cell in origin, has been linked to mutations in the *SH2D1A* gene, which encodes the SH2D1A protein. Finally, autosomal recessive agammaglobulinemia results from mutations in mu immunoglobulin heavy chain gene (*IGHM*), gamma 5 light chain gene (*IGLL1*), B-cell linker protein gene (*BLNK*), and Ig alpha (*CD79A*).

Genetic Disorders in Laryngology

Within the otolaryngology practice, there are, additionally, various syndromes and disorders of genetic etiology that manifest with the phenotype of laryngeal disorder and dysfunction. Opitz-Frias syndrome is a congenital disorder inherited by an X-linked or autosomal dominant mode of inheritance. It is characterized by hypertelorism, cleft lip, cleft palate hypospadias, and laryngeal cleft. The X-linked form of Opitz-Frias syndrome is associated with a mutation within the *MID1* gene; the autosomal dominant form is associated with a mutation with in the short arm of chromosome 22, 22q11.2 (104,105). As mentioned previously, mutations within this same loci of chromosome 22 are associated with numerous syndromes including DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome, and Cayler cardiofacial syndrome.

Pallister-Hall syndrome is a rare autosomal dominant disorder with associated laryngeal anomalies. The phenotypes of laryngeal cleft, hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, postaxial polydactyly, and bifid epiglottis are associated with Pallister-Hall syndrome. Mutations within the *GLI3* gene are causative (106).

Additionally, laryngeal clefting and tracheoesophageal fistulae are associated with VACTERL association (vertebral anomalies, anal atresia, cardiovascular anomalies, tracheoesophageal fistula, esophageal atresia, renal/radial anomalies, and limb defects). Various genetic disorders including Goldenhar syndrome, trisomy 18, and Klippel-Feil syndrome are associated with VACTERL.

Finally, among the laryngeal disorders of potential genetic inheritance is congenital (hereditary) angioedema. Approximately 75% of patients with congenital angioedema inherit the disorder via an autosomal dominant mode of inheritance; the remainder of cases present sporadically. Mutations within the *C1NH* gene resulting in a deficiency in the C1 esterase inhibitor are responsible (107–109).

DIAGNOSIS OF GENETIC DISORDERS

The diagnosis and treatment of the otolaryngologic patient with genetic disorders often requires a multidisciplinary approach with our genetic colleagues playing a critical and

integral role. Knowledge of the human genome and identification of the genetic etiology of a plethora of genetic disorders has facilitated the detection and diagnosis of various genetic disorders. As technology continues to advance, techniques for the diagnosis genetic disorders continue to evolve in terms of speed and accuracy.

Methods for genetic analysis and diagnosis may broadly be classified as indirect detection (linkage analysis) and direct detection methods. By and large, the vast majority of techniques utilized for diagnosis of genetic disorders are within the direct detection class of technology. Direct detection, however, requires knowledge of the gene and encountered mutations responsible for the disease phenotype is required. Several methods for direct analysis are available, which provide rapid and cost-effective detection of known mutations (Table 9.3). The most precise method of direct detection currently utilized is polymerase chain reaction analysis, which amplifies short sequences of single-stranded DNA homologous to genomic DNA allowing for evaluation of mutation within specific gene regions. Despite all of the technologic advances, the diagnosis of certain genetic disorders still poses a challenge particularly in disease processes with unidentified mutations or complex genetic etiologies.

MOLECULAR THERAPY IN GENETICS

The decoding of the human genome presents a world of opportunity for future innovation by means of molecular therapy. Although still in its infancy, molecular therapy houses great potential in advancing treatment in various disease processes that remain a therapeutic challenge. Stem cell therapy and genetic therapy stands on the horizon as potential therapeutic techniques that could revolutionize medical care.

TABLE 9.3 METHODS USED FOR DIRECT DETECTION OF GENETIC MUTATIONS

Direct Detection Techniques
Allele refractory mutation system
Allele-specific oligonucleotide hybridization
Deletion analysis
Denaturing gradient gel electrophoresis
Heteroduplex analysis
Mismatch cleavage (chemical or enzymatic)
Oligonucleotide ligation assay
Protein truncation test
Restriction enzyme analysis
Reverse dot blotting (DNA chip technology)
Sequencing
Single-strand conformation polymorphism analysis
Sizing of trinucleotide repeats
Southern blotting

Stem cells are pluripotent, progenitor cells with the propensity for differentiation into various cell and tissue types. Current research is underway to identify pathways to facilitate targeted differentiation of stem cells into specific cell and tissue types. The ultimate goal is one of replacement of absent or dysfunctional cell populations leading the presentation of various disease processes. There are currently five forms of stem cells under investigation: human embryonic stem cells, adult somatic stem cells (i.e., bone marrow stem cells), cord blood stem cells, fetal stem cells, amniotic stem cells, and recently developed induced pluripotent stem cells. For more than 30 years, bone marrow stem cell and, more recently, umbilical and core blood stem cells have been have been utilized successfully in the treatment genetically inherited hematogenous diseases including thalassemia major and sickle cell anemia (110–112). Stem cell therapy is currently under investigation in a wide range of disease processes including cardiovascular disease, diabetes mellitus, and cancer. The challenge remains in improving the accuracy and consistency of differentiation to ensure targeted issue differentiation as well as localization of stem cells to target tissue.

Genetic therapy is an experimental technique with the potential for correcting defective genes responsible for the disease phenotype. Gene therapy may be performed via several approaches including insertion of a normal gene into a nonspecific location within the genome to replace the nonfunctional gene, replacement of the abnormal gene with a normal gene through homologous recombination, repair of the abnormal gene through selective reverse mutation rendering the gene functional, and silencing or regulation of the abnormal gene through alteration of promoters. The most commonly employed mechanism of genetic therapy is the insertion of a normal gene in to the genome in a nonspecific location to replace the nonfunctional gene.

Gene insertion and replacement is commonly performed utilizing a viral vector targeted at cells expressing the disease phenotype. Infection of target tissue with the viral vector allows for unloading of the desired genetic material and incorporation of the desired normal gene into the target cell genome. Various viruses have been used as vectors in gene therapy including retroviruses, adenoviruses, adeno-associated viruses, and herpes simplex viruses. In addition to viral vectors, various other techniques have been described that are utilized less frequently. Liposomes, lipid spheres with aqueous cores, may be utilized to introduce therapeutic DNA material. Alternatively, therapeutic DNA may be introduced directly into target cell; however, this technique is limited in that it requires large volumes of DNA and is limited to use in only certain tissue types. Although the efficacy is limited, therapeutic DNA may also be introduced by chemically linking the DNA to specific cell receptor ligands.

In addition to genetic therapies targeted at the replacement on nonfunctional genes or silencing of malfunctioning

genes, research in genetic therapy has also been targeted at selective termination of target cell populations. This has been of particular interest in the management of head and neck cancers. Cell populations expressing certain genetic mutations in the form of marker proteins or receptors may be targeted in an attempt to alleviate the malignant cell presentation.

Throughout its history, research into genetic therapy has experienced a number of setbacks including fatally in early clinical trials. Despite this, genetic therapy houses great promise in the management of challenging and debilitating genetic disorders. Further research is necessary to perfect these techniques and ensure patient safety in this potentially revolutionary method of treatment.

HIGHLIGHTS

- Genetics are the backbone of human existence.
- DNA provides the basic code from which all proteins and enzymes essential to life are formed.
- DNA is transcribed to RNA, which in turn is translated into a series of nucleotide triplets that form proteins.
- Mendelian genetics describes autosomal dominant, autosomal recess, and sex-linked inheritance.
- Non-Mendelian forms on inheritance include mitochondrial inheritance, genetic imprinting, gene silencing, bookmarking, x-chromosome inactivation, digenic inheritance, complex genetics, and chromosomal anomalies.
- Genetic disorders may present with variable penetrance (proportion of individuals carrying a gene variant that express the phenotypical changes) or variable expression (variation in the phenotype associated with a genetic mutation).
- A wide variety of genetic disorders are encountered in the various subspecialties of otolaryngology.
- Various methods are on the horizon in the management of genetic disorders to correct genetic mutations including genetic therapy and stem cell therapy.

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Microbiology, Infections, and Antibiotic Therapy

10

Thuy-Anh N. Melvin *Murugappan Ramanathan Jr.*

INTRODUCTION

Infections of the ears, nose, throat, and head and neck constitute a tremendous number of physician office visits and subsequently antibiotic treatment. Therefore, it is crucial that the otolaryngologist be familiar with common infections of the head and neck and management of these disease processes. In this chapter, we provide a brief overview of commonly prescribed antibiotics and discuss their utility in treating otolaryngologic infections based on current evidence. Due to emerging trends of antibiotic resistance and the introduction of new antibiotics, the reader is urged to supplement this material with The Sanford Guide to Antimicrobial Therapy, the online Johns Hopkins Antibiotic Guide, as well as current infectious diseases literature.

Commonly Utilized Antimicrobial Agents in Otolaryngology

Listed below are brief overviews of commonly prescribed antibiotics, which include their mechanism of action and common side effects. The antimicrobial coverage is discussed in more detail in the management section.

Penicillins

Penicillins target actively dividing cells affecting the third stage of cell wall synthesis in bacteria. This group of drugs is active against gram-positive cocci (*Streptococcus*, Group A and B) and bacilli (*Corynebacterium*), gram-negative cocci (*Neisseria*) and bacilli (*Streptobacillus*), some anaerobes (*Fusobacterium*, *Clostridium*, *Bacteroides*), and other bacteria such as *Treponema*, *Leptospira*, *Enterobacter*, and *Acinetobacter*. Adverse reactions include 1% to 5% risk of rash, which does not preclude future use of penicillin since recurrence of rash only occurs in 50% of patients. More serious allergic reactions can involve anaphylaxis, hives, angioedema, and bronchospasm, which require lifelong contraindication to penicillin use. However, allergy testing for major and minor determinants of penicillin is available and currently identifies 90–97% of those with allergy to penicillin. There have also been reported cases of nephropathy. Resistance has emerged through alterations in penicillin-binding proteins, inability to penetrate bacterial cell walls via porin channel blockage, beta-lactamase production, and enzymatic hydrolysis of penicillin (1). The spectrum of coverage for the various types of penicillins is depicted in Table 10.1.

Cephalosporins

Similarly, cephalosporins act by inhibiting the third stage of cell wall development. They also affect the binding of specific proteins on cell membranes, cause cell permeability changes, and inhibit protein synthesis and autolysin release. There are four generations of cephalosporins with the first having the most gram-positive efficacy and with the third and fourth generations being more active against gram-negative anaerobes (see Table 10.2). A newer fifth-generation cephalosporin class is emerging with activity toward *methicillin-resistant Staphylococcus aureus* (MRSA) (2,3). Side effects include hypersensitivity, neutropenia, thrombopenia, gastrointestinal disturbances, and renal impairment. Resistance has evolved through beta-lactamase and decreased cell wall permeability. Since penicillins and cephalosporins are structurally related, patients with a penicillin allergy are often not given cephalosporins for concern for cross-reactivity. Studies have examined the tolerability of cephalosporins in penicillin-allergic patients and found that there is a low risk of allergic reactions or anaphylaxis. Generally, first-generation cephalosporins such as cephalexin and cefazolin show higher rates of allergic reactions in patients with penicillin allergy. On the other hand, second- and third-generation cephalosporins such as cefuroxime, cefprozil, and cefdinir seem to have lower rate of allergic reactions in people with penicillin allergy. Overall, the clinician must err on the side

TABLE 10.1 PENICILLIN ANTIBIOTIC COVERAGE AND RESISTANCE

Penicillin Class	Antibacterial Spectrum	Resistance Pattern
Penicillin G or V	*S. pyogenes* (group A beta hemolytic), some *S. pneumoniae*	*S. pneumoniae*
Aminopenicillins (ampicillin, amoxicillin)	*H. influenza*, *S. pneumonia* (intermediate resistance), *S. pyogenes*, *E. coli*, *Proteus*, anaerobes	*S. aureus* resistance, emerging resistance to *H. influenza*, *M. catarrhalis*, *S. pneumoniae*
Antistaphylococcal penicillins (methicillin, oxacillin, dicloxacillin, nafcillin)	*S. aureus* (Not MRSA)	MRSA strains
Antipseudomonas penicillins (IV only) (mezlocillin, ticarcillin, piperacillin)	*P. aeruginosa*	*S. aureus* and anaerobe resistance
Augmented aminopenicillins (combined with beta lactamase inhibitor): amoxicillin/clavulanate (PO), ampicillin/sulbactam (IV)	*S. aureus* (not MRSA), *H. influenza*, *M. catarrhalis*, *S. pneumoniae*, *S. pyogenes*, *E. coli*, *Proteus*, and anaerobes	Emerging resistance to *S. pneumoniae*
Augmented antipseudomonas penicillins (combined with beta lactamase inhibitor): ticarcillin/clavulanate (IV), piperacillin/tazobactam (IV)	*P. aeruginosa*, *S. aureus* (not MRSA), anaerobes	Some strains of *P. aeruginosa*

MRSA, methicillin resistant *S. aureus*.

of caution when giving a penicillin-allergic patient cephalosporins and an oral challenge under medical supervision is recommended prior to use (4,5).

Macrolides

Macrolides, for example, erythromycin, exhibit bacteriocidal activity by binding to the 50S subunit of the 70S rRNA complex, thereby inhibiting protein synthesis. Effective against similar pathogens such as penicillins, they are also effective against atypical bacteria such as *Mycobacterium*, *Legionella*, and *Actinomyces* species. Adverse reactions are hypersensitivity, gastrointestinal upset, and cholestatic hepatitis. Resistance in macrolides has emerged through alterations of the 50S subunit and plasmids, which primarily affects *Haemophilus influenza*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*.

Clindamycin

Clindamycin inhibits protein synthesis by binding to the 50S ribosomal subunit. It is useful against anaerobic gram-negative (e.g., *Prevotella*, *Fusobacterium*, and *Bacteroides*), gram-positive cocci (e.g., *S. aureus*, community-acquired MRSA and *S. pneumoniae*), and aerobic gram-negative (e.g., *Pseudomonas*, *Legionella*, *H. influenzae*, and *Moraxella*) bacteria. Untoward reactions include the development of pseudomembranous colitis, nausea/diarrhea, hypersensitivity, and leukopenia.

TABLE 10.2 CEPHALOSPORIN ANTIBIOTIC COVERAGE AND RESISTANCE

Cephalosporin Class	Spectrum of Activity	Resistance Patterns
First generation: cephalexin (PO), cefazolin (IV)	*S. aureus* (not MRSA), *S. pyogenes*, some *S. pneumoniae*, *E. coli*, *Proteus*	Emerging *S. pneumonia and S. aureus* resistance *H. influenza*, *Pseudomonas*, and *M. catarrhalis* resistance
Second generation: cefuroxime, cefdinir, loracarbef, cefprozil, etc.	*H. influenza*, *S. pneumonia* (PCN susceptible), *S. pyogenes*, *M. catarrhalis*, *N. gonorrhoeae*	Emerging *S. pneumoniae* resistance Resistant to *Pseudomonas* and anaerobes
Third generation: ceftibuten (PO) cefotaxime (IV), ceftriaxone (IV) (Excellent CSF penetration)	*S. Pneumoniae* (all strains except multidrug resistant), *H. influenza*, *M. catarrhalis*, *N. meningitides/gonorrhoeae*	Resistant to *Pseudomonas*, Emerging resistance to *S. pneumonia*
Fourth generation (antipseudomonal): cefepime, ceftazidime	*P. aeruginosa*, *S. aureus*, multidrug resistant *S. pneumonia*	Emerging resistance to *S. pneumoniae* (similar to third generation)
Fifth generation: ceftaroline, ceftobiprole	MRSA (Not FDA approved as of 2011), *P. aeruginosa*, multidrug resistant *S. pneumonia*	None known

MRSA, methicillin resistant *S. aureus*; PCN, penicillin; MDR, multidrug resistant; CSF, cerebrospinal fluid; FDA, Food and Drug Administration.

Similar to macrolides, resistance has developed through alteration in the protein component of the 50S subunit.

Fluoroquinolones

Fluoroquinolones are bactericidal agents that work by interfering with DNA replication via inhibiting DNA gyrase and topoisomerase II enzymes. They work well against a broad range of bacteria including *Pseudomonas*, *Streptococcus pyogenes*, and *S. pneumoniae*, *S. aureus*, *Moraxella catarrhalis*, and *H. influenzae*. However, resistance has evolved rapidly through mutations in DNA gyrase and topoisomerase enzymes as well as plasmid-mediated resistance.

Fluoroquinolone antibiotics are associated with risk of neurotoxicity and multiple musculoskeletal complications, most commonly, tendon rupture (6). Although once the most commonly prescribed antibiotic to adults, a black box warning was issued by the Federal Food and Drug Administration in 2008 citing increased risk of tendon rupture and tendonitis (7). More recently, another black box warning for levofloxacin was issued from its manufacturer in 2011 for an increased risk of tendon rupture specifically in adults over 60 when given in combination with oral corticosteroids as is commonly prescribed to chronic rhinosinusitis (CRS) patients. Given this well-known side effect, judicious use of this antibiotic is recommended, and when prescribed, patients should be appropriately informed of this possible side effect.

Trimethoprim–Sulfamethoxazole

Trimethoprim and sulfamethoxazole act together synergistically by inhibiting sequential steps in the folic acid synthesis pathway. It is effective against *Escherichia coli*, *S. aureus, community-acquired MRSA*, and *Listeria*. Side effects include mild to severe hypersensitivity (especially in sulfa allergic patients), Stevens-Johnson syndrome, myelosuppression, mydriasis, agranulocytosis, and severe liver damage. Mechanisms of resistance include binding alterations due to folic acid enzyme mutations.

Aminoglycosides

Aminoglycosides, for example, gentamicin, tobramycin, and streptomycin, inhibit protein synthesis by binding to the 30S ribosomal subunit. This class of drugs is useful against aerobic, gram-negative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter*, *Enterobacter*, and some *Mycobacteria*. Adverse reactions to consider include nephrotoxicity and ototoxicity, which is mediated by injury to the outer hair cells of the cochlea, specifically in patients that harbor a mutation in the 12S rRNA gene (8,9). Since this mutation is maternally transmitted, eliciting a detailed history can often prevent unnecessary administration of aminoglycosides to susceptible patients preventing deafness.

Vancomycin

Like penicillins, vancomycin targets and interferes with proper cell wall formation in gram-positive bacteria. Vancomycin resistance can emerge from alterations in the tail amino acids to which the drug binds. Nephrotoxicity and ototoxicity have been reported but are rare adverse reactions. Red man syndrome is an infusion reaction that occurs a few minutes after infusion characterized by erythematous rash. It is related to nonspecific mast cell degranulation and is not an IgE-mediated phenomenon. Occasionally, angioedema and hypotension can happen. To prevent red man syndrome, slow infusion is recommended over at least 60 minutes at a maximum rate of 10 mg/min for doses greater than 500 mg. Antihistamines can be used for premedication.

Topical Application of Antibiotics

In light of recent studies that suggest that chronic otolaryngological infections such as sinusitis and otitis media may be caused by bacterial biofilms (10–13), concurrent topical application of antibiotics in addition to systemic antibiotics may be beneficial in disrupting biofilms (14). Although numerous antibiotics are utilized topically, their efficacy compared to oral antibiotics remains unclear. The best documented topical antibiotics are bacitracin/neomycin/polymyxin-B and mupirocin.

Combinations of bacitracin and neomycin/polymyxin-B, in the form of skin ointments and ototopical preparations (along with hydrocortisone), are utilized for localized skin infections, prevention of skin infections, and otitis externa/media (in the setting of myringotomy tubes). The combination of these agents has efficacy against most gram-negative and gram-positive aerobic organisms and *P. aeruginosa* (primarily polymyxin-B). In addition, fluoroquinolone-based ototopicals are also effective against *P. aeruginosa*. The primary adverse reaction of bacitracin/neomycin/polymyxin-B is hypersensitivity. Mupirocin is another topical antibiotic primarily used in the sinonasal cavities to eradicate colonization and infection by MRSA and works by binding to bacterial isoleucine tRNA ligase thereby interfering with protein translation of bacterial ribosomal RNA.

Antifungals

Although numerous antifungal compounds exist, the primary classes of drugs are azole antifungals and polyene antifungals. Azole antifungals (e.g., voriconazole, fluconazole, and ketoconazole) inhibit the enzyme lanosterol 14 α-demethylase, which allows conversion of lanosterol to ergosterol. Therefore, azole antifungals inhibit fungal growth by depleting ergosterol in the fungal membrane thereby disrupting its structure. In general, voriconazole is active against systemic fungal infections with *Aspergillus* and *Candida* but lacks efficacy against *Mucor*. In addition, fluconazole is effective against *Candida* and *Cryptococcus* and has excellent CSF penetration. A major disadvantage of azole antifungals is that they have numerous drug–drug interactions with common agents such as statins, oral anticoagulants, and phenytoin.

Polyene antifungals, such as amphotericin B, bind to ergosterol in the fungal cell membrane causing a change

in the transition temperature of the cell membrane. Ultimately, this results in a disrupted cell membrane and cellular electrolyte imbalance leading to fungal death. Intravenous amphotericin B is also active against serious systemic fungal infections such as *Aspergillus* and *Mucor* but carries potentially serious adverse reactions such as nephrotoxicity, hepatotoxicity, hypotension, high fever, and shaking chills. A newer liposomal formulation of amphotericin B is highly effective against *Aspergillosis* and *Candidiasis* refractory to traditional amphotericin with fewer side effects. Liposomal amphotericin B is also the drug of choice for empiric therapy of presumed fungal infections in patients with febrile neutropenia.

Newer more potent antifungals with fewer side effects have emerged in recent years such as caspofungin. Caspofungin exerts antifungal action through inhibition of β-(1,3)-D-glucan in the fungal cell wall, and is highly effective against invasive *Aspergillosis* in patients who are refractory to other antifungal therapy.

Antiviral Agents

Antiviral agents are rarely used in otolaryngologic infections since viral infections are usually self-limiting. Common antiviral agents such as acyclovir, valacyclovir, and famciclovir are used to treat Herpes simplex and zoster in the setting of Ramsay-Hunt syndrome and Bells palsy. Acyclovir, valacyclovir, and famciclovir are prodrugs that are converted into a phosphorylated form ultimately exerting antiviral activity by inhibiting viral DNA polymerase.

Emerging Pathogens in Head-and-Neck Infections

While numerous pathogens have been implicated in infections of the head and neck, much attention has focused on anaerobic infections, MRSA, *P. aeruginosa*, and *Aspergillus* infections.

Anaerobes

Anaerobes are very common in the mucosal membranes of the head and neck as well as normal skin flora (15). Anaerobic infections comprise a large portion of endogenous infections. Challenges in the management of these infections include their slow growth, increasing resistance, and polymicrobial nature. There are five categories of antimicrobial agents active against anaerobes: carbapenems, metronidazole, chloramphenicol, tigecycline, and combinations of penicillin and a beta-lactamase inhibitor.

Pseudomonas Aeruginosa

Infections of the head and neck due to *P. aeruginosa* are common under certain circumstances. Paranasal sinus culture samples from patients with cystic fibrosis most commonly grow out *P. aeruginosa* followed by *S. aureus* and *Streptococcus viridans* (16). In addition, CRS patients with relapsing mucopurulent infections frequently harbor *Pseudomonas* (17,18). The antibiotic categories to consider when choosing an effective therapy against *Pseudomonas* include: fluoroquinolones or augmented fluoroquinolones (pipericillin/sulbactam), aztreonam, cefepime, colistin, gentamicin (or tobramycin). Cultures with sensitivities are crucial as there is increasing resistance with certain fluoroquinolones, such as ciprofloxacin and levofloxacin, as well as anti-*Pseudomonas* penicillins such as ticarcillin (19). The primary mechanism of resistance is through multidrug efflux pumps with chromosomally encoded antibiotic resistance genes (*mexAB-oprM*, *mexXY*, etc.) (20,21). Recent studies have also shown that phenotypic resistance patterns may be due to biofilm formation with poor antibiotic penetration (22).

Methicillin-Resistant Staphylococcus aureus

The evolution of methicillin resistance in *S. aureus* was recently linked in part to the acquisition of the mecA gene, which encodes for a penicillin binding protein with low affinity for beta-lactam antibiotics (23). The mecA gene has therefore emerged into a molecular target for identifying MRSA and recent studies have identified new divergent homologues of mecA in *S. aureus* that were previously thought to be methicillin sensitive (24).

Community-acquired methicillin-resistant *S. aureus* (CA-MRSA) infections are a growing problem (25). Treatment can frequently be managed as an outpatient; however, when infections are severe, inpatient management is necessary. Chemotherapy options vary and reported resistance rates can range significantly as seen in Table 10.3 (26). MRSA outbreaks in hospitals pose a great challenge. One study looking at widespread use of topical mupirocin showed no advantage, whereas, increasing hand hygiene audits and staff training did correlate with better control of MRSA outbreaks in the ICU setting (27).

Aspergillus

Aspergillus is histologically distinct from other fungi through its septate hyphae with 45-degree branching, in contrast to nonseptate hyphae branching at 90 degrees, which is frequently seen with *Rhizopus* and *Mucor*. *Aspergillus* is a chronic colonizing pathogen of the paranasal sinuses and ear. In the sinuses, *Aspergillus* infection can manifest through various diseases. Invasive fungal sinusitis in the immunocompromised host can be managed with early detection, surgery, and recovery of host immunocompetence. Allergic fungal rhinosinusitis can be effectively managed with surgery and oral corticosteroids. Lastly, mycetoma (i.e., fungal ball) can usually be cured with surgery. In the setting of chronic antibiotic use, *Aspergillus* otologic infections can arise. This disease process usually resolves with the use of topical antifungals (28).

Antimicrobial Management of Common Otolaryngological Infections

Upper Respiratory Infections

Although upper respiratory infections (URIs) are frequently viral in etiology, they are most commonly treated

TABLE 10.3 ANTIMICROBIAL AGENTS EFFECTIVE AGAINST CA-MRSA AND THEIR RESISTANCE RATES

Antimicrobial Agent	Dosing	Adverse Reaction	Mechanism	Resistance (%)
Oral				
Ciprofloxacin	500 mg QD	Seizures, prolonged QTc, photosensitivity, tendon rupture	Topoisomerase II inhibition	7–85
Doxycycline	100 mg q12h	Tooth discoloration, bone toxicity, photosensitivity	Protein synthesis: inhibits 30S ribosomal subunit	0–20
Clindamycin	300–450 mg q6–8h	GI upset, *C. difficile* colitis	Protein synthesis: inhibits 50S ribosomal subunit	3–66
Trimethoprim–sulfamethoxazole	160 mg q12h	Stevens-Johnson syndrome, hyperkalemia, hypersensitivities	Inhibits folic acid synthesis and growth	0–10
Linezolid	600 mg q12h	Myelosuppression, monoamine oxidase inhibition	Protein synthesis by 23S ribosomal subunit	0–4
Parental				
Daptomycin	4 mg/kg q24h	Myopathies	Bacterial membrane disruption by forming transmembrane channels	0
Vancomycin	10–15 mg/kg q12h	Red man syndrome, nephrotoxic	Inhibits cell wall synthesis	0
Tigecycline	100 mg, then 50 mg q12h	Nausea/vomiting	Protein synthesis: 30S ribosomal subunit	0–1.5
Linezolid	600 mg q12h	As above	As above	As above
Topical				
Mupirocin	0.05%	Local site reaction	Binds to tRNA ligase and prevents translation of bacterial ribosomal RNA	30% recolonization within 4 wk of therapy

with antibiotic therapy. In order to differentiate between bacterial and viral infections, it is advisable to wait 5 to 7 days prior to initiating antimicrobial therapy. Amoxicillin is often the first-line agent for the most common otolaryngologic infections: acute otitis media (AOM), acute rhinosinusitis (ARS), and pharyngotonsillitis. Failure of amoxicillin therapy is frequently secondary to the emergence of beta-lactamase producing bacteria. In such cases, augmented penicillins with a beta-lactamase inhibitor such as amoxicillin/clavulanate are preferred. Also, cephalosporins can overcome beta-lactamase resistance and preserve interfering bacteria that help cure URIs (29).

Otitis Media

AOM is a very common medical condition in children. In many cases, AOM is self-limiting and therefore observation alone is a suitable starting point for uncomplicated cases in children older than 2 years of age when adequate follow-up can be ensured (30,31). *S. pneumoniae* and nontypeable *H. influenzae* are the two main pathogens (32). Spontaneous recovery is more commonly seen with AOM caused by *H. influenzae* than by *S. pneumoniae*; however, *H. influenzae* AOM is associated with older patients and recurrent disease (33). According to the American Academy of Pediatrics (AAP) and American Academy of Family Practice 2004 practice guidelines for AOM, amoxicillin, 80 to 90 mg/kg/d, is the recommended first-line antibiotic therapy geared towards these microbes. If there is no improvement after 48 to 72 hours, switching to a cephalosporin or augmented penicillin is recommended. The overall efficacy in antibiotic therapy in treating AOM remains controversial. A recent study by Coker et al. (34) reported that antibiotics are only modestly more effective than no intervention and can additionally cause adverse effects in 4% to 10% of children. On the other hand, Hoberman et al. (35) demonstrate the efficacy of antibiotics in AOM in a double-blinded placebo-controlled trial. Among 291 children aged 6 to 23 months randomized to placebo or amoxicillin/clavulanate, treatment with amoxicillin/clavulanate for 10 days tended to reduce duration of symptoms and reduced overall symptom burden and the rate of persistent signs of acute infection on otoscopy.

Despite the advent of the 7-valent pneumococcal conjugate vaccine (PCV7), AOM still continues to be a major reason for antibiotic prescriptions (36); however, the makeup of pathogens has evolved and the number of office visits for AOM has decreased (37). Six to eight years after the advent of the vaccine, nasopharyngeal and middle ear fluid composition has changed to have almost no vaccine-type stereotypes of *Streptococcus*. Nontypeable *H. influenzae* and non-PCV7 strains of *Streptococcus* continue to be major causes of AOM (38). In the first 2 years of life, the vaccine

is associated with reduced number of AOM episodes, need for ventilating tubes, and emergency visits (39). Since the introduction of this vaccination, *M. catarrhalis* has become more common as a cause of AOM in children (40). AOM caused by *M. catarrhalis* is thought to be milder than AOM from *S. pneumoniae*, which may help explain the decreased number of office and emergency visits. Additionally, the incidence of *S. aureus* AOM may have risen in the setting of pneumococcal vaccination (41).

AOM and otitis media with effusion (OME) should be distinguished for the management differs between the two disease entities. The Subcommittee on OME, which was convened by the AAP, the American Academy of Family Physicians (AAFP), and the American Academy of Otolaryngology—Head and Neck Surgery (AAO—HNS) released evidence-based guidelines for the management of OME in 2004 which do not support the use of antimicrobials as an effective long-term treatment. In some cases, antibiotics are an option if parents are against surgical management but are not considered first-line management for OME (42).

Chronic suppurative otitis media (CSOM) is characterized by a persistently draining ear with a nonintact tympanic membrane and can often cause destructive irreversible changes in the bony structure of the ear. Most CSOM infections are polymicrobial with *P. aeruginosa* and *S. aureus* along with anaerobes including *Peptostreptococcus*, *Bacteriodes*, and *Fusobacterium* (43). In general combination, antimicrobial therapy using clindamycin (due to the high rate of penicillin resistance) and fluoroquinolones (for antipseudomonal coverage) is utilized sometimes in combination with ototopical drops. Due to the chronic nature of this polymicrobial disease, middle ear cultures are often crucial to identify organisms and their antibiotic susceptibilities. In general, antimicrobial therapy alone is insufficient and tympanoplasty is usually required at a later age with cholesteatoma removal if present.

Although rare in the United States, tuberculosis is one of the most common infections of developing countries and can affect the middle ear. Tuberculosis otitis media is characterized by painless copious otorrhea, which typically fails first-line antimicrobial treatment. Examination often reveals multiple tympanic membrane perforations and granulation tissue. It can lead to sequelae such as bone erosion and hearing loss. Preauricular lymphadenopathy can be associated with this disease process. Management requires combination antitubercular therapy (44). Additionally, surgical treatment to remove necrotic bone and inflamed soft tissue and to improve middle ear ventilation may be warranted.

Lastly, otitis media can lead to extracranial and intracranial complications if left untreated. Extracranial complications include tympanic membrane perforation, subperiostial abscess, mastoiditis that can spread to soft tissue planes (Fig. 10.1), facial paralysis, petrositis, and labyrinthitis (45). Untreated otitis media can break down the natural barriers of the bony skull base and result in intracranial complications such as meningitis, extradural abscess, intracerebral/subdural abscess, subdural empyema, and otitic encephalitis.

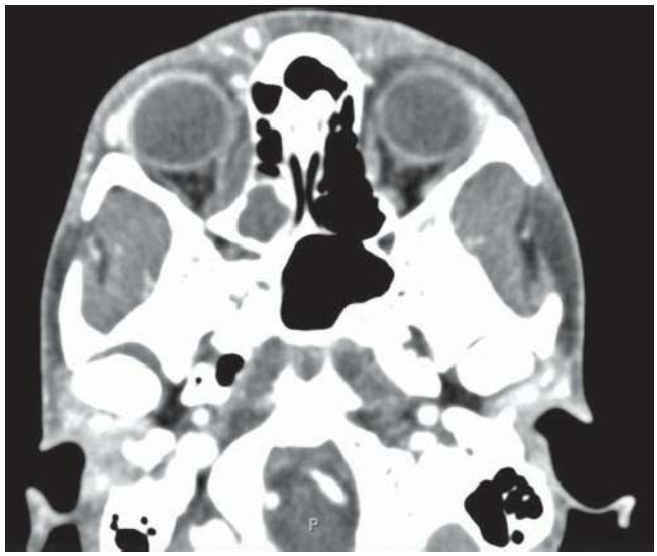


Figure 10.1 Maxillofacial CT scan in the axial plane without contrast. Right-sided subperiostial collection extending along the medial wall of the orbit with mild inflammatory changes in the adjacent medial extraconal space measuring 2 × 0.5 × 1.3 cm. This collection is causing mild mass effect on the medial rectus muscle. There also exists a small bony dehiscence of the right posterior lamina papyracea communicating with an opacified posterior ethmoid cell that is likely the origin of the subperiostial collection.

Otitis Externa

Otitis externa, also known as "swimmer's ear," is a cellulitic inflammation of the external auditory canal skin and soft tissue. Infection can alter the pH of the external auditory canal making bacterial growth more favorable. Reestablishing an acidic environment by using topical preparations, such as topical fluoroquinolones, can be achieved (46). The 2006 Clinical Practice Guideline recommends use of ototopical antibiotic drops as initial therapy in uncomplicated acute otitis externa limited to the external auditory canal skin (47,48). When a tympanic membrane perforation is present, care should be taken to not prescribe ototoxic drops. Systemic antibiotics are sometimes indicated if the infection has spread beyond the skin of the external auditory canal. Resistance to gentamicin and ciprofloxacin topical therapy for MRSA otorrhea is rapidly emerging; however, trimethoprim–sulfamethoxazole susceptibility remains largely intact (49).

Malignant necrotizing otitis externa (MNOE) is frequently a life-threatening condition that requires prolonged antibiotic management and therefore poses a diagnostic challenge. In one retrospective study, 68% of otolaryngologists were initially consulted for something other than MNOE in patients who ultimately had the diagnosis of MNOE (50). A significant risk factor is immunosuppression, for example, diabetes, chemotherapy, organ transplantation with immune modulating drug therapy, and HIV. There is a subset of necrotizing otitis externa that

is coined as benign necrotizing otitis externa (BNOE). It is characterized by soft tissue ulceration overlying bony necrosis found in the floor of the external auditory canal. Management of BNOE differs from that of MNOE in that although antimicrobial therapy is usually warranted, surgical debridement is usually not necessary (51).

Candida and *Aspergillus* are the most common fungal pathogens isolated in the setting of otomycosis (52). Patients with noninvasive otomycosis should be treated with debridement and topical antiseptics and acidifying agents such as acetic acid and isopropyl alcohol containing drops or Gentian violet. Occasionally, antifungal topical agents such as clotrimazole can be utilized.

Sinusitis

As with many URIs, most ARS is viral in etiology and a fraction of patients are thought to eventually develop a secondary bacterial infection. The most common bacteria implemented in community-acquired acute sinusitis with purulent drainage are *S. pneumoniae, H. influenzae, M. catarrhalis,* and *S. pyogenes* (53). However, in one retrospective study (54), the most common organism isolated from paranasal cultures in clinically infected patients was found to be *S. aureus*, 20% of which are MRSA. This may reflect the shift in causative bacteria in ARS—a phenomenon seen in AOM due to the advent of the pneumococcal vaccination.

Antibiotic use in acute bacterial rhinosinusitis (ABRS) has been controversial. There is some evidence of overprescribing of antibiotics in ABRS as clinical studies have confirmed that roughly 60% of presumed ABRS episodes have a bacterial etiology. In addition, recent data show that antibiotics are prescribed in 81% to 92% of ARS cases (55,56). Although there is no clear consensus regarding the management of presumed ABRS due to numerous conflicting studies in the literature, amoxicillin is the first-line therapy in children and adults with uncomplicated bacterial ABRS with symptoms persisting beyond 5 days (57–60). Other agents recommended for symptomatic relief include short-term topical decongestants, intranasal corticosteroids, and nasal saline. However, if symptoms do not improve after initiation of amoxicillin, changing to amoxicillin/clavulanate or a cephalosporin is recommended (29,61). A double-blinded randomized-controlled trial examining amoxicillin/clavulanate efficacy in the setting of pediatric ABRS found a significantly higher cure rate as reported by parents (62).

Although there is some overlap between ABRS and CRS, CRS tends to be more heterogeneous despite its classification by duration of illness greater than 12 weeks or with the presence of nasal polyps. The microbiology of CRS is distinct from ABRS. Most common isolates are *S. aureus* and anaerobic pathogens such as *Prevotella, Porphyromonas, Fusobacterium,* and *Peptostreptococcus* (63). Pediatric CRS may also involve colonization of the sinonasal tract and adenoid pad with coagulase-negative *Staphylococci* (40.8%), *S. aureus* (22.3%), *S. pneumoniae* (18.4%), *H. influenzae* (16.5%), and group A *Streptococci* (15.5%) (64). The pathogenesis of the inflammatory response in CRS is poorly understood and may arise independently from infection itself causing a defective mucociliary clearance ultimately setting the stage for further infections.

In terms of management, there is a lack of consensus for the treatment of CRS due to the paucity of controlled studies. The design and interpretation of CRS clinical trials have been hindered by the inherent heterogeneity of the disease. Although controversial, primary treatment generally involves empiric antibiotic therapy with coverage for both aerobic and anaerobic bacteria in addition to intranasal and oral corticosteroids. In addition, studies have demonstrated that antibiotic therapy for CRS is sometimes not effective (65) perhaps in part due to the complexity of the disease process (57,66) indicating a role for endoscopic sinus surgery. A recent multi-institutional prospective study by Bhandarkar et al. (67) demonstrates that endoscopic sinus surgery reduces overall antibiotic utilization in CRS and recurrent ABRS (67).

Topical antibiotic agents have been shown to have added benefit over placebo in CRS, specifically the use of mupirocin irrigations in patients with prior sinus surgery with active MRSA infections (14,68,69). Although topical preparations offer favorable localized delivery of medication thereby minimizing side effects, the mode of delivery (low pressure, high volume irrigation vs. nebulization) and the efficacy of various compounds including antifungal therapy remain inconclusive.

There are differences found between the bacteriology in patients undergoing primary versus revision endoscopic sinus surgery. Of those undergoing endoscopic sinus surgery, *P. aeruginosa* is significantly more common in those undergoing revision sinus surgery whereas *S. viridans* is significantly more common in those undergoing primary sinus surgery (70).

Nosocomial or "ICU" sinusitis often involves *P. aeruginosa* and MRSA. Empiric therapy usually entails IV cephalosporins or fluoroquinolones until endoscopically guided cultures can be obtained. Febrile neutropenic patients with sinusitis frequently harbor invasive fungal infection with *Aspergillus* or *Mucor*. Timely endoscopic evaluation with biopsy of mucosa is crucial. Although surgical debridement was once the primary modality of treatment adjuvant use of the newer more potent systemic antifungals such as voriconazole or amphotericin B is recommended (71,72).

Complications of sinusitis include involvement of adjacent structures such as the orbit and the skull base. Orbital complications secondary to acute sinusitis in children may become a precursor to meningitis and usually involve *S. pneumoniae* or *H. influenza*. Diagnosis should occur in a timely manner and treatment expedited with intravenous antibiotics that can penetrate the blood–brain barrier (ceftriaxone, or fluoroquinolones) in addition to clindamycin with or without surgical debridement depending on the presence of drainable subperiosteal or intraorbital purulence (73) (Fig. 10.2). Additional antibiotics can be added depending on the resistance patterns of *S. pneumoniae*.

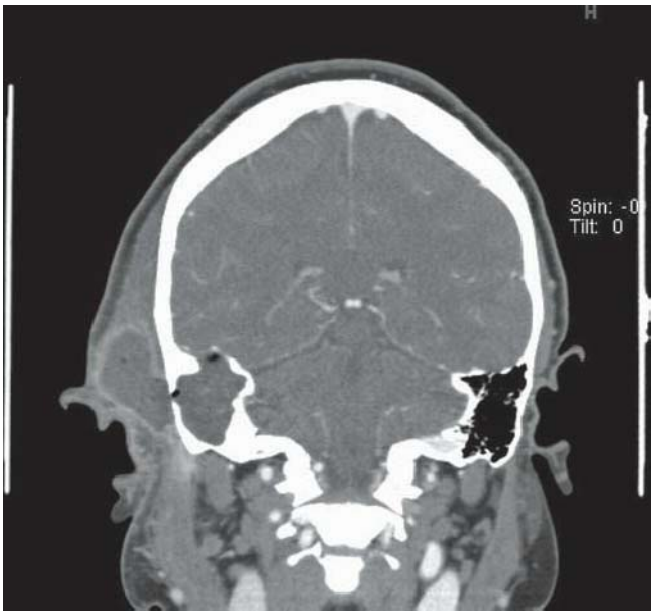


Figure 10.2 Temporal Bone CT in the coronal plane without contrast. The right mastoid cavity is opacified with soft tissue density and complete destruction of the septae. There is dehiscence of the medial wall, with mild inward bowing of the sigmoid sinus. There is dehiscence of anterior and anterolateral walls of the mastoid complex with a large well-formed abscess.

Pharyngitis

Pharyngitis is viewed as a self-limiting disease process in most scenarios. There are substantial discrepancies in the recommendations for the management of pharyngitis among national guidelines in Europe and North America. In select cases, where *Streptococcal* pharyngitis has been diagnosed with rapid antigen detection testing, patients should receive penicillin or amoxicillin or amoxicillin/clavulanate as first-line therapy for a total of 10 days (61,74) and cephalosporins can be used when the disease relapses (75). Macrolides or clindamycin can be reserved for penicillin-allergic patients.

Deep Space Neck Abscess/Peritonsillar Abscess

Acute tonsillitis can lead to a peritonsillar abscess (PTA) if not appropriately treated. PTAs and other deep neck abscesses are usually polymicrobial with anaerobic bacteria such as *Fusobacterium necrophorum* and group A *Streptococcus* involved (76). Treatment decisions are made empirically with clindamycin or augmented penicillins or on the basis of a gram stain of pus.

Supraglottitis

Acute supraglottitis, also known as epiglottitis, can be a challenging diagnosis to make for symptoms and signs can be nonspecific and can mimic a common URI (77).

In the era of post–*H. influenzae B* vaccination, epiglottitis is relatively rare and there has been a substantial shift in the patient demographics. After diagnosis is achieved, patients should be admitted for intravenous antibiotics with close monitoring of the airway. Effective antibiotic regimens have comprised of IV ceftriaxone and ampicillin/sulbactam (78). If securing the airway is necessary, intubation can be achieved with awake nasotracheal intubation and in some instances via direct laryngoscopy.

Croup

Croup has been defined as an acute clinical syndrome that typically affects those 6 years old or younger. The pathogenesis is thought to be from a viral URI that leads to upper airway inflammation characterized by edema of the subglottic mucosa. The effect on the upper airway can lead to untoward deterioration and urgent need for intubation. Corticosteroids are now an accepted part of the standard management of croup (79–81). In the setting of hypoxia, supplemental oxygen should be delivered.

Salivary Gland Infections

The parotid gland is the most common salivary gland affected by infectious inflammation. Risk factors for acute bacterial parotitis are dehydration and immunosuppression. Responsible pathogens include *S. aureus*, *Streptococcus* species, and anaerobes such as *Peptostreptococcus* and gram-negative bacilli (e.g., *Prevotella*, *Porphyromonas*, *Fusobacterium* species) (82,83). Empiric therapy can be commenced with clindamycin or augmented penicillins, but antibiotic therapy should be culture-directed whenever possible. If an abscess forms, surgical drainage is also necessary.

HIGHLIGHTS

- Macrolides and clindamycin work through inhibiting the 50S ribosomal subunit while aminoglycosides act on the 30S subunit.
- Amoxicillin is the first-line antimicrobial agents for the most common otolaryngologic infections including AOM and acute bacterial sinusitis.
- *S. pneumoniae* and *H. influenzae* remain the two most common bacteria in the pathogenesis of AOM; however, in the setting of vaccinations the specific types have evolved to include nontypeable *H. influenzae* and non-PCV7 strains of *Streptococcus*.
- MecA mediates methicillin resistance to *S. aureus* through encoding for an altered penicillin binding protein.
- *Pseudomonas* infections are commonly seen in chronic diseases such as CRS, acute diseases such as otitis externa, and nosocomial infections. Fluoroquinolones are effective agents; however, there is growing resistance as well as risk of tendon rupture that patients should be informed of prior to starting therapy. Resistance is mediated by efflux pumps and biofilm formation.

- Antibiotics should only be prescribed in presumed cases of ABRS after at least 5 days of observation. The role of antimicrobial therapy in CRS remains controversial due to the heterogeneity of the disease.
- Complications of both sinusitis and otitis media can result in orbital and intracranial extension, which can be managed with a combination of surgery and ceftriaxone and clindamycin or ampicillin/sulbactam.
- Pharyngitis is often a self-limited process; however, in the setting of positive rapid antigen testing, amoxicillin is first-line therapy.
- The most common infected salivary gland is the parotid gland and frequently *S. aureus* is the offending microbe.

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Head and Neck Imaging

11

Tanya J. Rath

Due to advances in cross-sectional imaging, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound have largely replaced conventional radiography in head and neck imaging and are invaluable primary imaging modalities used to evaluate pathology in the head and neck. They are complementary to a thorough physical exam and essential to characterize the deep tissue extent of mucosal lesions as well as evaluate pathology originating in the other spaces of the neck. Nuclear medicine has poor spatial resolution but provides useful functional and metabolic information. This chapter provides an overview of the various imaging modalities available in the head and neck as well as describes the application, strengths, and weaknesses of these modalities as they pertain to head and neck imaging. A thorough discussion of the physics of these modalities and image interpretation is beyond the scope of this chapter and is described in detail in several dedicated imaging and physics textbooks (1–4).

COMPUTED TOMOGRAPHY

Imaging Principles

CT employs the use of ionizing radiation to image patients. An x-ray tube rotates 360 degrees around the patient, while a well-collimated x-ray beam is generated and passed through the patient. The beam is partly absorbed or scattered as it passes through the patient. Tissues of different density and thickness attenuate the beam to varying degrees. A circumferential bank of detectors opposite the beam measures the degree of x-ray transmission through the patient. Each volumetric imaging unit (voxel) is assigned a numeric value, called a Hounsfield unit (HU). Water is assigned a value of 0 HU. The matrix of HUs is then displayed in a gray scale, resulting in an anatomic cross-sectional image. Various algorithms can be applied to optimize evaluation of different structures such as bone, soft tissue, or lung parenchyma (Fig. 11.1).

Most scanners are now multidetector helical or spiral scanners in which the patient translates through the x-ray tube while it continuously rotates around the patient. Using this design, spatial resolution is improved and large volumes can be imaged with reduced scan time, resulting in greater anatomic coverage with decreased motion artifact. Data can be acquired in less than 1-mm-thick slices and reconstructed at various intervals in the axial, coronal, and sagittal planes. Images can be obtained during quiet respiration or in a short single breath hold and the entire neck can be scanned in less than 1 minute.

Applications and Technique by Region of Interest

Temporal Bone

CT is the study of choice to evaluate osseous integrity of the temporal bone including the otic capsule, ossicular chain, cortical plates, and air spaces. Main indications include evaluation of temporal bone fracture, congenital anomalies of the otic capsule, conductive hearing loss, inflammatory disease, and erosive neoplastic processes affecting the temporal bone.

Direct coronal images are typically no longer necessary due to high-resolution helical multidetector imaging. A small field of view is employed with a high-resolution matrix. Technique is optimized to evaluate bony detail and 0.5- to 0.625-mm-thick axial images and thin-cut coronal reconstructions are routinely provided (Fig. 11.2). Additional oblique reformats such as Stenvers view and Pöschl view can be useful to demonstrate semicircular canal dehiscence (Fig. 11.3). All data are displayed in bone algorithm windows. Thicker 2.5-mm axial images to evaluate the soft tissues and posterior fossa structures are useful as well. Contrast is typically not necessary but can be helpful in evaluating the soft tissues

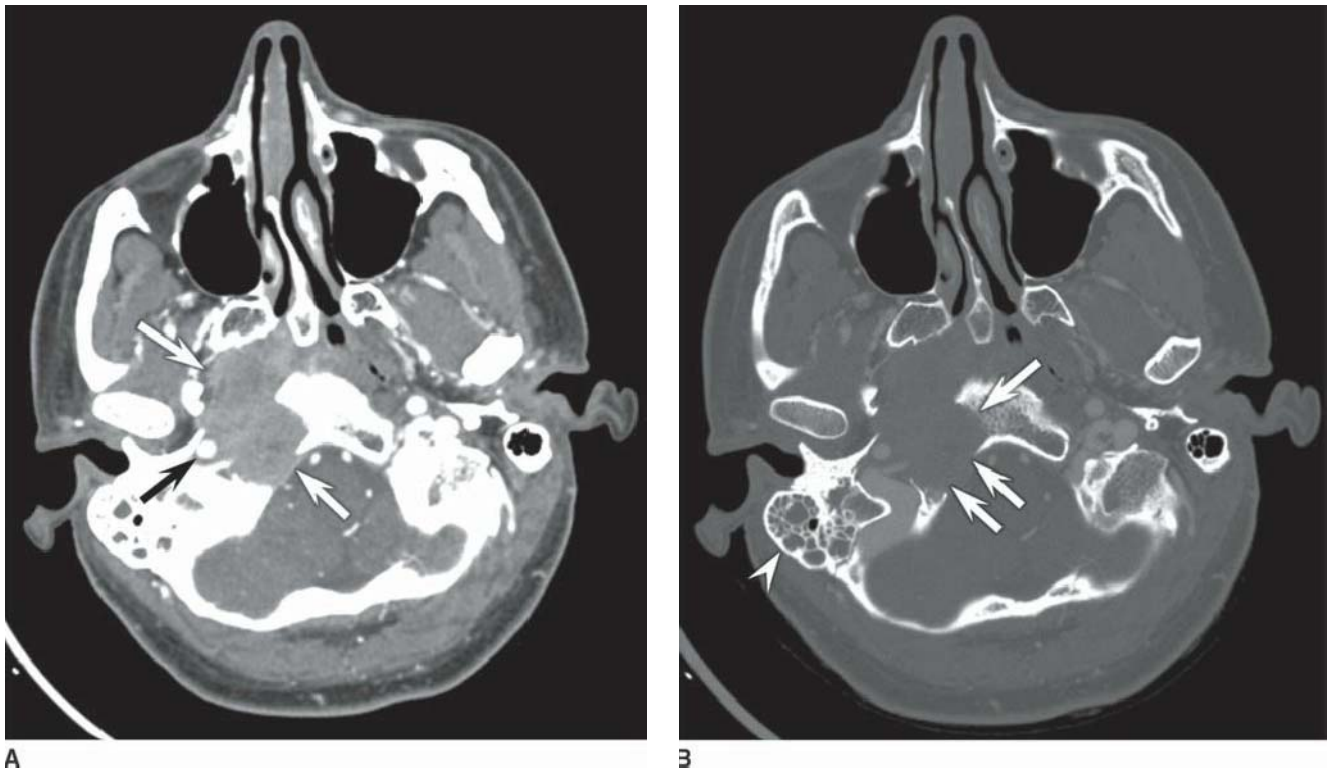


Figure 11.1 Nasopharyngeal carcinoma. **A:** Axial contrast-enhanced neck CT. The large right enhancing nasopharyngeal mass (*white arrows*) and its relationship to the right ICA (*black arrow*) along the posterolateral margin of the mass is best seen on the soft tissue windows. **B:** Bone windows at the same level better demonstrate erosion of part of the clivus and the right hypoglossal canal (*arrows*). The right mastoid effusion (*arrowhead*) from eustachian tube dysfunction is also better seen.

and intracranial compartment for complications related to otomastoiditis. It may also be useful in the evaluation of tumors involving the temporal bone, particularly if MRI is contraindicated.

Central Skull Base

Skull base CT technique is similar to the temporal bone in that it is typically performed without contrast and displayed in high-resolution bone algorithm with axial, sagittal, and

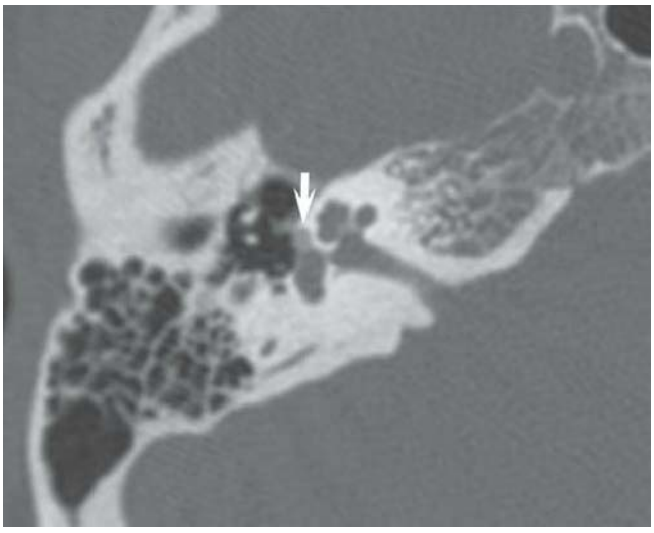


Figure 11.2 Fenestral otosclerosis (otospongiosis). Axial temporal bone CT. The thin-cut high-resolution bone algorithm technique nicely demonstrates demineralization (*arrow*) anterior to the oval window in the fissula ante fenestram, characteristic of fenestral otosclerosis.

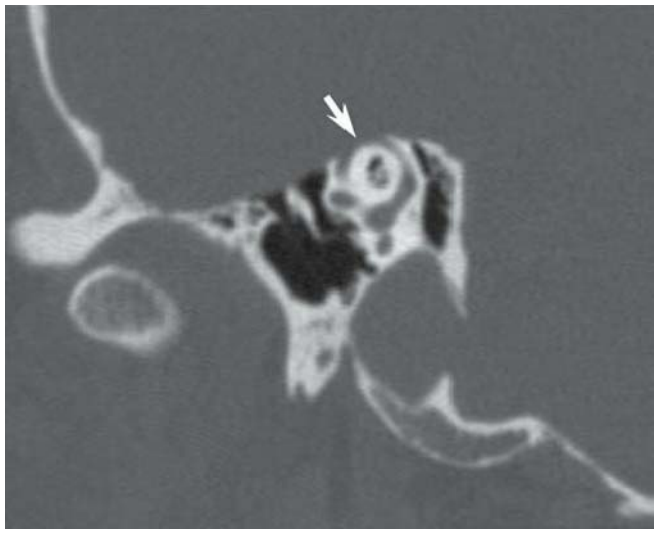


Figure 11.3 Superior semicircular canal dehiscence. A sagittal oblique reformatted image in the Pöschl plane parallel to the superior semicircular canal clearly demonstrates dehiscence of the bone (*arrow*) overlying the roof of the superior semicircular canal.

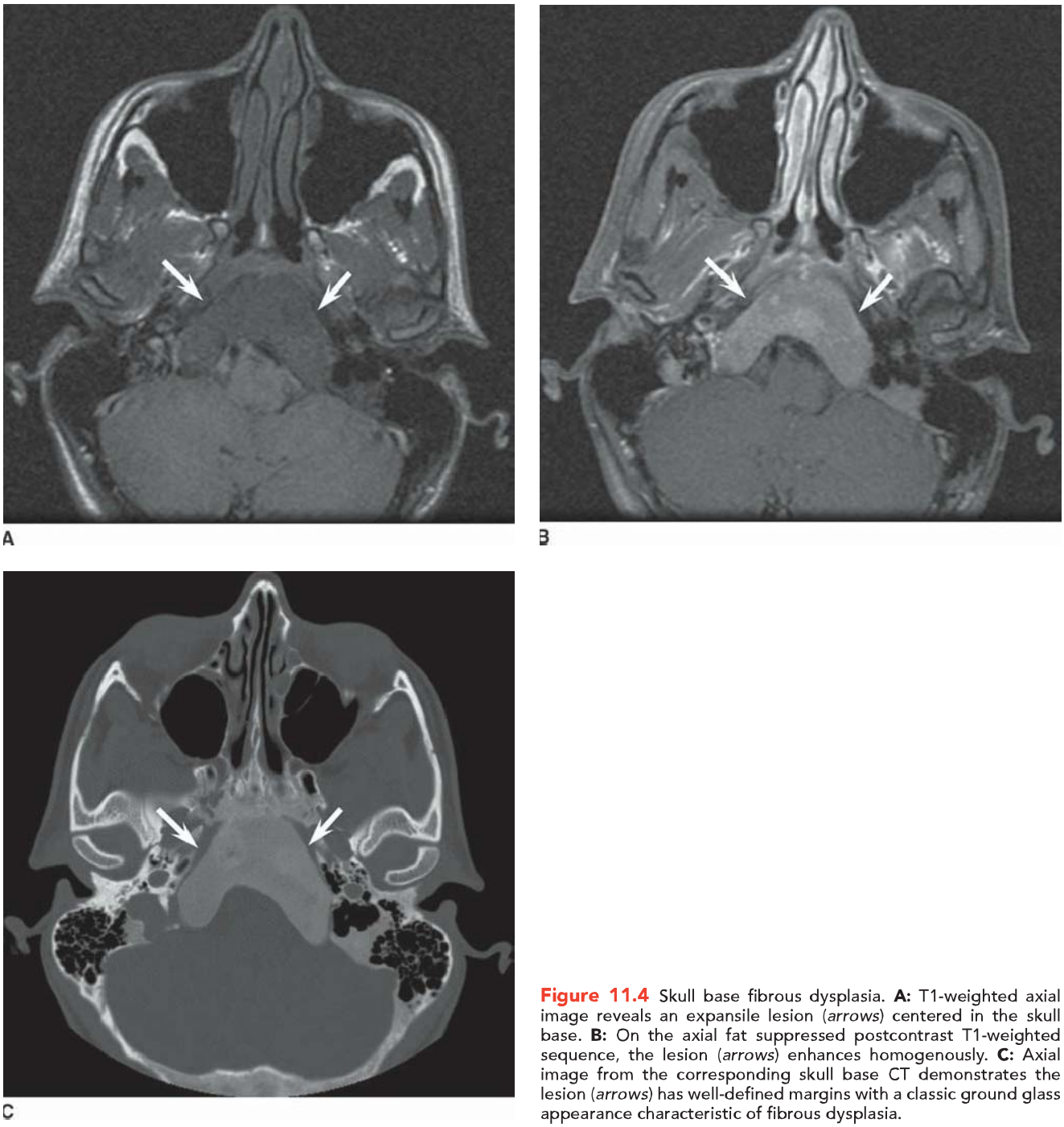


Figure 11.4 Skull base fibrous dysplasia. **A:** T1-weighted axial image reveals an expansile lesion (*arrows*) centered in the skull base. **B:** On the axial fat suppressed postcontrast T1-weighted sequence, the lesion (*arrows*) enhances homogenously. **C:** Axial image from the corresponding skull base CT demonstrates the lesion (*arrows*) has well-defined margins with a classic ground glass appearance characteristic of fibrous dysplasia.

coronal reconstructions using a typical slice thickness of 1.25 mm. However, the field of view is larger, focused on the central skull base, including the basiocciput and the sphenoid bone. The main indications for skull base CT include evaluation of fractures, dysplasias, primary bone lesions of the skull base, and secondary neoplastic involvement of the skull base. It nicely demonstrates the characteristic "ground-glass" appearance of fibrous dysplasia. This is particularly useful when fibrous dysplasia is incidentally found on MRI where it can be easily mistaken for a skull base tumor due to its variable signal characteristics and enhancement pattern (Fig. 11.4). CT evaluates the osseous integrity of the skull base and skull base foramina affected by neoplastic processes including but not limited to nasopharyngeal carcinoma, pituitary lesions, chordoma, chondrosarcoma, meningioma, Langerhans cell histiocytosis, metastasis, and myeloma. Enlargement or distortion of skull base foramina related to perineural spread of neoplasm can sometimes be appreciated, though direct imaging of perineural spread of neoplasm and intracranial extension is better demonstrated by MRI.

Maxillofacial Structures and Sinonasal Cavities

CT is the first study of choice to evaluate the osseous structures and adjacent soft tissues of the face and the sinonasal cavity, particularly in the setting of trauma or suspected inflammatory sinonasal disease. Normal anatomy and anatomic variations, mucosal disease and osseous integrity of the anterior skull base, and maxillofacial structures are well demonstrated.

Evaluation of the paranasal sinuses with plain film radiography has largely been replaced with CT. At some institutions, a screening sinus CT is performed to look for inflammatory disease with thick cuts in the axial or coronal plane performed at skip intervals with the technical parameters optimized for low-radiation exposure similar to plain films. This technique, however, does not well evaluate the anatomy and all walls of the sinonasal structures. It has fallen out of favor with the advent of helical multidetector CT and CT dose reduction strategies.

A high-resolution helical CT of the sinonasal structures is performed if detailed evaluation of maxillofacial trauma, sinus inflammatory disease, odontogenic disease, sinonasal neoplasm, or anatomy for presurgical planning is required. The widespread availability of helical multidetector CT precludes the previous need for direct coronal imaging to demonstrate the anterior ostiomeatal unit and replicate the endoscopic view of the paranasal sinuses. A typical protocol includes contiguous helical scanning with 1.25-mm-thick images obtained through the paranasal sinuses with multiplanar reformats created in the axial, sagittal, and coronal planes. The mandible can be included in the field of view if required. In the setting of trauma, three-dimensional (3-D) volume–rendered shaded surface display reconstructions can be helpful for planning craniofacial reconstruction, creating 3-D models and evaluating surgical results. Advantages of high-resolution helical imaging with multiplanar reformats include patient comfort, better demonstration of the anterior and posterior walls of the sinuses, and decreased motion and dental amalgam artifact. Contrast is not required for routine inflammatory sinus disease or trauma. In patients with acute odontogenic infection, contrast delineates associated soft tissue abscess and cellulitis. It can be helpful in defining the extent of sinonasal neoplasms or complications of sinusitis such as orbital cellulitis, subperiosteal abscess, or intracranial abscess (Fig. 11.5).

Orbit

Both CT and MRI are useful for evaluation of the orbit. CT is typically the initial study of choice when patients present to the emergency room with acute orbital symptoms. MRI is preferable if intracranial pathology or optic neuritis is suspected on the basis of clinical and physical exam. MRI better images the optic nerve and nerve sheath complex as well as the intracranial compartment, which can be affected when patients present with visual symptoms. Noncontrast CT is useful in cases of orbital trauma, evaluation of osseous orbital lesions, foreign body, calcifications, and thyroid orbitopathy (Fig. 11.6). In cases of acute

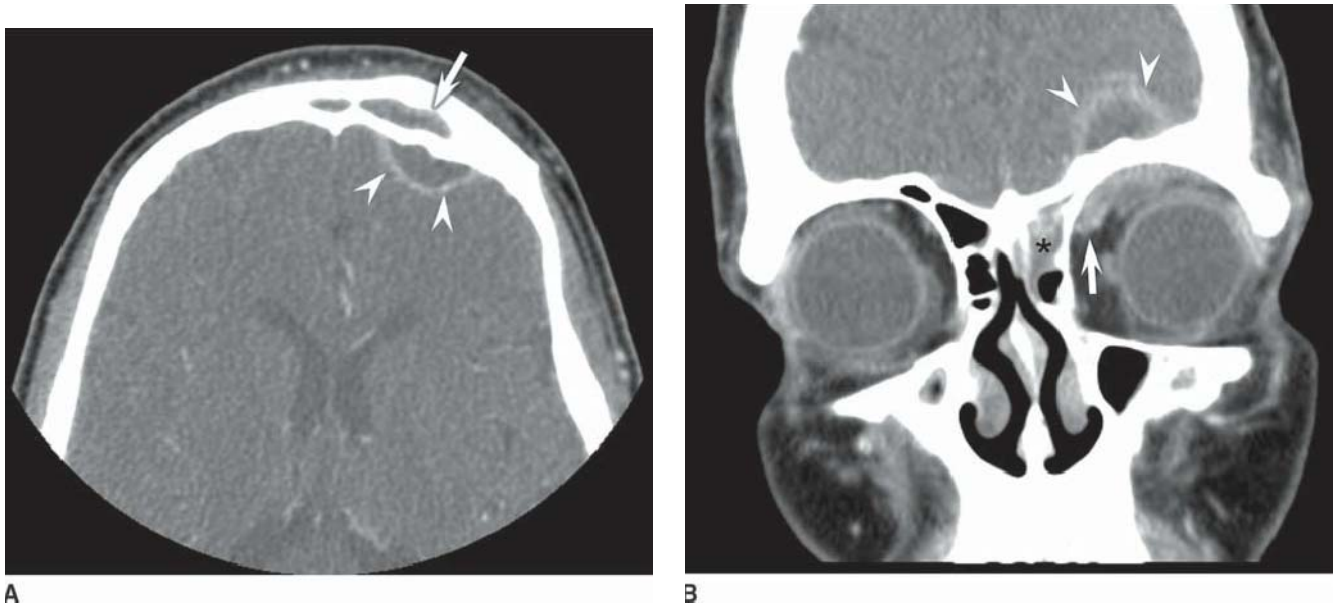


Figure 11.5 Intracranial abscess and orbital phlegmon as a complication of frontal sinusitis. **A:** Axial contrast enhanced maxillofacial CT. There is opacification of the left frontal sinus (*arrow*) due to sinusitis. The contrast nicely demonstrates the associated left frontal rim enhancing epidural abscess (*arrowheads*). **B:** Contrast-enhanced coronal CT reconstruction better demonstrates the associated phlegmon (*arrow*) in the superior left orbit as well as the left frontal epidural abscess (*arrowheads*). There is opacification of the adjacent left frontal sinus drainage pathway and ethmoid air cells (*asterisk*).



Figure 11.6 Thyroid orbitopathy. Coronal reconstruction from orbits CT without contrast. There is enlargement of all of the extraocular muscles bilaterally, typical of thyroid orbitopathy. The coronal reconstruction demonstrates the relationship of the extraocular muscles to the optic nerves (*arrows*).

orbital cellulitis, contrast-enhanced orbital CT is the first study of choice. Thin-cut images are obtained in the axial plane and reconstructed in the coronal and sagittal planes to better demonstrate the relationship of the optic nerve to the extraocular muscles.

Neck, Soft Tissues

A standard contrast-enhanced soft tissue neck CT evaluates the suprahyoid and infrahyoid soft tissues of the neck, including the aerodigestive tract, lymph nodes, glandular structures, and larynx. While soft tissue contrast is greater with MRI, contrast-enhanced CT is frequently the first study of choice in the evaluation of a neck mass or mucosal lesion of the upper aerodigestive tract because of its short acquisition time, universal availability, and reduced cost as compared to MRI. Generally speaking, neck CT is the preferred modality for evaluation of sialolithiasis, inflammatory neck processes, posttraumatic evaluation of the neck soft tissues, and evaluation of osseous cortex. There are few indications for noncontrast neck CT, including sialolithiasis, evaluation of patients with thyroid cancer who may require future treatment with radioactive I-131 and evaluation of neck pathology in patients with an absolute contraindication to IV administration of iodinated contrast. Contraindications to iodinated contrast administration include advanced renal insufficiency (not on dialysis), acute renal failure, and history of anaphylactic reaction to iodinated contrast. Patients with a history of milder allergic reactions to iodinated contrast should receive pretreatment with steroids to reduce the likelihood of a contrast reaction.

Good soft tissue contrast can be achieved with most lesions in the neck when iodinated contrast is administered and appropriate technique is employed with contrast present in both arteries and veins during the image acquisition. Contrast administration technique is critical to delineating the mucosal–submucosal interface, optimizing mucosal enhancement, and maximizing lesion detectability (Fig. 11.7). Using a helical scanner, 100 to 150 mL of contrast is administered via a power injector with an initial delay in image acquisition following the contrast injection to ensure adequate arterial and venous opacification. Exact protocols vary according to the scanner and institution. Scanning too early during the arterial phase may cause poor soft tissue contrast and lesion detectability, resulting in a false-negative study.

A routine contrast-enhanced neck CT typically extends from above the internal auditory canals caudally through the aortic arch, to include the course of the left recurrent laryngeal nerve (Fig. 11.8). Images are displayed at a slice thickness of 2 to 3 mm in the axial plane in both soft tissue and bone algorithm. In patients with dental amalgam or metal causing streak artifact, reangled images to avoid dental amalgam should be obtained because it can obscure pathology (Fig. 11.9). Coronal and sagittal reconstructions are commonly used to supplement axial images.

Modifications to a soft tissue neck CT protocol can be tailored to an area of interest or specific clinical question. In cases of a laryngeal mass, thin axial reconstructions through the larynx parallel to the laryngeal ventricle in bone and soft tissue algorithm are created to evaluate the extent of the lesion, paraglottic extension, and evidence of laryngeal cartilage erosion. Coronal reconstructions are helpful to evaluate for transglottic spread of tumor in the paraglottic space. At some institutions, additional images using the modified Valsalva maneuver (exhaling against a closed glottis or blowing through a straw) and phonation (patient exhales and makes the sound "eeee") are obtained, which dilates the laryngeal ventricle and pyriform sinuses in an attempt to better demonstrate the extent of tumor and anatomy. The added benefit of such techniques is controversial and must be weighed against added radiation exposure (5,6). In patients with a buccal mucosal lesion, a "puffed cheek" technique can be used to increase conspicuity of the lesion (7). If sialolithiasis is suspected, a noncontrast CT through the major salivary glands and oral cavity can be performed to evaluate for radio-opaque sialoliths that can be obscured by iodinated contrast. This can be followed by a routine contrast-enhanced neck CT in patients with clinical evidence of acute sialoadenitis. A good clinical history and communication between the referring clinician and radiologist is required to ensure that the protocol is tailored to answer the clinical question.

Neck, CT Angiogram

Helical multidetector CT angiography (CTA) has revolutionized vascular imaging in the past decade. Conventional angiography is still considered the "gold standard" for evaluation of vascular injury and vascular anatomy, but it has significant disadvantages including lengthy procedure, cost, and invasiveness with numerous risks including

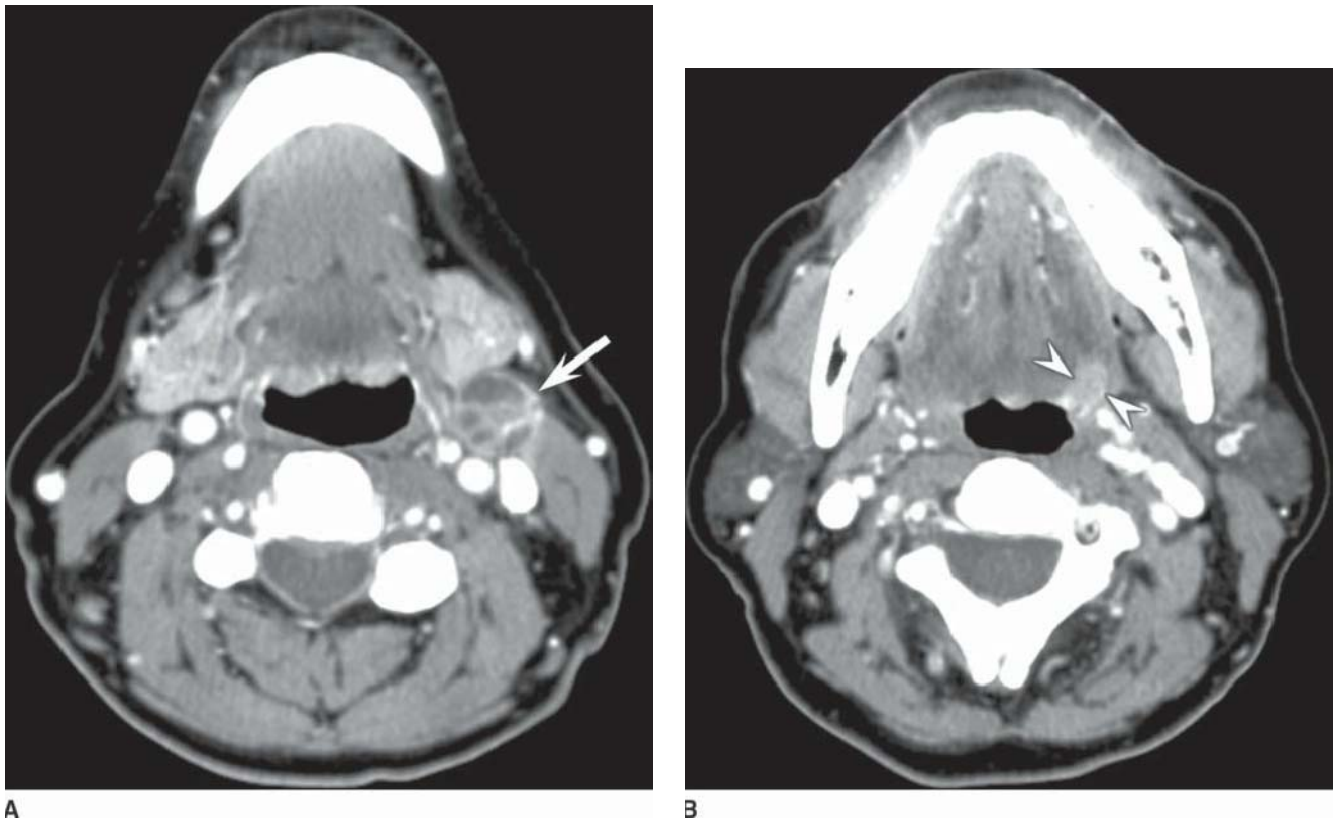


Figure 11.7 Left base of tongue squamous cell carcinoma with a metastatic left level II lymph node in a patient presenting with a palpable left neck mass. **A:** Axial contrast enhanced neck CT. The palpable mass is a malignant necrotic appearing left level II lymph node (*arrow*). **B:** Good contrast enhancement reveals the cause is an enhancing small left base of tongue squamous cell carcinoma (*arrowheads*).

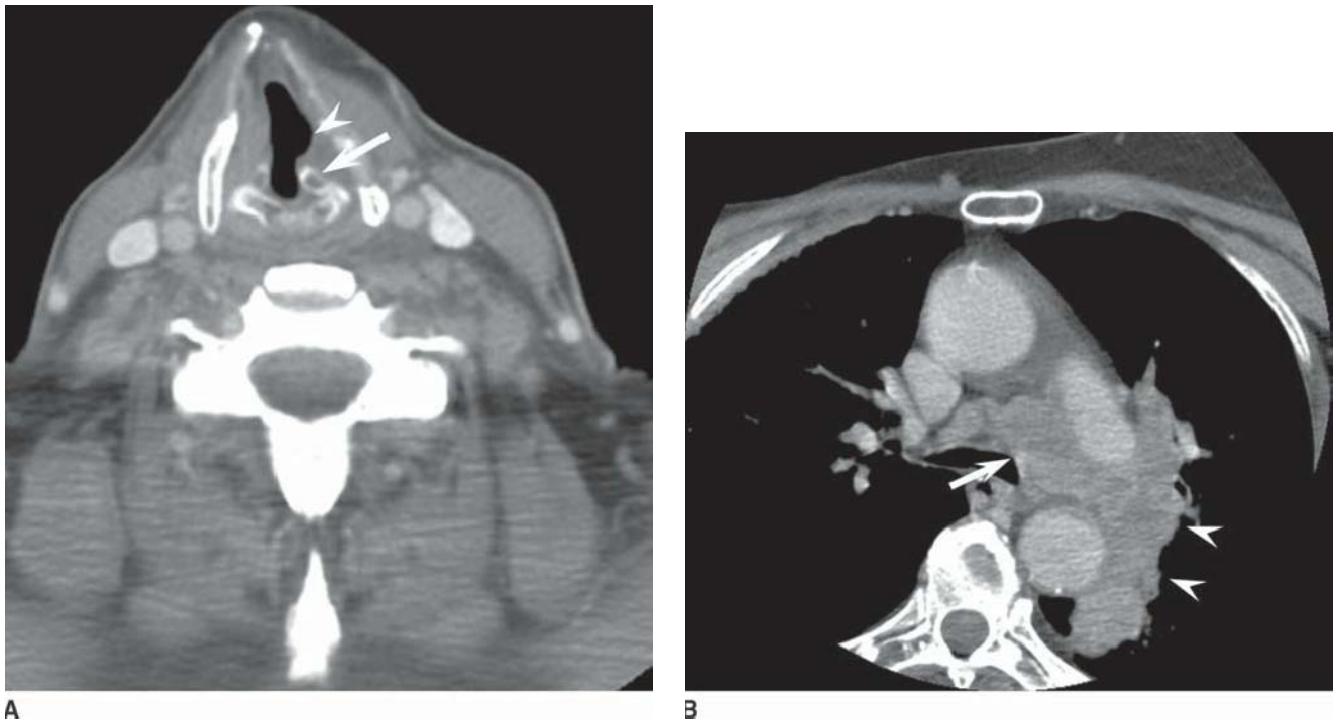


Figure 11.8 Aortopulmonary (AP) window metastatic lymphadenopathy and left hilar lung neoplasm in a 68-year-old male presenting with hoarseness and left vocal cord paralysis. **A:** Axial contrast-enhanced neck CT. The left arytenoid cartilage (*arrow*) is rotated and there is associated dilation of the left laryngeal ventricle (*arrowhead*), consistent with the patient's left vocal cord paralysis. **B:** Contrast-enhanced image from the neck CT extending through the superior mediastinum reveals the cause is a large left AP window nodal metastasis (*arrow*) from a left hilar lung neoplasm (*arrowheads*).

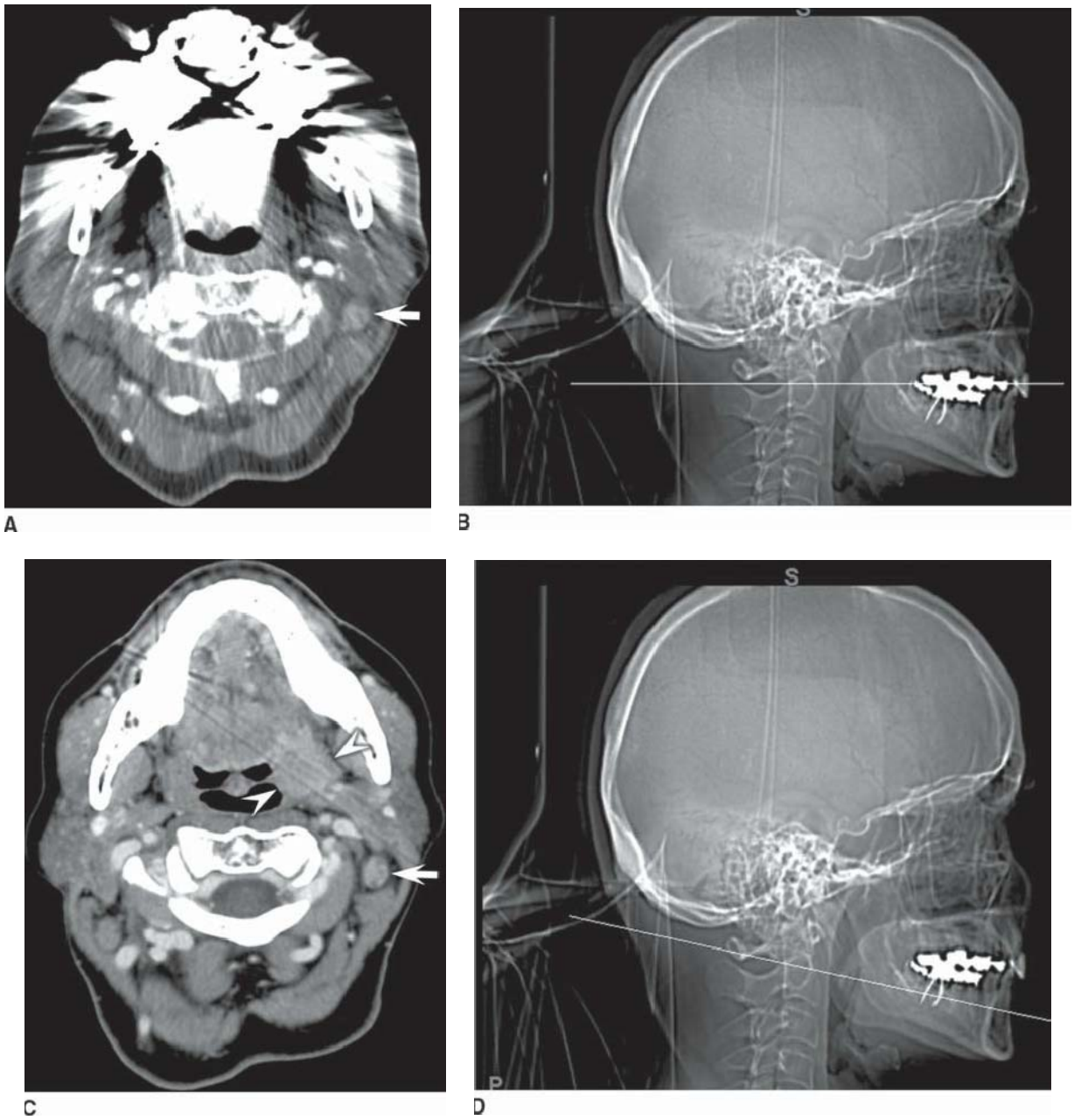


Figure 11.9 Left faucial tonsil carcinoma. **A,B:** Axial contrast-enhanced neck CT and corresponding scout view with a localizer line indicating the standard plane of imaging. **A:** Extensive streak artifact from dental amalgam completely obscures the oral cavity and portions of the oropharynx. An abnormal faucial tonsil mass is not demonstrated. The metastatic left level II lymph node (*arrow*) is poorly imaged due to the streak artifact. **B:** The plane of imaging indicated by the line courses directly through the patient's dental amalgam. **C, D:** Reangled contrast-enhanced axial CT from the same patient and corresponding scout view with a localizer line indicating the reangled plane of imaging. **C:** The large left faucial tonsil squamous cell carcinoma (*arrowheads*) extending into the left parapharyngeal fat and glossotonsillar sulcus is now clearly visible. Areas of low attenuation early necrosis in the enhancing metastatic left level II lymph node (*arrow*) are better demonstrated. **D:** The reangled plane of imaging indicated by the line avoids the dental amalgam.

dissection and stroke. Because of its accessibility, speed, and noninvasiveness, CTA is commonly used as a screening tool for vascular injury in patients with a history of blunt and penetrating neck trauma (8,9). CTA is also the primary imaging modality at many institutions prior to carotid endarterectomy. Conventional angiography is largely reserved for equivocal cases or cases requiring percutaneous intervention. CTA is best performed on a MDCT scanner (at least 16-slice or greater) using very thin cuts (e.g., 0.5-mm collimation) following the administration of iodinated contrast. Data are obtained from the thoracic aortic arch through the skull base. Multiplanar reformats are created

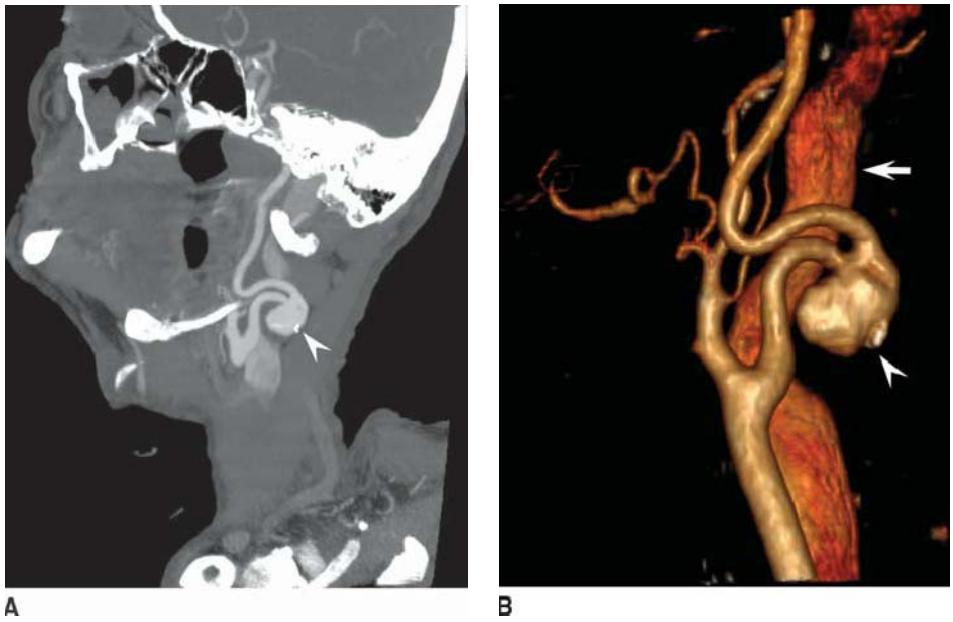


Figure 11.10 Right internal carotid artery (ICA) pseudoaneurysm in a 73-year-old male complaining of palpable right neck mass. **A:** Sagittal oblique reconstruction from contrast-enhanced CTA neck. There is a large saccular pseudoaneurysm (*arrowhead*) arising from the mid cervical right ICA projecting posteriorly. A small calcification in the pseudoaneurysm indicates it is chronic. **B:** 3-D volume-rendered shaded surface display reconstruction provides a better 3-D depiction of the pseudoaneurysm (*arrowhead*) directed posteriorly. The right internal jugular vein (*arrow*) is seen lateral to the right ICA.

and ideally 3D volume rendered reconstructions should be created by the interpreting radiologist because essential data can be lost during the postprocessing (Fig. 11.10).

MAGNETIC RESONANCE IMAGING

Imaging Principles

When a patient is placed in a strong magnetic field, the protons within the soft tissues of the body align with the field. To create an MR image, a radiofrequency pulse is applied that displaces the protons from alignment with the magnetic field. When the pulse is terminated, the displaced protons release a radiofrequency signal as they realign with the applied magnetic field. A receiving coil detects the signal emitted from the protons in the patient's tissues and spatially localizes it using gradient magnetic fields. A computer then applies complex mathematical algorithms to reconstruct the radiosignals into a final image. The appearance of the soft tissue contrast can be manipulated by changing the pulse sequence parameters. Most clinical MRI units use a field strength of 1.5 tesla (T) or 3 T. Lower field strengths are more commonly employed in open bore magnets. The greater the field strength, the better the signal-to-noise ratio, which can result in better image quality and/or throughput, although artifacts may be greater on 3 T units.

Technical advantages of MRI include good soft tissue contrast, multiplanar imaging capabilities, and lack of ionizing radiation. Disadvantages include motion artifact, pulsation artifact (from physiologic vascular motion and swallowing), and metal artifact. The longer the pulse sequence or overall time of the study, the greater the motion artifact. Voluntary swallowing and heavy breathing can cause substantial motion artifact. This can be particularly problematic in dyspneic patients with laryngeal pathology or chronic obstructive pulmonary disease. Dental amalgam artifact varies with the type and extent of amalgam, the scanner strength, and the sequences employed. There are also numerous contraindications including cardiac pacemaker, cochlear implant, metallic orbital foreign body, and ferromagnetic aneurysm clips, to name a few. Manufacturer recommendations regarding MRI safety for implanted medical devices must be sought before placing a patient in the scanner. Careful use of gadolinium-based contrast in patients with renal insufficiency must be employed due to the small but increased risk of developing nephrogenic systemic fibrosis (a systemic disease characterized by progressive multiorgan fibrosis following exposure to gadolinium-based contrast agents) in this population (10,11). Gadolinium use is contraindicated in pregnant patients.

Technical Considerations

Judicious use of MRI is required because of the relatively greater cost, reduced availability, and longer scan times as compared to CT. Scan time particularly influences image quality and excessively long imaging protocols or inappropriate use of MRI as a screening modality frequently results in motion degraded images with loss of diagnostic information. It is often complimentary to CT in the evaluation of head and neck pathology and protocols are usually focused to answer a specific clinical question (12).

Useful applications of MRI include evaluation of skull base pathology, perineural spread of neoplasm, neoplastic marrow space involvement, neoplastic cartilage invasion in the larynx and evaluation of oral cavity pathology, particularly when compromised by dental amalgam artifact on CT. Furthermore, when ultrasound is not adequate, MRI is the preferred modality in pediatric imaging to minimize radiation exposure in this population.

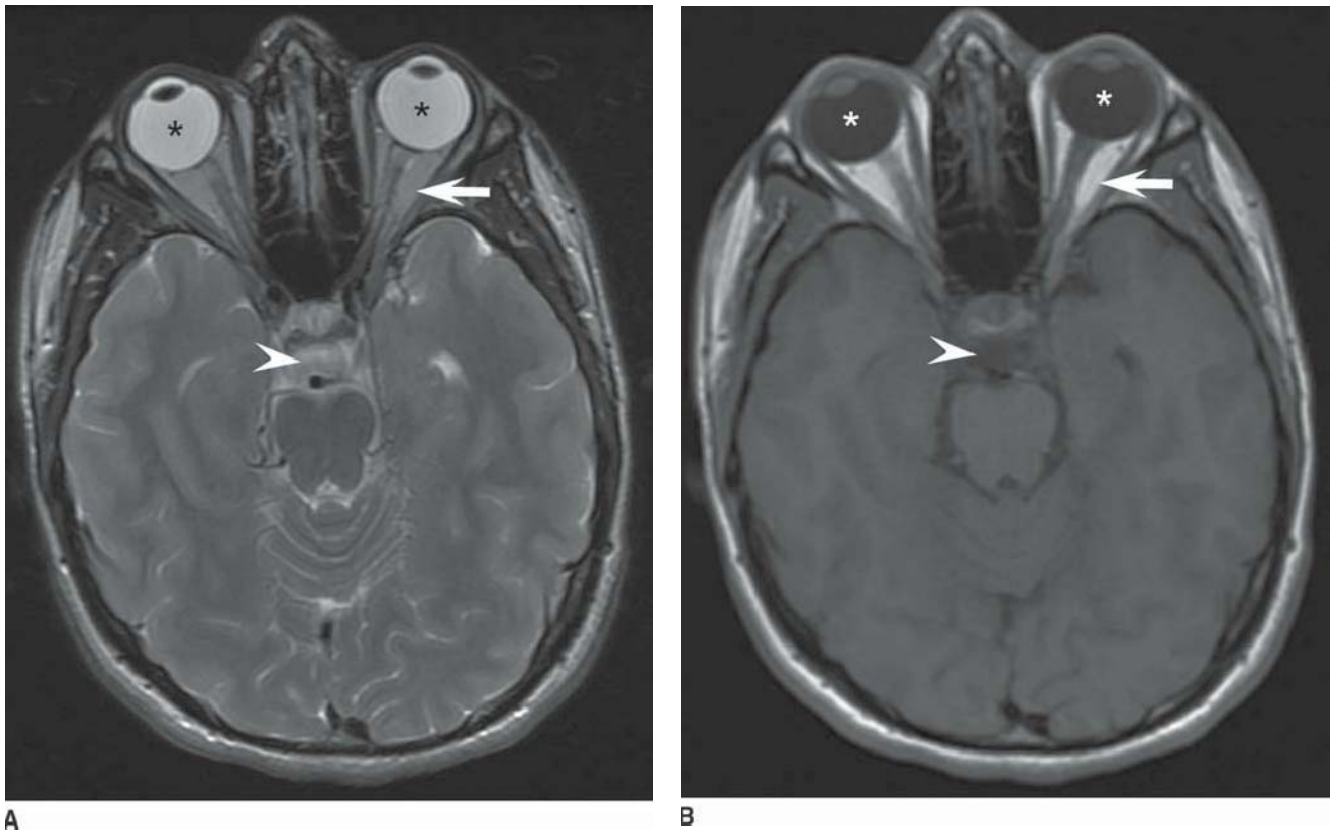


Figure 11.11 Normal brain MRI. **A:** Axial-T2 weighted image. Simple fluid is bright (*white*) signal as can be seen in the vitreous (*asterisk*) and in the normal CSF of the prepontine cistern (*arrowhead*). **B:** Axial T1-weighted image. Simple fluid in the vitreous (*asterisk*) and CSF of the prepontine cistern (*arrowhead*) are dark signal. **A** and **B:** Fat, as is seen in the orbits (*arrows*), is bright signal on both sequences.

Most basic MRI protocols of the neck and/or skull base include axial and coronal T1-weighted pre- and postcontrast images and T2-weighted sequences. T1-weighted images provide good anatomic detail and soft tissue contrast. On T1-weighted sequences, fat is high signal intensity, displayed as bright/white. Fluid, including normal cerebrospinal fluid (CSF) and vitreous, is low signal intensity, displayed as dark/black. On T2-weighted fast spin-echo (FSE) images, the most commonly employed T2-weighted sequence, CSF is displayed as bright/white signal and fat is also bright/white (Fig. 11.11). Muscle is intermediate on both T1- and T2-weighted sequences, displayed as gray. Contrast-enhanced T1-weighted images are used to delineate cystic from solid lesions.

Fat suppression techniques that null the bright/white fat signal are frequently applied to T2-weighted FSE and contrast enhanced T1-weighted sequences to improve tissue contrast of T2 hyperintense lesions and enhancing lesions surrounded by or distorting adjacent fat. Fat suppression techniques are also applied in orbital imaging where suppression of orbital fat signal increases conspicuity of orbital pathology, particularly evaluation of the optic nerves. The most common fat suppression techniques employed include short T1 inversion recovery (STIR) in which fat is placed at the null point of signal intensity and frequency selective presaturation spin-echo sequences in which fat signal is selectively suppressed (example sequences include T1-weighted postcontrast with fat suppression/fat saturation or T2-weighted with fat suppression/fat saturation) (Fig. 11.12).

Slice thickness varies from 3 to 5 mm. Focused thin section volumetric acquisitions can be employed to evaluate a specific area of interest such as the cavernous sinus or the facial nerve. The slice thickness is limited by the sequences employed. Unlike CT, imaging the entire neck from the skull base through the superior mediastinum typically requires two separate acquisitions. Additional sequences can be added to protocols in order to evaluate specific structures or answer-specific clinical questions as described in the following section.

Applications and Special Considerations by Region of Interest

Soft Tissue Neck, Aerodigestive Tract, and Larynx

For most pathology in the neck, CT is preferable to MRI because of its speed, accessibility, and lower cost. In the era of multidetector helical CT, the ability to create multiplanar reformats negates the traditional MRI advantage of multiplanar imaging capability. In many cases, the choice to use MRI versus CT in the evaluation

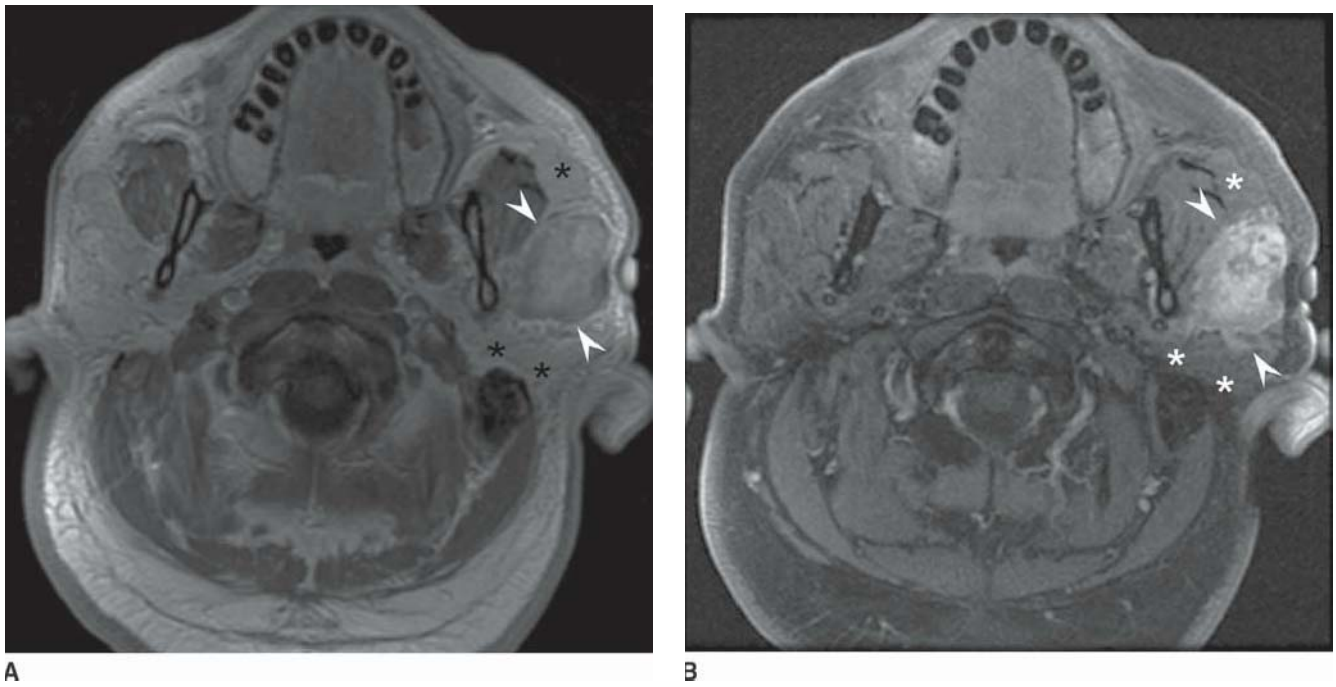


Figure 11.12 Left parotid carcinoma ex pleomorphic adenoma. **A:** Axial contrast-enhanced T1-weighted image. The large enhancing left parotid mass (*arrowheads*) is difficult to see because it has similar signal characteristics to the surrounding T1 hyperintense fatty parotid parenchyma (*asterisk*). **B:** Axial contrast-enhanced T1-weighted image with fat saturation. The same large enhancing left parotid mass (*arrowheads*) is much easier to see when soft tissue contrast is improved by suppressing the fat signal of the parotid parenchyma (*asterisk*), which is now displayed as dark signal.

of neck pathology is user preference or convenience though there are some instances where MRI offers distinct advantages.

In patients with laryngeal squamous cell carcinoma, MRI offers better soft tissue contrast and is more sensitive for the detection of cartilage invasion (13) (Fig. 11.13). Thin-cut or volumetric imaging to improve staging accuracy should be employed (14). With a high negative predictive value in the range of 94% to 96%, MRI is useful to exclude cartilage invasion. Unfortunately, MRI features of neoplastic cartilage invasion overlap with peritumoral inflammation, resulting in a less than optimal positive predictive value. Comparing the signal characteristics of the cartilage with the primary tumor may be helpful in improving specificity (15).

Additional useful applications of MRI in the head and neck include the following: evaluating cranial nerve palsies, excluding prevertebral invasion in patients with extensive mucosal space neoplasm, characterizing oral tongue and hard palate lesions, assessing oral cavity lesions obscured by dental amalgam, predicting resectability of squamous cell carcinoma involving the carotid artery, assessing preepiglottic fat invasion in head and neck neoplasms, and evaluating perineural spread of neoplasm associated with oral cavity and oropharyngeal tumors (16). While MRI is sensitive for the detection of mandibular marrow space involvement in patients with oral cavity and oropharyngeal cancer, it lacks specificity due to false positives from dental disease and sequela of radiation therapy (16). Traditionally, CT was considered more sensitive than MRI for the detection of nodal metastasis (17,18). With advances in MRI imaging, the sensitivity of MRI for detecting abnormal lymph nodes may be comparable to CT but for practical purposes, CT is the preferred modality for evaluating lymph node pathology in the neck (19,20). MRI should be reserved for problem solving or targeted imaging.

Temporal Bone

Patients presenting with facial nerve symptoms and adults presenting with sensorineural hearing loss are initially best evaluated with MRI. It evaluates for pathology affecting the brainstem (ischemic or demyelinating disease), the 7th and 8th cranial nerve complexes and the membranous labyrinth. Facial neuritis, schwannoma, hemangioma, and neoplastic processes affecting the 7th and 8th cranial nerves, inner ear and cerebellopontine angle are well demonstrated with high-resolution MRI.

Neoplastic, inflammatory, and infectious processes occurring in the petrous temporal bone frequently have a soft tissue component that affects the osseous integrity of the bone. MRI and CT are complimentary in evaluating such lesions. MRI characterizes the soft tissue component of the lesion and helps to differentiate inflammatory processes (petrous apicitis) or sequela of inflammatory processes

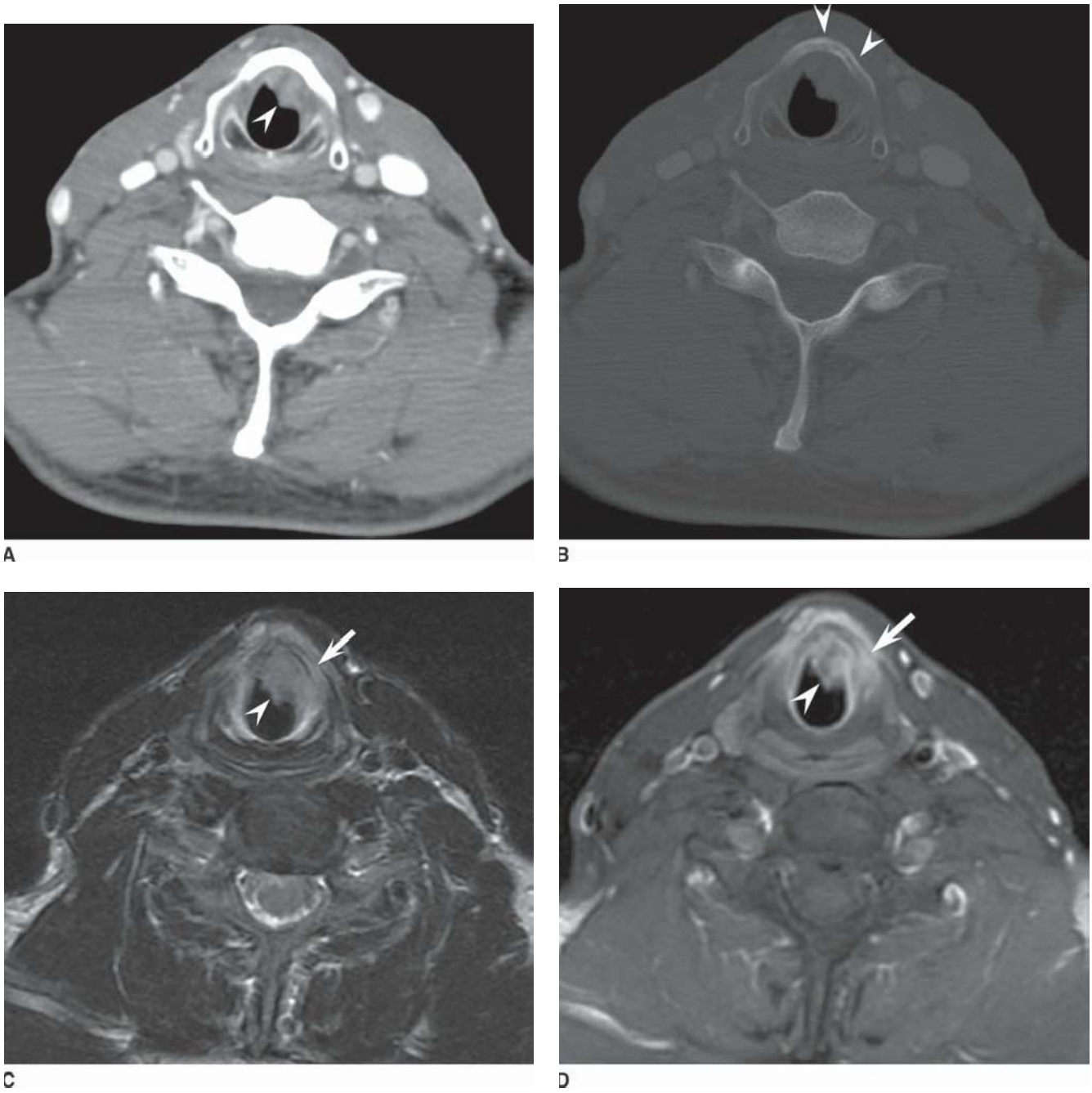


Figure 11.13 Laryngeal cartilage invasion from glottic squamous cell carcinoma with subglottic extension. **A,B:** Contrast-enhanced axial neck CT in soft tissue. **A:** There is tumor (*arrowhead*) within the subglottis anteriorly adjacent to the thyroid cartilage. **B:** On bone windows, there is no destruction or asymmetric sclerosis of the adjacent thyroid cartilage (*arrowheads*) to suggest thyroid cartilage invasion. **C:** Axial T2-weighted image reveals abnormal T2 hyperintense signal in the left anterior thyroid cartilage (*arrow*) similar to the tumor (*arrowhead*) in the subglottis. **D:** Contrast-enhanced axial T1-weighted image with fat suppression. There is associated enhancement in the left anterior thyroid cartilage (*arrow*) similar to the subglottic tumor (*arrowhead*), suggesting thyroid cartilage invasion. Neoplastic invasion of the thyroid cartilage was confirmed pathologically.

(cholesterol granuloma and mucocele) from neoplastic processes (metastasis, eosinophilic granuloma, chondrosarcoma). It also delineates the intracranial extent of disease and its effect on the adjacent brain parenchyma. CT better demonstrates associated osseous abnormalities.

Most temporal bone MRI protocols will include thin-cut precontrast T1-weighted images in the sagittal and axial planes to evaluate for high signal lesions and demonstrate anatomy. Contrast-enhanced T1-weighted images with fat suppression in the coronal and axial plane are used to look for enhancing lesions in the temporal bone or along the course of the 7th and 8th cranial nerve complexes. Various high-resolution T2 sequences (such as "CISS" or "FIESTA") can be used to delineate the 7th and 8th cranial nerves in their canalicular and cisternal segments where they appear dark against the background bright signal of the CSF resulting in a "cisternogram" effect (Fig. 11.14) (21–23). Many of the other cranial nerves, most notably the 5th cranial nerve, can be imaged in a similar manner. This technique can be useful to evaluate for tiny vestibular schwannomas (particularly if contrast is contraindicated) or compression of the 7th nerve root entry zone which can contribute to hemifacial spasm. Diffusion-weighted imaging can be useful in evaluation of petrous apex lesions and in postoperative temporal bone evaluation. Both epidermoid cyst of the petrous apex (congenital cholesteatoma) and recurrent acquired cholesteatoma in the postoperative temporal bone demonstrate high signal intensity compared to brain tissue on diffusion-weighted images. Recent research suggests nonecho planar-based diffusion-weighted sequences with thinner sections and decreased susceptibility artifacts are the most useful for helping distinguish scar tissue and granulation tissue from recurrent cholesteatoma in the postoperative temporal bone (24,25). In patients with dehiscence of the tegmen tympani or tegmen mastoideum, thin-cut high-resolution coronal T2-weighted images and contrast-enhanced T1-weighted images are used to evaluate for meningocele or encephalocele.

Nasopharynx and Skull Base

Imaging plays a critical role in the evaluation of the skull base and nasopharynx because this area is centrally located and difficult to evaluate clinically. Skull base pathology can be categorized into processes originating above the skull base, below the skull base, or centered within the skull base. Consequently, it is important to tailor imaging protocols to include the relevant adjacent intracranial compartment and/or extracranial soft tissues. The soft tissue component of skull base pathology and potential routes of perineural spread of aggressive neoplasms are best imaged with MRI (26,27). CT better demonstrates osseous erosion and matrix associated with lesions, so both modalities are often employed (Fig. 11.15).

In order to optimize evaluation for perineural spread of tumor, protocols should use a small field of view focused on the area of interest using thin-cut 3-mm slices. Possible routes of direct or perineural spread of neoplasm in the orbits, hard palate, pterygopalatine fossa, skull base foramina, cavernous sinus, and temporal bone extending back to

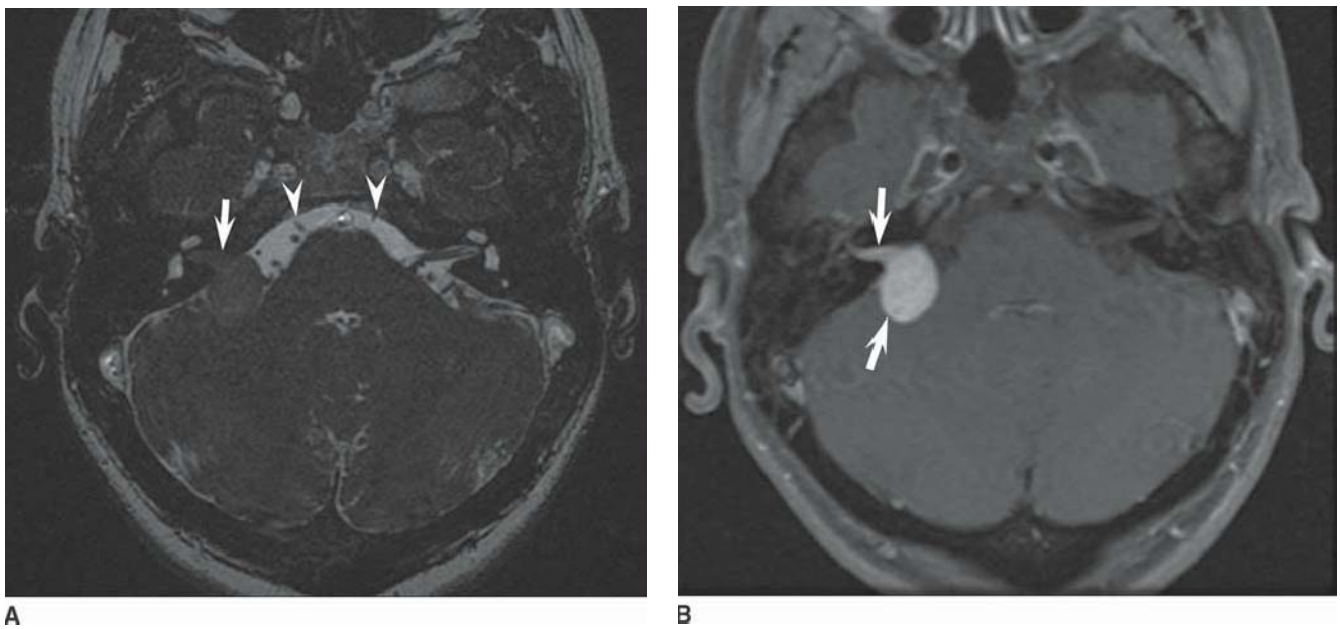


Figure 11.14 Right vestibular schwannoma. **A:** Axial FIESTA through the cerebellopontine angle. There is a large right vestibular schwannoma (*arrow*) filling the right internal auditory canal up to the fundus. It protrudes into the cerebellopontine angle and flattens the ventral margin of the right cerebellar hemisphere. The normal 7th and 8th cranial nerves are seen in the contralateral internal auditory canal. The 6th cranial nerves (*arrowheads*) are also seen in the prepontine cistern; the left 6th nerve is entering Dorello's canal. **B:** Axial contrast enhanced T1-weighted image with fat suppression. The right vestibular schwannoma (*arrows*) avidly enhances.

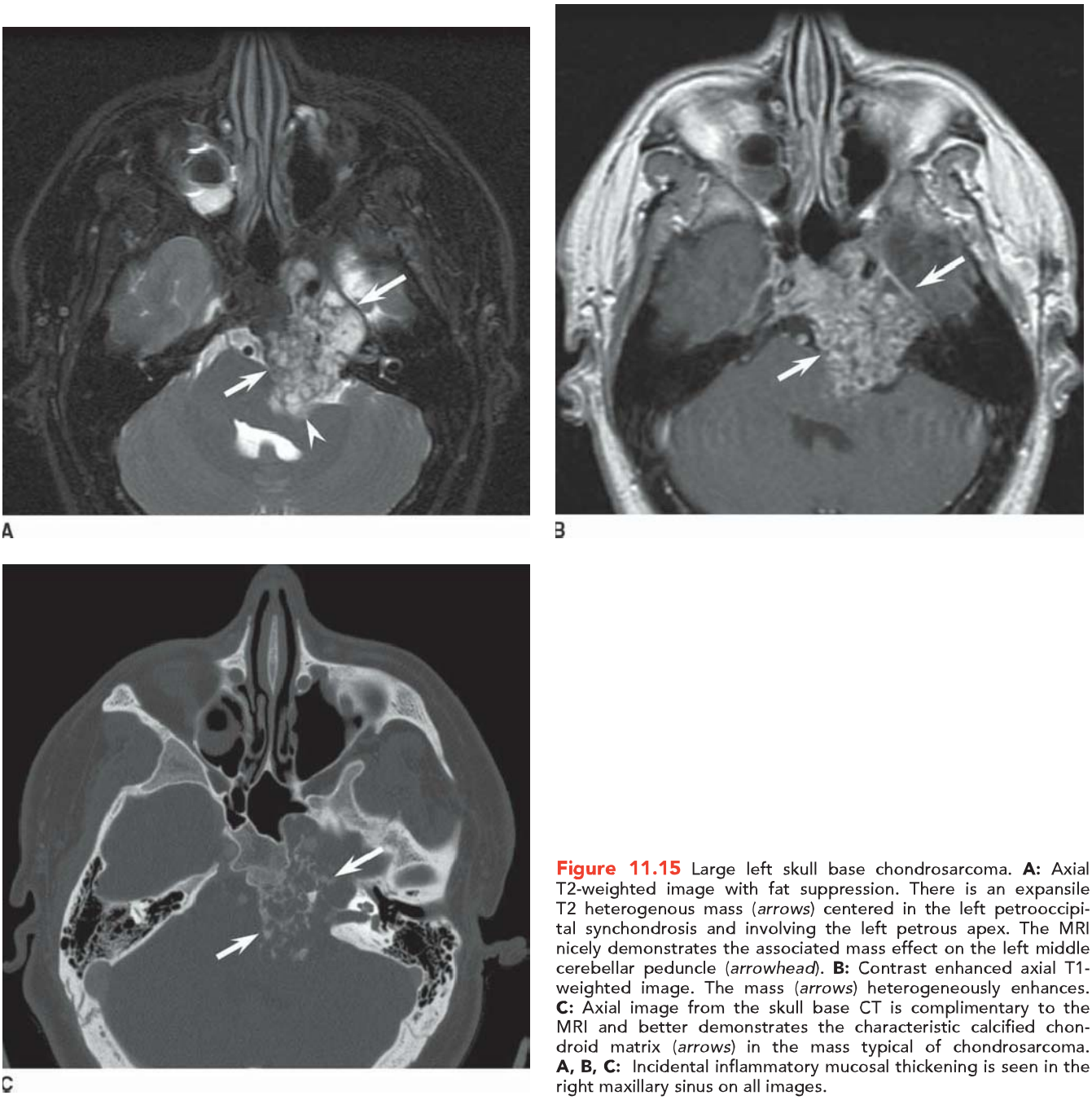


Figure 11.15 Large left skull base chondrosarcoma. **A:** Axial T2-weighted image with fat suppression. There is an expansile T2 heterogenous mass (*arrows*) centered in the left petrooccipital synchondrosis and involving the left petrous apex. The MRI nicely demonstrates the associated mass effect on the left middle cerebellar peduncle (*arrowhead*). **B:** Contrast enhanced axial T1-weighted image. The mass (*arrows*) heterogeneously enhances. **C:** Axial image from the skull base CT is complimentary to the MRI and better demonstrates the characteristic calcified chondroid matrix (*arrows*) in the mass typical of chondrosarcoma. **A, B, C:** Incidental inflammatory mucosal thickening is seen in the right maxillary sinus on all images.

the 5th and 7th nerve root entry zones should be imaged. Fat suppressed T1 postcontrast images are useful to directly image the nerves traversing the skull base to evaluate for excessive enhancement along nerve branches or widening within the pterygopalatine fossa, skull base foramina, Meckel's cave or cavernous sinus, all of which can be seen with perineural spread of neoplasm (Fig. 11.16). Thin-cut T1-weighted images without contrast are essential to evaluate for loss of the normal fat surrounding nerves in the pterygopalatine fossa, within the infratemporal fossa and as they enter neural and skull base foramina as this can also be a sign of perineural spread of tumor. In Adults, Axial T1-weighted images are important to evaluate for loss of the normal fatty skull base marrow signal, which can be seen with neoplastic marrow infiltration, skull base osteomyelitis, blood dyscrasias, and other primary bone lesions (28).

Paranasal Sinuses

CT and MRI are complimentary in the evaluation of sinonasal neoplasms (29). The main utility of MRI of the paranasal sinuses and maxillofacial structures is to evaluate the extent of sinonasal neoplasms and associated perineural spread of neoplasm that will influence surgical approach and treatment planning. MRI delineates the margins of the

mass from adjacent obstructed secretions and inflammatory mucosal disease. It directly images skull base invasion, perineural spread of neoplasm, intraorbital involvement and intracranial extension of neoplasm, including dural and brain parenchyma invasion. Similarly, in cases of invasive fungal disease, MRI better characterizes the intracranial and perineural spread of disease. CT evaluates the osseous integrity of the orbits, anterior skull base, and maxillofacial structures (Fig. 11.16). A protocol similar to the described skull base protocol should be used with the field of view tailored to include the relevant portions of the craniofacial structures, orbits, sinonasal cavity, skull base, and mandible.

Salivary Glands

MRI is the study of choice for evaluation of a painless salivary mass, particularly if it is accompanied by a cranial nerve deficit (30). It offers good special resolution with superior soft tissue contrast compared to CT. In patients with a suspected inflammatory or infectious process involving the salivary glands, CT is the preferred imaging modality because sialoliths are difficult to see with MRI.

Imaging should extend to the skull base and posterior fossa to include the course of 5th and 7th cranial nerves to adequately assess for extent of perineural spread of neoplasm. In adults, parotid masses are well delineated on T1-weighted images because of the fatty background of the gland, which serves as a natural contrast agent. The margins of a parotid mass including extension into the adjacent parapharyngeal fat, masticator space, and bone marrow are well delineated on this sequence. Fat suppressed contrast-enhanced T1-weighted images are used to distinguish cystic from solid masses and evaluate for perineural spread and marrow space invasion. Fat suppressed T2-weighted images can be helpful in suggesting a lesion is malignant as most high grade malignant neoplasms will have low to intermediate signal on T2-weighted images and most benign parotid masses are T2 hyperintense (Fig. 11.17). There is, however, overlap between the signal characteristics of benign and malignant lesions. Low grade mucoepidermoid and adenoid cystic carcinomas can be T2 hyperintense while benign Warthin tumors can be T2 intermediate or low signal. Imaging does not serve as a substitute for soft tissue sampling.

Orbits

MRI is frequently the study of choice for many neuro-ophthalmic conditions. It offers better soft tissue evaluation of the optic pathways, cavernous sinus region, sella turcica, and brain parenchyma, all of which can be affected when patients present with visual or neuro-ophthalmic symptoms. All orbital protocols should include imaging in two orthogonal planes, typically the axial and coronal plane to demonstrate the relationship of the extraocular muscles with the optic nerve, osseous orbital margins, and orbital apex. T1-weighted precontrast images should be included to evaluate for T1 hyperintense choroidal lesions, which can be seen with melanoma. Utilizing fat suppression when imaging the orbits is critical on T2 and contrast-enhanced T1-weighted sequences to increase tissue contrast of orbital mass lesions surrounded by fat in the orbit and detect optic nerve and nerve sheath enhancement (Fig. 11.18).

Many orbit protocols will include an axial fluid attenuated inversion recovery sequence of the brain to evaluate for any evidence of demyelinating disease, which supports a diagnosis of multiple sclerosis in patients with optic neuritis. Protocols can be modified to include MR angiogram, MR venogram, or MRI of the brain, skull base, or neck depending on the patient's clinical presentation (optic neuropathy, visual field deficit, cranial nerve deficit, optic disc swelling, Horner syndrome) and the suspected pathology (31).

Temporomandibular Joint

MRI is the preferred modality to evaluate for internal derangement in patients with temporomandibular joint (TMJ) dysfunction (32,33). Proton density or T1-weighted images may be used to demonstrate the margins of the disk relative to the joint capsule and bone (Fig. 11.19). Small field of view high-resolution imaging is employed. A typical protocol includes proton density coronal images and sagittal oblique images in closed and open mouth views. Open mouth images are used to evaluate disk function. Coronal images in the closed mouth view are used to look for medial or lateral displacement of the disc. T2-weighted images in the oblique sagittal closed mouth view are used to look for marrow edema and joint effusion.

Dynamic and pseudodynamic MRI of the TMJ has been the subject of research in an attempt to better characterize joint range of motion and to demonstrate pathology that may only be seen during mouth opening and closing (34–36). Image noise, suboptimal disc visualization, and temporal resolution remain barriers to the routine use of dynamic TMJ MRI at this time and the technique still requires validation. Currently, dynamic TMJ MRI may be used as an adjunct to standard open and closed mouth TMJ MRI but is not a replacement for it (34). CT is complimentary to MRI and provides good bone detail in cases of neoplastic involvement of the TMJ, posttraumatic deformity, and inflammatory arthropathy.

Brachial Plexus

Because it is inaccessible to direct palpation, clinical evaluation of the brachial plexus is challenging and imaging plays a critical role. MRI is well suited to evaluate the complex anatomy and pathology of the brachial plexus due to its multiplanar imaging capability and excellent soft tissue contrast. T1-weighted images demonstrate the anatomy best as the fat surrounding the brachial plexus acts as a natural contrast to delineate the roots, trunks, divisions, and cords. T2-weighted FSE images with fat suppression are used to identify pathologic signal changes in the plexus. Postcontrast images are useful when neoplasm, inflammation, infection, or stretch injury is suspected (37). The sagittal plane is particularly useful to evaluate

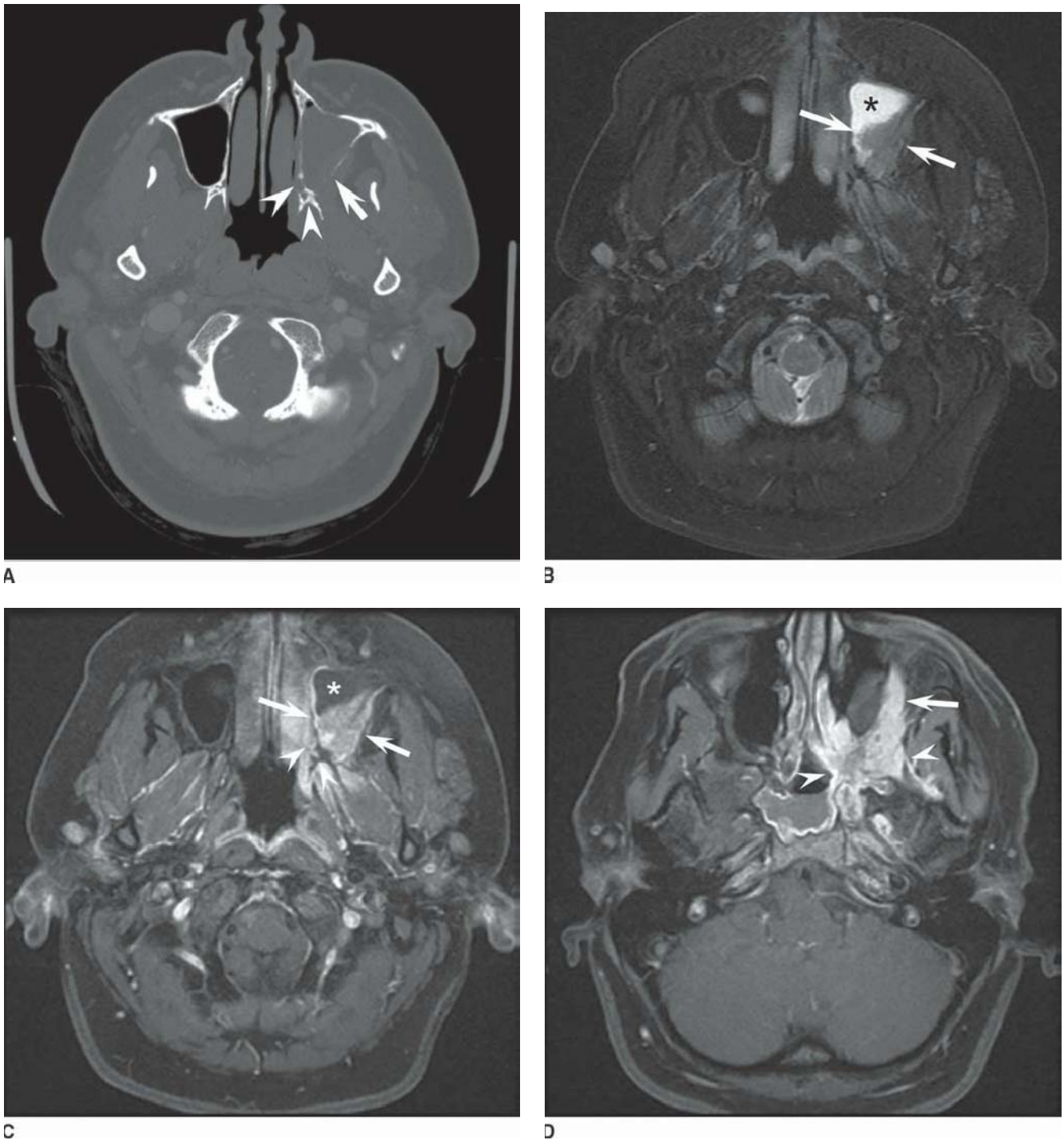


Figure 11.16 Adenoid cystic carcinoma in a 22-year-old female with left facial pain. **A:** Axial contrast-enhanced CT displayed in bone algorithm. There is complete opacification of the left maxillary sinus. Areas of erosion of the posterolateral wall of the left maxillary sinus (*arrow*) and widening of the left greater and lesser palatine foramina (*arrowheads*) suggest an underlying sinonasal neoplasm with perineural spread of tumor. **B:** Axial T2 with fat saturation. There is a T2 intermediate mass (*arrows*) in the dorsal aspect of the left maxillary sinus extending into the left retroantral fat. The mass is easily distinguished from inflammatory secretions (*asterisk*) within the anterior left maxillary sinus that are T2 hyperintense. **C–E**: Contrast-enhanced axial T1-weighted images with fat suppression. **C:** The mass (*arrows*) avidly enhances. The inflammatory secretions do not (*asterisk*). Enhancing perineural spread of tumor is seen in the enlarged left greater and lesser palatine foramina (*arrowheads*). **D:** There is extensive enhancing perineural spread of tumor along the markedly enlarged left infraorbital nerve (*arrow*) and within the left pterygopalatine fossa extending into the left pterygomaxillary fissure (*arrowheads*). There is incidental inflammatory opacification in the right sphenoid sinus. *(continued)*



Figure 11.16 *(Continued)* **E:** Perineural spread of tumor extends intracranially along V2 into the left cavernous sinus and Meckel's cave (*arrows*). There is also involvement of the enlarged enhancing left greater superficial petrosal nerve extending to the geniculate ganglion of the left facial nerve (*arrowheads*). Tumor is also seen in the left orbital apex (*asterisk*).

the relationship of the brachial plexus to the adjacent subclavian vessels and clavicle (Fig. 11.20). While unilateral high-resolution imaging in at least two or three planes is preferred, bilateral coronal STIR or axial T1 postcontrast fat suppressed images may be helpful to compare with the unaffected side, particularly if the reader is inexperienced (38).

ULTRASOUND

Imaging Principles

Ultrasound employs a pulse echo technique to generate images. The transducer applied to the patient's skin generates a high-frequency sound wave that is partially transmitted and partially reflected at each interface where there is a difference of acoustic impedance. The same transducer detects the reflected sound energy (echo) from these interfaces, with the depth of each echo estimated by assuming an average speed of sound and using the time of flight. The data are displayed as 2D or 3D gray scale images of the tissues. Using the Doppler frequency shift generated by moving red blood cells, Doppler ultrasound can image the vasculature in the neck (color Doppler sonography) or display the velocities and direction of flow in a vessel (spectral Doppler sonography).

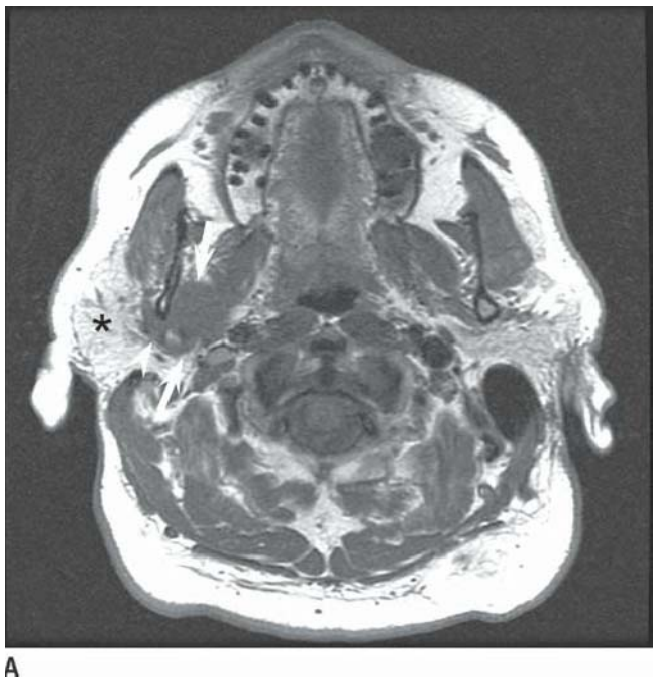
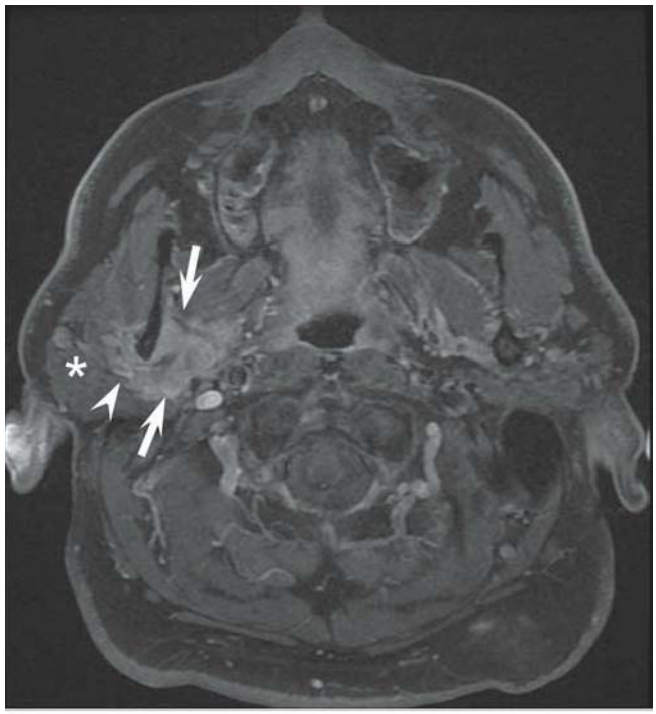




Figure 11.17 Adenoid cystic carcinoma right parotid gland. **A:** Axial T1-weighted image nicely demonstrates an infiltrative T1 intermediate mass (*arrows*) involving the deep portion of the right parotid gland and perineural spread of tumor extending around the ramus of the mandible along the course of the thickened right auriculotemporal nerve (*arrowhead*). The mass is easily distinguished from the surrounding hyperintense fatty parotid parenchyma (*asterisk*). **B:** Axial T2 fat suppressed image. The mass has T2 intermediated signal characteristics (*arrows*), suggesting a malignant neoplasm. There is poor tissue contrast between the mass and the dark fat signal (*asterisk*) in the surrounding parotid parenchyma on this fat suppressed sequence, making it difficult to delineate the margins of the mass. (*continued*)



C

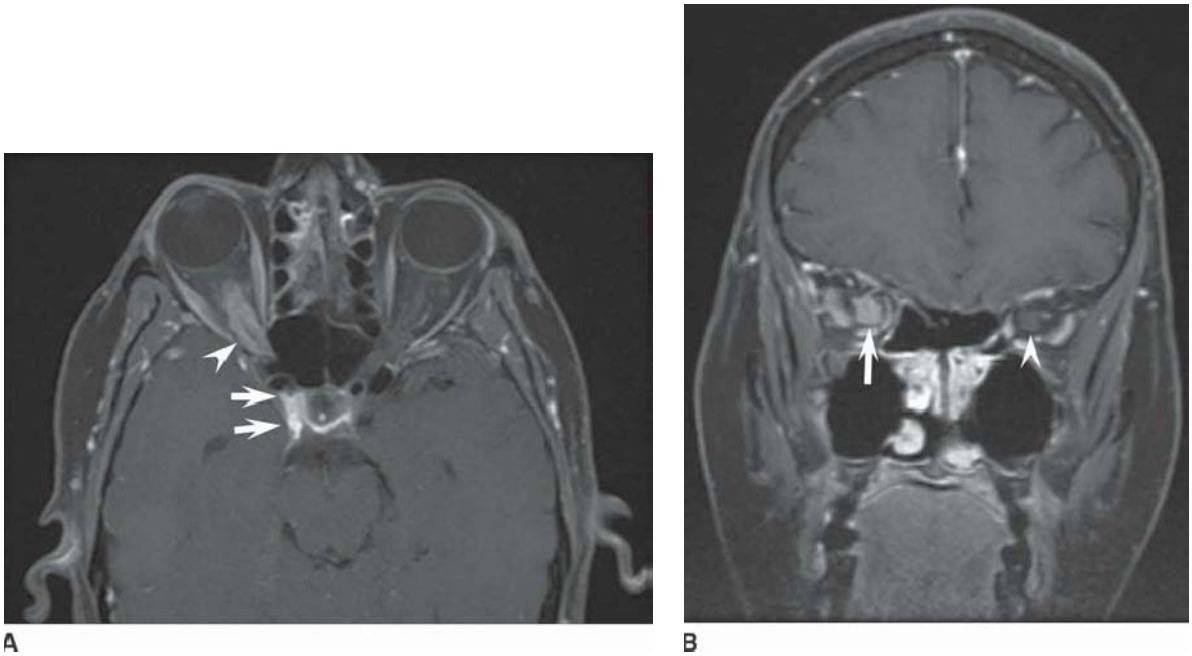
Figure 11.17 *(Continued)* **C:** Axial contrast-enhanced fat suppressed image nicely demonstrates central solid enhancement in the mass (*arrows*), and perineural spread along the thickened enhancing right auriculotemporal nerve (*arrowhead*), easy to see because the fat signal in the surrounding parotid parenchyma (*asterisk*) is dark due to the fat suppression technique.

Advantages of ultrasound include its lack of ionizing radiation, relatively low cost, portability, and real time and multiplanar imaging capabilities. At the energies used for medical imaging, there are no known harmful effects. Disadvantages include operator dependence, small field of view in some instances, and difficulty in mastering the anatomy as presented in nonstandard planes.

Indications and Technique

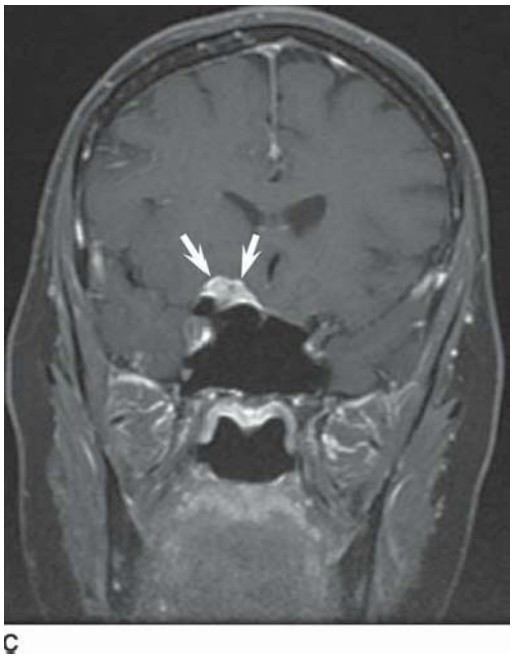
Ultrasound is well suited to evaluate superficial structures in the head and neck, including palpable lymph nodes, parotid masses, thyroid lesions, and parathyroid disease. Ultrasound provides the highest resolution for evaluating focal and diffuse thyroid pathology. Detection of intrathoracic and retrotracheal extension of the thyroid as well as invasion of the esophagus and trachea by thyroid neoplasm is not well imaged with ultrasound and better demonstrated with CT (39). In the management of patients with thyroid cancer, ultrasound is the most sensitive imaging modality to detect nodal metastasis (40).

The portability, low cost, and real-time imaging capabilities of ultrasound are particularly advantageous to perform convenient image guided biopsy of superficial head and neck masses (Fig. 11.21). Ultrasound allows for precise needle tip placement with real-time adjustment of the needle biopsy path during the procedure to avoid critical neurovascular structures. Doppler ultrasound assesses vessel



A B

Figure 11.18 Right paraclinoid and optic nerve sheath meningioma. **A:** Contrast-enhanced axial T1-weighted image with fat suppression through the orbits reveals tram-track enhancement of the right optic nerve sheath complex (*arrowhead*) characteristic of meningioma. The abnormal enhancement is well demonstrated because of fat saturation technique applied to the orbital fat. The portion of the mass extending intracranially along the right aspect of the sella (*arrows*) is difficult to see in the axial plane. **B** and **C**: Contrast-enhanced coronal T1-weighted image with fat suppression. The relationship of the enlarged enhancing right optic nerve sheath complex (*arrow*) to the extraocular muscles is seen on the coronal sequence. The left optic nerve sheath complex (*arrowhead*) is normal in appearance. *(continued)*



C

Figure 11.18 *(Continued)* **C:** The right paraclinoid portion of the mass (*arrows*) extending along the posterior planum sphenoidale is better imaged in the coronal plane.

patency and serves as a good screening tool for carotid artery stenosis. Ultrasound is the first study of choice for evaluation of a neck mass in the pediatric population because of its lack of harmful effects and because it does not require preparation, sedation, or contrast administration. Portability and lack of ionizing radiation allow caregivers to be present with the child during imaging which may improve patient cooperation, decrease patient anxiety, and facilitate evaluation of abnormalities. In cases where malignancy is suspected or the lesion is too large to be adequately imaged, MRI or CT can be performed. Ultrasound is more widely utilized in Europe than in the United States, probably because of its operator dependency and cost.

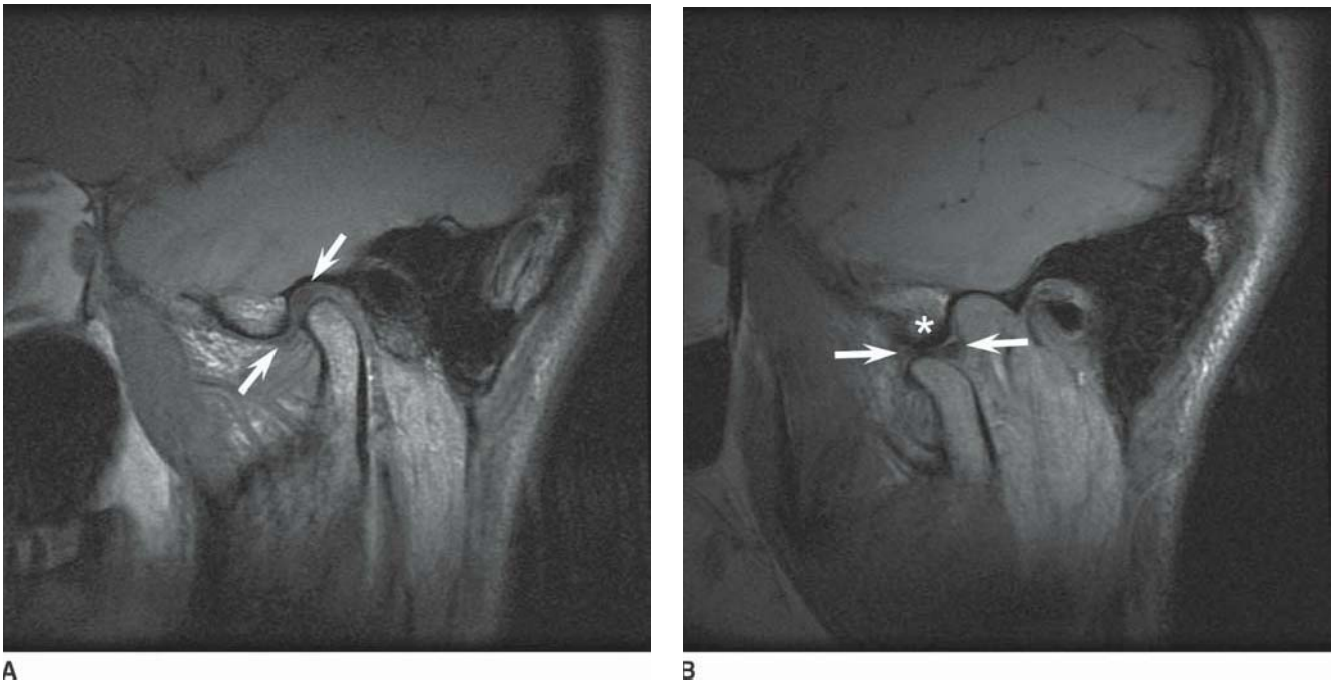
NUCLEAR MEDICINE

Nuclear radiology has both diagnostic and therapeutic applications. While its spatial resolution is poor, it provides functional and physiological information not provided by conventional CT, MRI, and ultrasound. In the head and neck, main applications include positron emission tomography (PET)/CT, thyroid and parathyroid scintigraphy, and to a lesser extent other tumor scintigraphic imaging.

POSITRON EMISSION TOMOGRAPHY

Imaging Principles

PET is a functional imaging technique that employs the use of a radiotracer to illustrate tissue metabolic activity. PET is now frequently performed as a hybrid technique, PET/CT, where PET images are fused with CT images to provide both functional and anatomical information. The



A B

Figure 11.19 Normal TMJ articular disk. **A** and **B**: Sagittal oblique T1-weighted images. **A:** In the closed mouth view, the normal biconcave shaped T1 intermediate disc (*arrows*) is seen between the mandibular condyle and the glenoid fossa. **B:** In the open mouth view, the condyle moves anterior and inferior, beneath the articular eminence (*asterisk*) of the temporal bone. The disc (*arrows*) maintains its normal shape and position interposed between the mandibular condyle and the temporal bone.

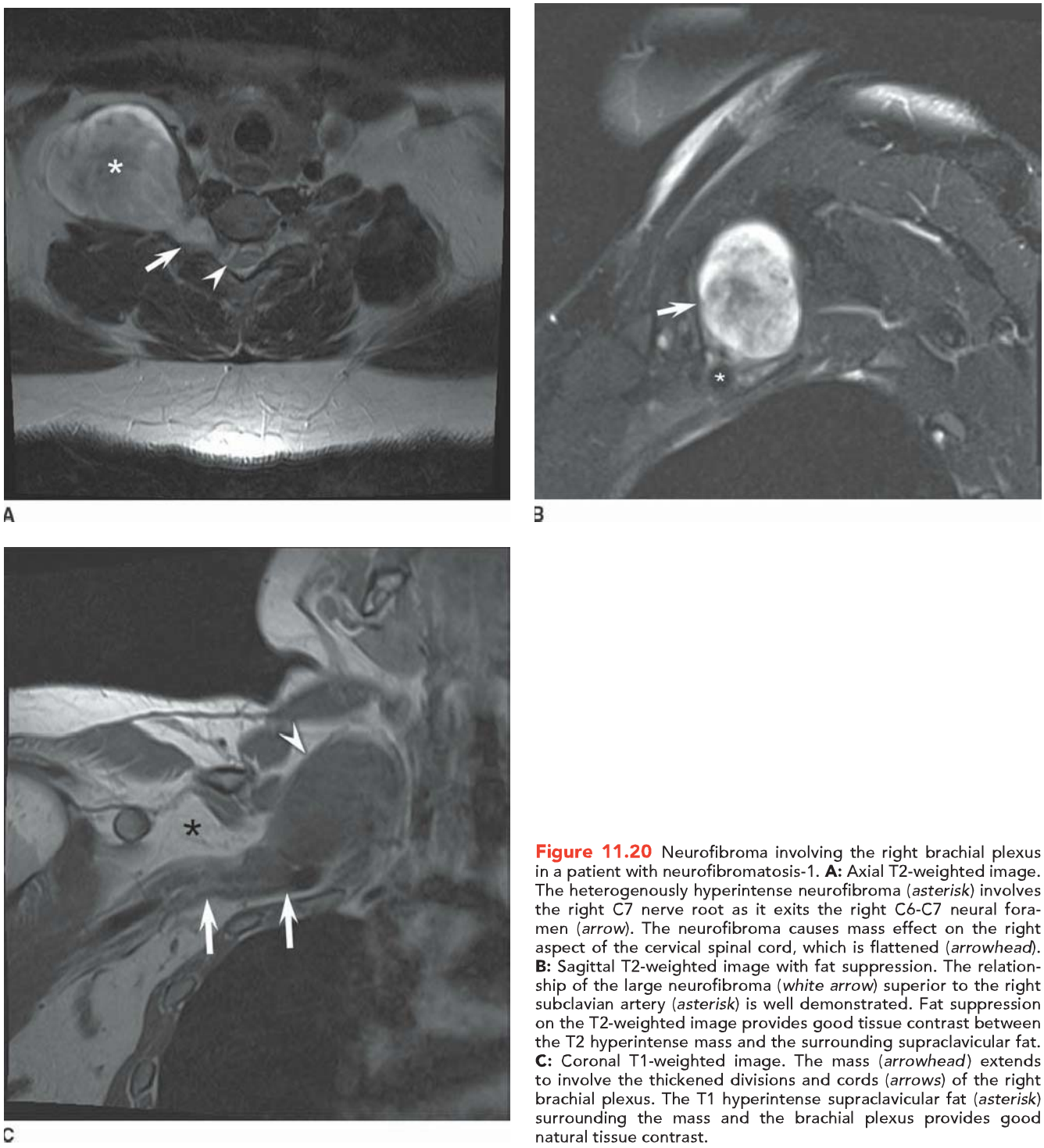


Figure 11.20 Neurofibroma involving the right brachial plexus in a patient with neurofibromatosis-1. **A:** Axial T2-weighted image. The heterogenously hyperintense neurofibroma (*asterisk*) involves the right C7 nerve root as it exits the right C6-C7 neural foramen (*arrow*). The neurofibroma causes mass effect on the right aspect of the cervical spinal cord, which is flattened (*arrowhead*). **B:** Sagittal T2-weighted image with fat suppression. The relationship of the large neurofibroma (*white arrow*) superior to the right subclavian artery (*asterisk*) is well demonstrated. Fat suppression on the T2-weighted image provides good tissue contrast between the T2 hyperintense mass and the surrounding supraclavicular fat. **C:** Coronal T1-weighted image. The mass (*arrowhead*) extends to involve the thickened divisions and cords (*arrows*) of the right brachial plexus. The T1 hyperintense supraclavicular fat (*asterisk*) surrounding the mass and the brachial plexus provides good natural tissue contrast.

most commonly used radiotracer in clinical practice is 18F-labeled fluorodeoxyglucose (FDG), a glucose analog that is actively transported into cells by glucose transport proteins. Once inside the cell, hexokinase phosphorylates the 18F-FDG, forming 18F-FDG-phosphate, which is trapped intracellularly. Many tumor cells have increased numbers of glucose transporters, higher concentrations of hexokinase and higher metabolic rates, all contributing to the preferential uptake of 18F-FDG in neoplastic cells as compared to normal cells. The PET scanner detects the radiation emitted from the 18F-FDG uptake in the patient. After the data are processed by a computer, the tracer distribution throughout the body is displayed coregistered with the CT for anatomic localization.

Modern PET/CT scanners consist of a full ring of coincident PET detectors combined with the CT system, allowing the patient to remain on the same scan table and in the same position to optimize image fusion. This system

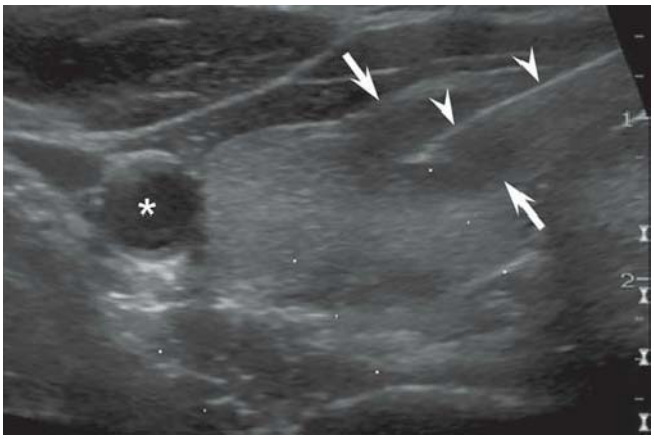


Figure 11.21 Ultrasound guided fine needle aspiration (FNA) of a right thyroid lobe nodule. A hypoechoic nodule (*arrows*) is present in the anteromedial right lobe of the thyroid gland. The linear hyperechoic needle path (*arrowheads*) that extends into the nodule during FNA is clearly seen. The right ICA is just lateral to the gland (*asterisk*). This was nodular hyperplastic goiter.

allows for a quality diagnostic contrast-enhanced neck CT to be obtained simultaneously with the PET and facilitates a comprehensive evaluation of the patient's disease. The PET portion is useful to evaluate nodal status and distant metastasis. The contrast-enhanced neck CT delineates the extent of the primary tumor and its relationship to critical structures and delineates areas of necrotic or cystic tumor that may not be FDG avid.

Disadvantages of PET include poor sensitivity for lesions less than 5- to 10-mm, low spatial resolution and suboptimal specificity. Increased 18F-FDG uptake is not specific to neoplastic cells and occurs in cells with elevated glycolytic activity and metabolism, including at sites of inflammation, infection, tissue repair, and hyperactivity (e.g., muscular).

Applications of PET

Most current applications of FDG-PET are performed using combined PET/CT because it is more accurate than FDG-PET alone, improves reader confidence, and can be used to plan biopsies and adjuvant therapy (41–43). In patients with advanced head and neck squamous cell carcinoma (HNSCC), staging FDG-PET and PET/CT are more sensitive for detecting regional or distant metastatic disease as well as synchronous neoplasms that may be occult by clinical exam or conventional imaging (44,45). When conventional evaluation fails in patients with metastatic carcinoma of the neck and an unknown primary, FDG-PET and PET/CT are useful adjuncts used to direct endoscopic biopsy or identify primary lesions outside the head and neck (Fig. 11.22). A negative PET/CT, however, does not preclude further evaluation with panendoscopy, tonsillectomy, and blind biopsies as the resolution of PET/CT is limited to approximately 5–10 mm and small or superficial lesions may be below the resolution of the study (44,45). Similarly, the spatial resolution limits the detection for microscopic metastasis and currently FDG-PET and PET/CT are not considered accurate enough to guide therapy in the clinically defined N0 neck.

In patients with HNSCC treated with nonsurgical organ preservation therapy (NSOPT) such as chemoradiation, PET/CT is more accurate than conventional imaging in detecting recurrent or residual neoplasm and is useful to monitor treatment response to therapy. Following chemoradiotherapy, the high negative predictive value of FDG-PET and PET/CT is useful to exclude locoregional disease and distant metastases (46–50) (Fig. 11.23). Some authors have suggested that a negative PET/CT may obviate the need for planned neck dissection (44,50,51). Furthermore, a negative PET/CT following NSOPT has prognostic value and has been associated with greater

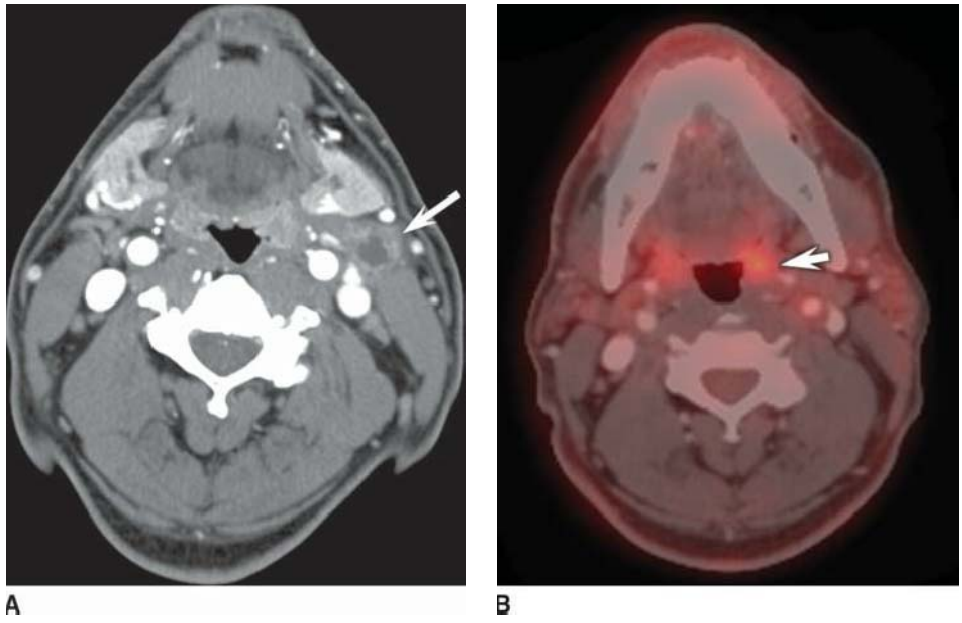


Figure 11.22 Left faucial tonsil carcinoma with metastatic left level II node. A 62-year-old male presented with complaint of palpable left neck mass. **A:** Axial contrast-enhanced neck CT. A malignant appearing necrotic left level II lymph node (*arrow*) is seen. No primary mucosal neoplasm was seen on the CT or clinical exam. FNA of the lymph node was consistent with squamous cell carcinoma. **B:** Fused F18-FDG PET/CT. Asymmetric FDG uptake in the left faucial tonsil (*arrow*) was suspicious for a primary left faucial tonsil carcinoma. Directed biopsy of the left faucial tonsil was positive for squamous cell carcinoma, confirming it as the source of the left level II lymph node metastasis.

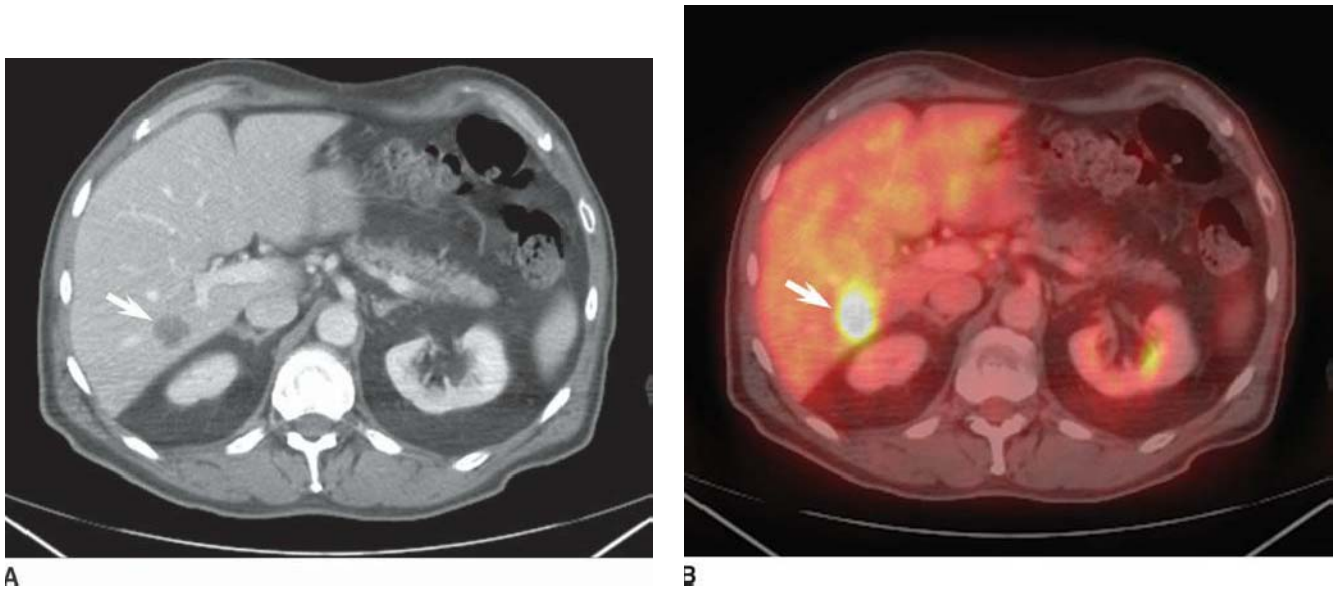


Figure 11.23 Isolated squamous cell carcinoma metastasis to the liver 6 months following completion of chemoradiotherapy for a T2N2b supraglottic squamous cell carcinoma. **A:** Contrast-enhanced CT from diagnostic whole body PET/CT study. A hypoattenuating mass (*arrow*) is seen in the posterior segment of the right lobe of the liver. **B:** Fused F18-FDG PET/CT image demonstrates intense F18-FDG avidity (*arrow*) in the mass suspicious for malignant neoplasm. This was biopsy proven isolated metastatic squamous cell carcinoma. The patient underwent partial hepatectomy.

2-year progression-free survival and overall survival rates (46,47,49).

FDG-PET and PET/CT have applications in the management of other head and neck malignancies as well. In patients with lymphoma and melanoma, PET/CT is useful for initial staging of disease, assessing response to treatment, and surveying for disease recurrence. Following treatment for differentiated thyroid carcinoma, FDG-PET and PET/CT are useful for the detection of recurrent or metastatic disease in patients with elevated serum thyroglobulin and a negative whole body radioiodine scan, with sensitivities ranging from 70% to 95%. PET/CT is more accurate for precise localization of recurrent tumor when compared with PET alone and may alter management (44,52). Following surgery for medullary thyroid carcinoma, FDG-PET may be helpful in the detection of recurrent or residual disease in patients with elevated calcitonin levels. However, reported sensitivities are variable and the absence of FDG uptake does not exclude disease (44,52,53). There has been research on other more specific PET radiotracers and early data suggest that 18 F-FDOPA PET has greater sensitivity than FDG-PET for detection of recurrent medullary thyroid carcinoma in this population (52).

SCINTIGRAPHY

Nuclear Scintigraphy

Imaging Principles with Single Photon Emitters

Aside from PET, most nuclear scintigraphy is performed with a standard gamma camera and radiopharmaceuticals containing isotopes emitting single gamma photons. Patients are administered a radionuclide which then distributes and accumulates in the body. The choice of radiopharmaceutical administered is determined by the clinical question, the normal biodistribution of the radiotracer and influenced by practical issues such as cost, half-life, image quality and radiation absorbed dose.

Thyroid Scintigraphy

Using the sodium/iodine symporter, the follicular cells of the thyroid gland concentrate iodide, which is then oxidized and organified into the protein thyroglobulin. Thyroglobulin is then used to produce the thyroid hormones triiodothyronine (T3) and thyroxine (T4). Because iodine is essential to thyroid physiology, iodine and its analogues are well suited to thyroid scintigraphy. The radionuclides used for thyroid imaging are listed in Table 11.1.

In otolaryngology, the main application of thyroid scintigraphy is in the management of patients with differentiated thyroid cancer. Following total thyroidectomy or near total thyroidectomy for thyroid cancer, radioactive iodine imaging is employed to identify thyroid remnant tissue, residual tumor, and metastasis amenable to I-131 treatment (Fig. 11.24). After definitive treatment for differentiated thyroid cancer, radioiodine whole-body imaging may be used to survey for local disease recurrence or distant metastasis (54).

In benign thyroid disease, diagnostic thyroid scintigraphy is most commonly used to evaluate causes of hyperthyroidism, though additional applications include

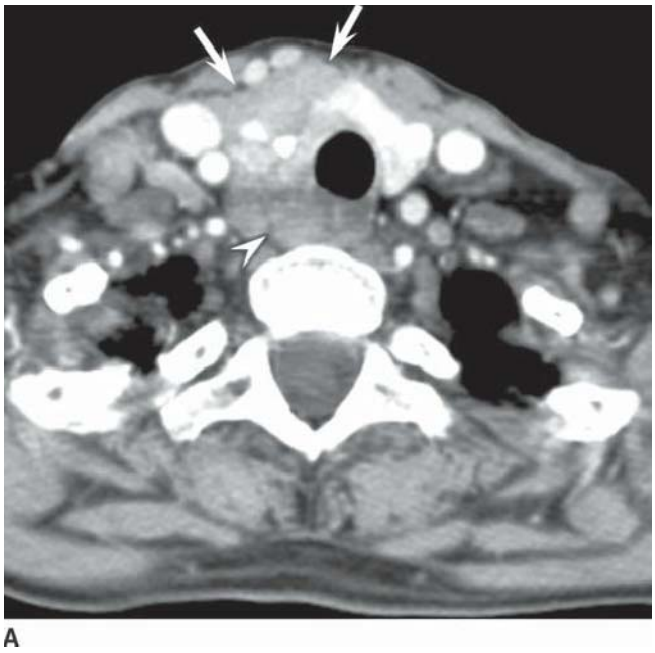
TABLE 11.1 RADIONUCLIDES USED FOR THYROID SCINTIGRAPHY

Radionuclide	Half-life	Principal Photon (keV)
I-123	13 h	159
I-131	8 d	364
^{99m}Tc	6 h	140

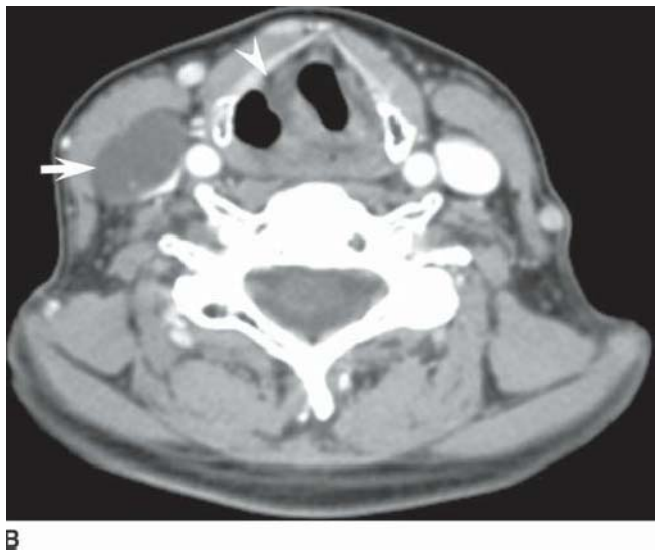
assessment of function in thyroid nodules and diagnostic work up of congenital hypothyroidism. Therapeutically, I-131 can also be used to treat Graves disease and toxic nodular disease.

Parathyroid Scintigraphy

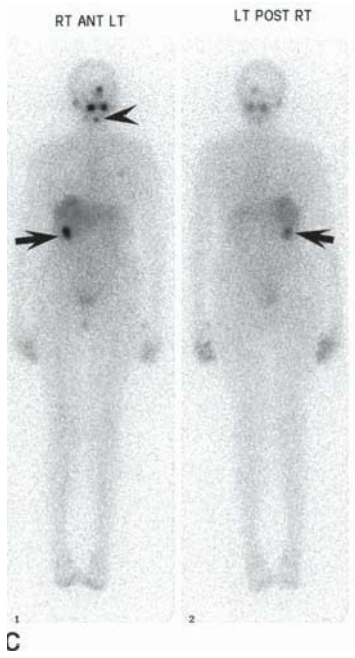
Hyperparathyroidism due to parathyroid adenoma is the most common type of parathyroid disease. Preoperative localization of parathyroid disease is crucial because of the increasing popularity of minimally invasive parathyroid surgery focused on limited dissection of the abnormal parathyroid gland (55,56). There are several parathyroid localizing radiotracers available, including technetium-^{99m}Tc sestamibi, technetium, ^{99m}Tc tetrofosmin, and thallous chloride Tl-201. Initially, Tl-201-chloride-^{99m}Tc pertechnetate subtraction imaging was the most widely accepted parathyroid scintigraphy, but it has been replaced with technetium ^{99m}Tc sestamibi, the current most commonly used radiotracer for parathyroid imaging.



A



B



C

Figure 11.24 Metastatic papillary thyroid carcinoma. **A,B:** Axial contrast-enhanced neck CT. **A:** A hypoattenuating partially calcified mass (*arrows*) is seen in the right lobe of the thyroid extending into the right tracheoesophageal groove (*arrowhead*). **B:** The right aryepiglottic fold (*arrowhead*) is medialized due to the right vocal cord paralysis and there is a cystic metastatic cystic right level III cervical lymph node (*arrow*), indicating the thyroid mass is malignant. **C:** Whole body I-131 scintigraphy following thyroidectomy and I-131 treatment of metastasis. There is focal increased uptake (*arrow*) in the right lobe of the liver and in the submental region (*arrowhead*) due to metastatic papillary thyroid carcinoma. Physiologic tracer uptake is seen in the salivary glands, nasopharynx, liver, bowel, and bladder.

Dual-phase imaging is preferred due to greater sensitivity (57). A typical protocol includes images obtained at 15 minutes and 2 to 3 hours after radiotracer administration. Sestamibi is taken up more avidly and usually retained longer by parathyroid adenoma and hyperplastic parathyroid tissue as compared to normal parathyroid and thyroid tissue. Parathyroid adenoma is characterized by delayed clearance of tracer. Images should extend from the base of the jaw to the apex of the heart to include potential ectopic sites in the neck and mediastinum. At some institutions, subtraction techniques are employed in which a second radiotracer taken up by the thyroid gland (such as ^{123}I or ^{99m}Tc pertechnetate) is administered simultaneously with ^{99m}Tc sestamibi. Subtraction images are produced to increase conspicuity of the parathyroid tissue, but have not been clearly shown to be superior to routine dual-phase imaging without subtraction technique (58). Two-dimensional planar versus three-dimensional single-photon emission computed tomography (SPECT) imaging techniques can be employed. The reported sensitivity of ^{99m}Tc-sestamibi parathyroid scintigraphy for the detection of solitary parathyroid adenoma ranges from 68% to 95% (56,59). False negatives are more common with multigland disease and parathyroid hyperplasia.

3-D single-photon emission computed tomography (SPECT 3-D) increases the sensitivity of parathyroid scintigraphy and improves resolution and anatomic localization by helping differentiate parathyroid activity from overlying thyroid tissue (60–62). More recently, the utility of coregistered ^{99m}Tc-sestamibi SPECT with CT (SPECT/CT) has been investigated. Initial results suggest SPECT/CT offers the advantage of improved anatomic localization particularly in the case of ectopic mediastinal parathyroid adenoma and may improve reader confidence and sensitivity, though further research is required to establish the appropriate use of this combined modality (Fig. 11.25) (56).

The functional information of parathyroid scintigraphy combined with the anatomic information of sonography offers the best sensitivity and accuracy for localization of solitary parathyroid adenoma (56,63). However, the sensitivity of each technique and the sensitivity of combining results of parathyroid scintigraphy and ultrasound remain suboptimal for the detection of multiglandular disease and parathyroid hyperplasia (56,64). MRI and CT are typically used as adjunctive imaging in difficult cases or cases of suspected ectopic parathyroid glands. Four-dimensional CT (4-D-CT) is a promising technique that relies on characteristic early enhancement of hyperfunctioning parathyroid tissue to localize parathyroid disease (65,66). It is a dynamic contrast-enhanced (DCE) CT that requires multiple acquisitions of CT data at several time points through the potential locations of normal and ectopic parathyroid tissue, increasing radiation dose from the study. It is typically reserved for cases with prior unsuccessful surgery or indeterminate ultrasound and parathyroid scintigraphy. Whether it offers a distinct reproducible advantage over a high-resolution single-phase contrast-enhanced CT is not yet established (67).

Somatostatin Scintigraphy

Somatostatin receptor scintigraphy (SRS) can be useful in the management of patients with neuroendocrine tumors in the head and neck, which overexpress somatostatin receptors and most notably include paragangliomas and medullary thyroid carcinoma. Paragangliomas or glomus tumors in the head and neck typically arise from parasympathetic paraganglia and are usually nonfunctioning. They can be sporadic or familial and multiplicity can occur with both, but is more common in familial paragangliomas (68). SRS using the radiolabeled somatostatin analogue 111In-DTPA-octreotide has been shown to be sensitive for the detection of paraganglia and may be useful when cross-sectional imaging is inconclusive, when staging is required, and in screening of familial cases (68,69).

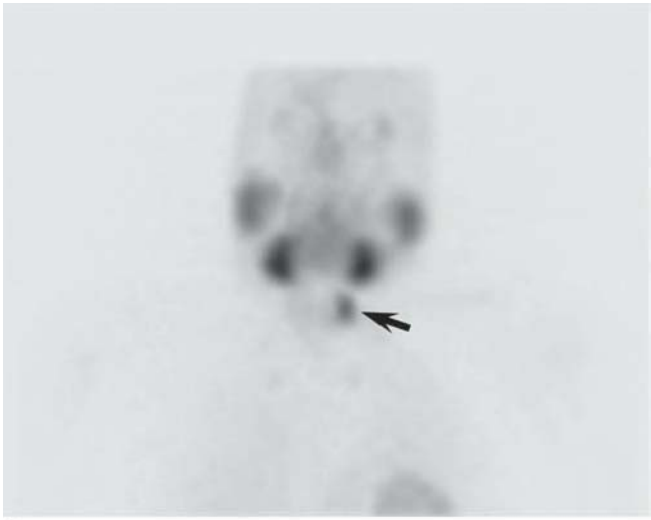
SRS may be helpful in localizing recurrent disease in postoperative patients with a history of medullary thyroid carcinoma and a high serum calcitonin level. Localization of tumor using 111In-DTPA-octreotide SPECT/CT is based on tumor expression of somatostatin receptors. The reported sensitivity of 111In-DTPA-octreotide scintigraphy for the detection of recurrent or residual disease is highly variable and the optimal imaging modality for detecting recurrent or residual disease is controversial (52).

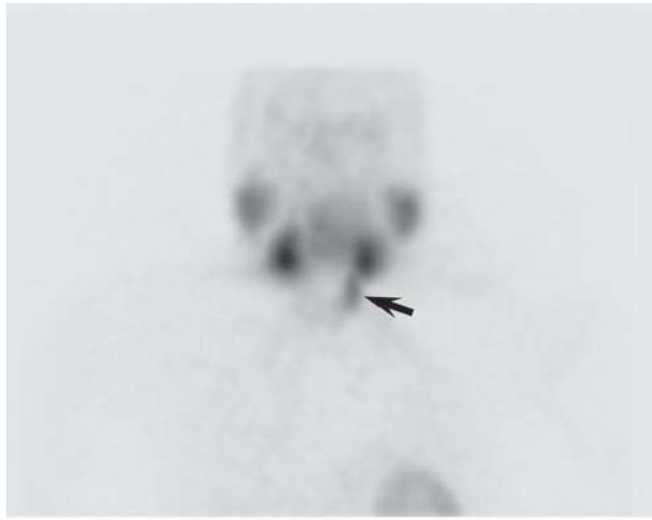
Other Miscellaneous Scintigraphic Applications

^{99m}Tc pertechnetate is taken up by the salivary glands and excreted into saliva. Both Warthin tumor and oncocytoma demonstrate increased ^{99m}Tc pertechnetate uptake due to the presence of mitochondrium-rich oncocytes. Pertechnetate scintigraphy can be useful to support a diagnosis of Warthin tumor if observation is being considered in a patient with a parotid mass (30).

SIALOGRAPHY

Conventional sialography is infrequently performed due to advances in cross-sectional imaging and the clinical management of nonneoplastic salivary gland disease, including improved autoimmune serologic testing and the development of sialoendoscopy. It employs the use of iodinated contrast to demonstrate the intraglandular and extraglandular anatomy of the parotid or submandibular gland ductal system. The opening of the Stensen or Wharton duct is located and dilated using a lacrimal probe, after which a small canula is inserted into the duct and a small amount of dense water-soluble iodinated contrast is gently hand injected. Plain radiographs in the anteroposterior (AP) and lateral projections are then obtained and repeated after a secretogogue is administered to ensure emptying of the gland. Conventional sialography is contraindicated in patients with acute sialoadenitis. Disadvantages include the invasiveness of the procedure,





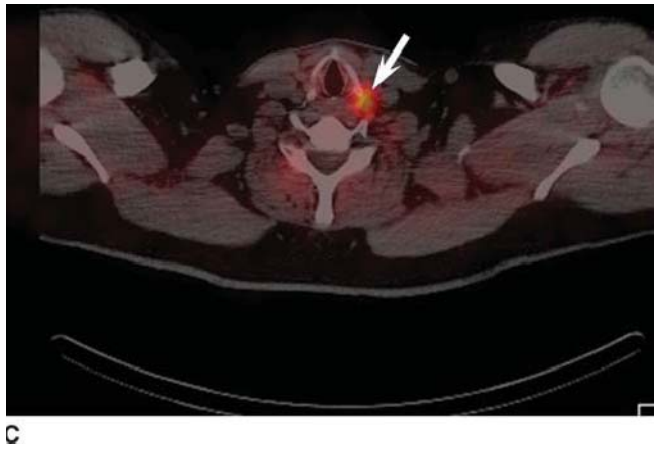


Figure 11.25 Ectopic parathyroid adenoma. A 42-year-old male with MEN-1 status post total thyroidectomy and parathyroid adenoma resection with persistent hypercalcemia. **A** and **B**: Planar SPECT images after ^{99m}Tc sestamibi injection at 20 minutes **(A)** and 2 hours **(B)**. **A:** At 20 minutes postinjection, there is a focus of increased tracer uptake (*arrow*) seen in the left neck **B:** It (*arrow*) persists on 2 hour delayed images and is consistent with parathyroid adenoma. Normal physiologic tracer uptake is seen in the salivary glands and heart. **C:** Fused axial SPECT/CT fused images localize the persistent radiotracer uptake (*arrow*) due to the ectopic parathyroid adenoma to the left tracheoesophageal groove.

use of ionizing radiation, risk of duct trauma, and potential risk of contrast reaction.

In the past, indications for sialography included detection of small sialoliths, evaluation of the extent of ductal damage as a sequela of infection, and differentiation of chronic sialoadenitis, Sjogren syndrome, and sialosis. Currently, conventional sialography is reserved for patients in which the clinical evaluation, autoimmune serology and CT, MRI, or ultrasound cannot identify the cause of the patient's symptoms and ductal disease is suspected (30). It may be helpful in evaluation of patients with mixed connective tissue disease, an overlap autoimmune disorder with clinical features commonly seen with systemic lupus erythematosus, scleroderma, and polymyositis. Sialography remains the only study to demonstrate the fine anatomy of the salivary ductal system (70). It is sensitive for the detection of ductal stricture and sialolithiasis, which can be seen as calcifications on plain films and filling defects during sialography. In the case of autoimmune disease, pruning of the intraglandular ducts and numerous areas of globular and spherical collections of contrast are seen throughout the gland that remain following administration of a secretogogue (Fig. 11.26). The central larger ductal system is sometimes spared (71).

MRI sialography is an emerging noninvasive way of imaging the parotid ducts that relies on the use of saliva within the ductal system as a natural contrast agent. Various protocols using heavily T2-weighted sequences typically with fat suppression are utilized. Advantages of MRI sialography include the noninvasive imaging technique as well as the ability to directly image the surrounding parenchyma and soft tissues with standard salivary gland MRI. In some cases, a sialogogue is administered prior to imaging to improve duct visualization. Typically, the fluid filled main duct, primary and secondary branches are well depicted but the tertiary branches that are seen with conventional sialography are not well delineated with MRI sialography (72,73). It performs well in detecting strictures; however, currently, suboptimal spacial resolution limits the sensitivity for detection of small sialoliths or early sialectasis (72–74). In one study, MRI sialography was reported to be accurate in the staging of Sjogren disease when correlated with conventional sialography, though some authors report discordant sialoectatic patterns when comparing

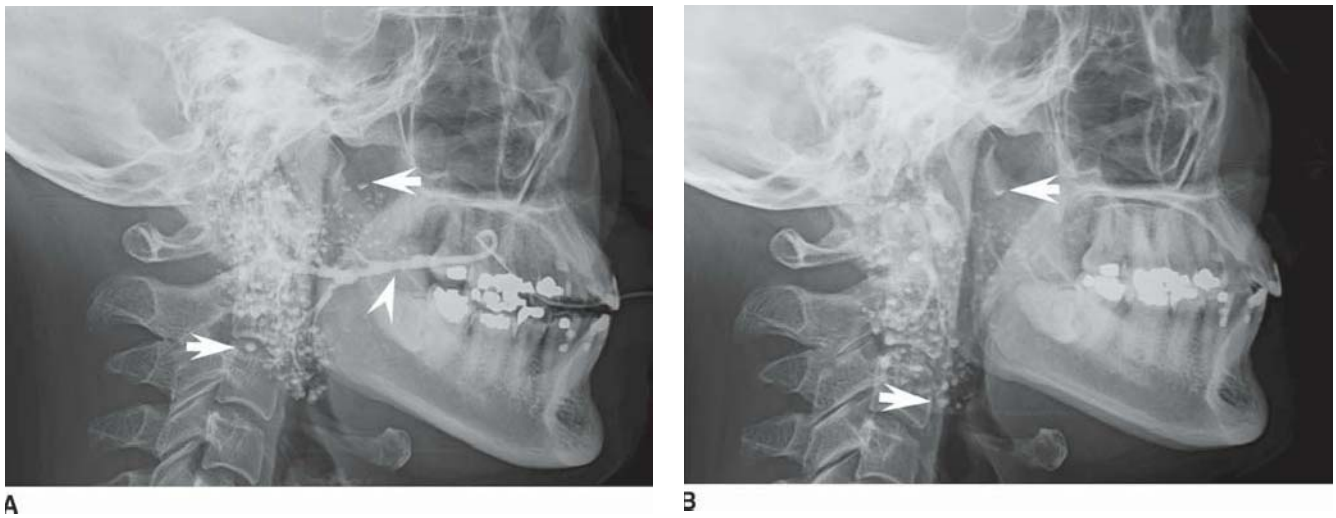


Figure 11.26 Sjogren syndrome. **A:** Conventional sialogram. There is marked irregularity of the intraglandular and extraglandular (*arrowhead*) ductal system with innumerable globular areas of acinar contrast pooling (*arrows*). **B:** Following administration of a sialogogue, there is retention of contrast within the intraglandular ducts and acinar pools (*arrows*). The Stensen duct empties.

MRI sialography and conventional sialography in later stages of disease (75,76). Further research to optimize and validate MRI sialography in a nonselected patient population is required before it becomes a routine part of salivary gland imaging protocols.

FLUOROSCOPY

Fluoroscopy is an imaging technique that employs the use of x-rays to provide real-time images of dynamic processes and procedures on a video monitor. The most commonly performed fluoroscopic studies in head and neck imaging are the modified barium swallow and the esophagram, which are complimentary to endoscopic evaluation and helpful in evaluating the anatomy, motility, and mucosa of the aerodigestive tract.

Modified Barium Swallow (Video Fluoroscopic Evaluation of Swallowing)

Oropharyngeal dysphagia frequently results as a disorder of the swallowing process. Dynamic swallowing is best evaluated with a modified barium swallow study, a real-time high definition videofluoroscopic exam of the oral and pharyngeal phases of swallowing. The study is ideally performed by a radiologist in conjunction with a speech pathologist trained in dysphagia management. A modified barium swallow study is indicated in patients with signs of pharyngeal dysphagia, including coughing and choking while eating or drinking and globus sensation. During a modified barium swallow, the mucosal space is imaged from the lips to the posterior pharyngeal wall and from the nasopharynx to the upper cervical esophagus. It focuses on the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, and cervical esophagus. Patients are administered controlled and uncontrolled volumes of various barium coated consistencies and imaged while seated upright, mainly in the lateral projection. The study is tailored to the patient's complaints, history, and risk of aspiration. The goal of the study is to simulate habitual swallowing and evaluate for aspiration and its causes. It differs from an esophagram (barium swallow), which is a fluoroscopic study focused on the hypopharynx and cervical and thoracic esophagus.

Esophagram (Barium Swallow)

An esophagram is a fluoroscopic study focused on evaluation of the motility, mucosa, and anatomy of the hypopharynx, cervical, and thoracic esophagus. A patient is administered barium and full column contrast images of the esophagus are obtained. Double-contrast imaging performed in the upright position evaluates for mucosal lesions in addition to assessing motility and contour abnormalities. Single-contrast imaging is performed in the prone position evaluating for stricture, contour abnormality, and motility. A 13-mm pill can be administered to evaluate for stricture at the gastroesophageal junction. Provocative maneuvers can be performed to assess for reflux. Common indications include evaluation for motility disorder, reflux, hiatal hernia, stricture, diverticulum, leak following surgery and symptoms of dysphagia (Fig. 11.27).

RADIOGRAPHY

With advances in cross-sectional imaging, plain film radiography has a limited role in head and neck imaging. Computed radiography and digital radiography have largely replaced screen-film techniques. Images are captured

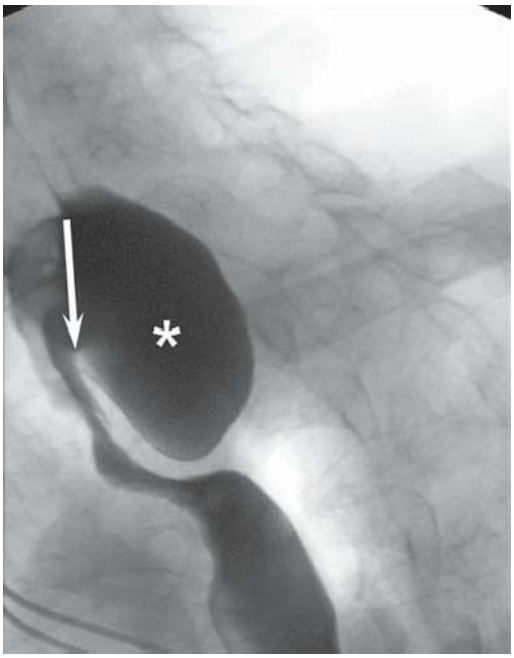


Figure 11.27 Zenker diverticulum. Oblique view from a single-contrast esophagram (barium swallow). There is a large Zenker diverticulum (*asterisk*) that originates posteriorly from the hypopharynx just above the cricopharyngeus muscle (*arrow*) and extends posteriorly to the lower cervical esophagus.

on reusable digital detectors and transferred to a computer for viewing. Advantages of digital imaging include the ability to postprocess the images, increased patient throughput, and widespread availability of images.

AP and lateral soft tissue plain films of the neck are still employed in pediatric imaging and may be particularly helpful to evaluate the airway in pediatric patients with signs of respiratory distress or to evaluate for radiodense foreign body. CT has replaced radiography as the preferred imaging modality for evaluation of the paranasal sinuses and temporal bones.

ADVANCED IMAGING TECHNIQUES

The conventional cross-sectional imaging modalities of CT, MRI, and ultrasound rely on morphological and soft tissue contrast to detect pathology in the head and neck. Unfortunately, conventional anatomic imaging lacks sensitivity for microscopic disease or early lesion detectability in cases of neoplasm. This is particularly problematic in the treated head and neck where treatment changes cause soft tissue distortion and can be difficult to distinguish from recurrent disease. Many of the areas of research in head and neck imaging focus on functional oncologic applications including metabolic and molecular imaging with the intention of overcoming the pitfalls of conventional anatomic imaging. Areas of research are vast, but include hypoxia and epidermal growth factor receptor (EGFR) imaging with novel PET radiotracers, CT and MRI perfusion imaging, and novel MRI contrast agents.

Tumor Hypoxia Imaging

Tumor hypoxia has been demonstrated in head and neck squamous cell carcinomas (HNSCCs) and is associated with resistance to the cytotoxic effects of radiotherapy and chemotherapy (77). It is associated with poor local control of tumor, disease-free survival, and overall survival (78). Consequently, PET/CT research has focused on tumor hypoxia imaging using hypoxic radiotracers such as 18F-fluoromisonidazole (18F-FMISO) and 60Cu-ATSM in an attempt to identify tumors at greater risk for resistance to standard chemoradiotherapy that would benefit from tailored alternate chemoradiotherapy or novel therapies such as radiation sensitizers or hypoxic cell cytotoxins (50,77,79–81).

EGFR Imaging

Epidermal growth factor is a protooncogene that promotes tumor progression and is frequently elevated in HNSCCs compared to normal mucosa. It has been associated with reduced survival and poor prognosis in patients with HNSCC (82). EGFR targeted therapy using monoclonal antibodies such as cetuximab when combined with radiation and conventional chemotherapy show promising results, though only in a subset of patients (83,84). As a result, targeted EGFR imaging using several novel PET probes has been the subject of research with the intentions of identifying patients who will respond to anti-EGFR therapy and monitoring clinical response in a specific manner (85–89). The best approach to EGFR imaging is controversial because of a lack of correlation between cetuximab response and total EGFR expression level (90).

Tumor Perfusion Imaging

NSOPT with chemoradiation has increasingly become the treatment of choice for locoregionally advanced head and HNSCC. In patients who fail NSOPT, salvage rates are poor. Attempts at diagnostic stratification of patients who will respond to NSOPT with functional imaging such as CT perfusion and DCE MRI have been sought (91–95). CT perfusion is a dynamic functional modality that noninvasively quantifies microvascular changes of neoplasms including blood volume (BV), blood flow (BF), mean transit time, and permeability surface area product (PS). Increased capillary permeability, BF, and BV in HNSCC as compared with normal tissues have been demonstrated (96). Promising potential applications include primary tumor staging and prediction of disease-free survival, prediction of tumor response to therapy and monitoring conventional cytotoxic therapy. Data suggest that HNSCC with elevated BF and BV are more responsive to NSOPT than tumors with low BF and BV (91,92,97,98). Preliminary data suggest that serial reductions in BV are predictive of response to therapy and BF may be useful to predict progression-free survival

in patients with advanced HNSCC treated with NSOPT (92,93). In addition, baseline elevated BF and PS may have long-term predictive value for local tumor control (99). Due to technical factors and efforts to minimize radiation dose (multiple acquisitions of CT data through the area of interest must be obtained), CT perfusion imaging cannot be applied to the entire volume of the neck and can only be used to image a localized area of interest.

Characterization of tumor perfusion using DCE-MRI with gadopentetate dimeglumine (Gd-DTPA) is also being investigated as a tool to predict treatment response and outcomes in patients treated for HNSCC. Its lack of ionizing radiation is advantageous. DCE-MRI evaluates changes in signal intensity over time related to Gd-DTPA administration and can be used to noninvasively characterize tumor perfusion, tumor-vessel permeability, and extracellular–extravascular volume fraction (100). The parameter K_{trans} (volume transfer constant) can be calculated and is thought to reflect tumor BF and microvascular permeability (101). K_{trans} and BV may predict early response to NSOPT in HNSCC (94,95). Further validation of CT perfusion and DCE-MRI is required before the routine use of these technologies is implemented into clinical practice.

Novel Contrast Agents

The application of superparamagnetic iron oxide nanoparticles as a novel contrast agent to improve sensitivity for detection of metastasis in morphologically normal appearing nodes is the subject of research. The particles are administered intravenously and theoretically accumulate in normal lymph nodes, which on T2*-weighted gradient echo sequences appears as dark or markedly decreased signal. Metastatic nodes usually have foci of T2 hyperintense signal. Initial trials suggest there is improved sensitivity for detection of nodal metastasis compared to conventional contrast agents (102,103).

RADIATION SAFETY AND DOSE

With the advent of helical multidetector CT, the increased utilization of CT imaging has led to a substantial increase in the population's cumulative exposure to ionizing radiation and concerns among the medical community and public regarding the potential adverse effects (104,105). In response to this public health concern, the American College of Radiology appointed a Blue Ribbon Panel on Radiation Dose in Medicine in 2006 that offered recommendations to counteract trends contributing to unnecessary radiation exposure (105). Since then numerous strategies for CT dose reduction have been implemented by the imaging community (105–107). In addition, the Alliance for Radiation Safety in Pediatric Imaging was formed in 2007, which implemented the successful Image Gently™ campaign to increase awareness of radiation risk in children and offer recommendations to minimize radiation dose when imaging this population.

Radiologists and medical physicists adhere to the As Low as Reasonably Achievable (ALARA) principle that advocates minimizing dose while obtaining quality diagnostic imaging. The radiologist is a good resource regarding radiation safety though some basic radiation exposure principles should be understood by clinicians ordering studies. The main risk associated with exposure to ionizing radiation in adults and children is cancer, and while the risk is low with medical imaging, it is not zero. The fetus is particularly sensitive to radiation exposure and potential adverse effects include mental retardation, organ malformations, and childhood cancer. Imaging studies outside of the abdomen result in minimal fetal exposure and, when clinically necessary, can be performed safely with modifications taken to minimize exposure to the fetus. Children are more sensitive to ionizing radiation and radiation-induced cancer mortality risk in children is three to five times higher than for adults due to both increased organ sensitivity and longer life expectancy (108). With increasing age, the risk of a radiation-induced cancer decreases. The most optimal way to reduce radiation dose is to avoid unnecessary exams and use alternate imaging modalities such as ultrasound and MRI when indicated. If ordered appropriately, the benefit of a medically indicated CT scan far exceeds the estimated risk of radiation exposure.

A "SPACE"-BASED APPROACH TO IMAGE INTERPRETATION

The head and neck region is divided by layers of fascia into spaces. The fascia act as barriers to the spread of disease and have been variably described by anatomists and surgeons (109–111). Advances in cross-sectional imaging lead to improved visualization of the deep structures of the head and neck and renewed interest among radiologists to understand the spaces and fascial planes (112–114). A space-based approach to image interpretation has since been popularized among radiologists as a way of simplifying the imaging differential diagnosis of pathology in the deep structures of the head and neck. The center of a lesion as well as patterns of displacement of the adjacent structures, particularly the parapharyngeal fat and carotid sheath, can help to assign a process to a space. Once the process is assigned to a space and knowing the structures that exist within the space, a limited meaningful space-specific differential diagnosis in the context of the patient's age, sex, and clinical presentation can be generated. The following is a brief summary of the spaces used by radiologists to approach pathology in the neck. It is not intended to teach image interpretation, but rather to provide a foundation for understanding the space-based approach to image interpretation. As previously stated, the description and terminology used to describe these spaces is variable and the following terminology presented has been chosen

TABLE 11.2 DIFFERENTIAL DIAGNOSIS OF MORE COMMON PATHOLOGY OCCURRING IN THE HEAD AND NECK BY SPACE[a]

Space	Differential Diagnosis
Pharyngeal mucosal	Infection and sequela of infection (including faucial tonsil abscess), squamous cell carcinoma, lymphoma, minor salivary gland neoplasm, Tornwaldt cyst
Masticator	Odontogenic infection and abscess, osteomyelitis, mesenchymal neoplasms, metastases/myeloma, secondary extension of tumors from adjacent spaces and skull base, perineural spread of neoplasm, nerve sheath tumors, vascular malformations
Parotid	Salivary gland tumors; squamous cell carcinoma; lymphadenopathy; perineural spread of tumor; parotitis; sialolithiasis; benign lymphoepithelial lesions; lipoma, branchial cleft cysts, and nerve sheath tumors
Buccal	Cellulitis/abscess, lymphadenopathy, minor salivary gland neoplasms, secondary involvement by squamous cell carcinoma, vascular malformations, lipoma, sialolithiasis, primary mesenchymal neoplasms
Retropharyngeal	Lymphadenopathy; edema, abscess; hematoma; direct extension of tumor from adjacent structures; extension of discitis/osteomyelitis
Prestyloid parapharyngeal	Deep portion parotid gland tumors, minor salivary gland tumors, extension of processes (typically infectious or neoplastic) from the adjacent spaces, atypical second branchial cleft cyst, lipoma, vascular malformations
Carotid sheath/poststyloid parapharyngeal	Lymphadenopathy, pseudoaneurysm/dissection, secondary extension of tumors and infection from adjacent spaces and skull base, paraganglioma, neuroblastoma, nerve sheath tumors, venous thrombosis
Submandibular	Lymphadenopathy, sialolithiasis, infection/abscess, salivary gland neoplasms, plunging ranula, secondary extension of oral cavity neoplasm, second branchial cleft cyst, thyroglossal duct cyst, vascular malformations, dermoid/epidermoid
Sublingual	Secondary extension of odontogenic infection and squamous cell carcinoma, ranula, sialolithiasis and obstructed submandibular duct, minor salivary gland neoplasms, lingual thyroid and thyroglossal duct cyst, vascular malformations, dermoid/epidermoid
Visceral	Thyroid lesions; lymphadenopathy; laryngeal masses (squamous cell carcinoma, chondrosarcoma); parathyroid lesions; thyroglossal duct cyst; esophageal diverticulum and neoplasm; abscess and infection
Prevertebral	Discitis/osteomyelitis, metastases, disc herniation, hematoma, secondary extension of tumor from adjacent spaces, vertebral artery dissection/pseudoaneurysm, primary bone tumors, nerve sheath tumors, mesenchymal neoplasms
Posterior triangle (cervical)	Lymphadenopathy, lipoma, nerve sheath tumors, vascular malformations, liposarcoma

[a]The term lymphadenopathy in the above table includes the possibility of the following etiologies: reactive, neoplastic (both metastatic and lymphoma), and suppurative.

in some cases for the sake of simplification and in other cases to reflect surgical anatomy. Table 11.2 lists the more common differential diagnoses that apply to each space. An example of pathology in each space is provided.

Spaces of the Neck

Excluding the orbit and sinonasal region, the soft tissues of the neck can be divided into supra and infrahyoid portions. The suprahyoid neck is divided into spaces by the three layers of the deep cervical fascia (which includes the superficial/investing layer, the middle/buccopharyngeal layer, and the deep/prevertebral layer). In the suprahyoid neck these spaces include the following: the pharyngeal mucosal space (PMS), the retropharyngeal space (RPS), the sublingual space, the submandibular space, the buccal space, the masticator space, the parapharyngeal space, the parotid space, the prevertebral space, and the posterior triangle (cervical) space. Within the infrahyoid neck the major spaces include the carotid sheath, the RPS, the visceral space, the posterior triangle (cervical) space, and the prevertebral space.

Pharyngeal Mucosal Space

The components of the PMS are variably described but include the mucosal surface and submucosa of the oral cavity, nasopharynx, oropharynx, and the suprahyoid portion of the hypopharynx (114). In addition to mucosa, its contents include minor salivary glands, the lymphoid tissue of Waldeyer ring, the pharyngeal constrictor muscles, the salpingopharyngeus muscles, and the pharyngobasilar fascia. Because squamous epithelium compromises the majority of this space, it is not surprising that the most common lesion of the PMS is squamous cell carcinoma. Small lesions may be occult on CT and MRI; imaging is mainly used to characterize the deep extent of mucosal lesions as well as evaluate for nodal metastasis (Figs. 11.1, 11.9, and 11.22).

Retropharyngeal Space

The RPS is a potential space bordered anteriorly by the visceral fascia and posteriorly by prevertebral fascia. The alar fascia divides the RPS into anterior and posterior



Figure 11.28 Retropharyngeal abscess in a 2-year-old male with fever and lymphadenopathy. Axial contrast enhanced neck CT reveals a large rim enhancing retropharyngeal abscess (*arrows*) causing mass effect on the posterior pharyngeal wall (*arrowhead*).

compartments and is not typically seen on imaging. The caudal extent of the space is variable but extends to approximately T4 where the alar fascia and visceral fascia fuse. The posterior compartment of the RPS has been referred to as the danger space because it extends to the diaphragm and can result in direct spread of infection into the posterior mediastinum (112). Within the suprahyoid neck, the RPS contains fat and retropharyngeal lymph nodes. Within the infrahyoid neck, it contains only fat. Few pathologies arise in the RPS. Common abnormalities in this space include edema (secondary to infection, trauma, radiation, longus colli tendinitis), suppurative and metastatic lymphadenopathy, abscess, and direct extension from nasopharyngeal carcinoma (Fig. 11.28).

Sublingual Space

The anterior and lateral margins of the sublingual space are the lingual cortex of the mandible and the posterior margin is the hyoid bone. The superior and inferior borders are the oral mucosa and the mylohyoid muscle, respectively. The mylohyoid muscle acts as a sling to contain the sublingual space. The following structures are included in the sublingual space: paired sublingual glands, the deep portions of the submandibular glands and the submandibular ducts, muscles, the lingual nerve, lingual artery and vein, and cranial nerves IX and XII. Common pathologies of the sublingual space include extension of squamous cell carcinoma, secondary spread of odontogenic infections, and sialolithiasis (Fig. 11.29).

Submandibular Space

The submandibular space is the most inferior space within the suprahyoid neck; its inferior border is the hyoid bone. It lies inferolateral to the mylohyoid muscle and posteriorly

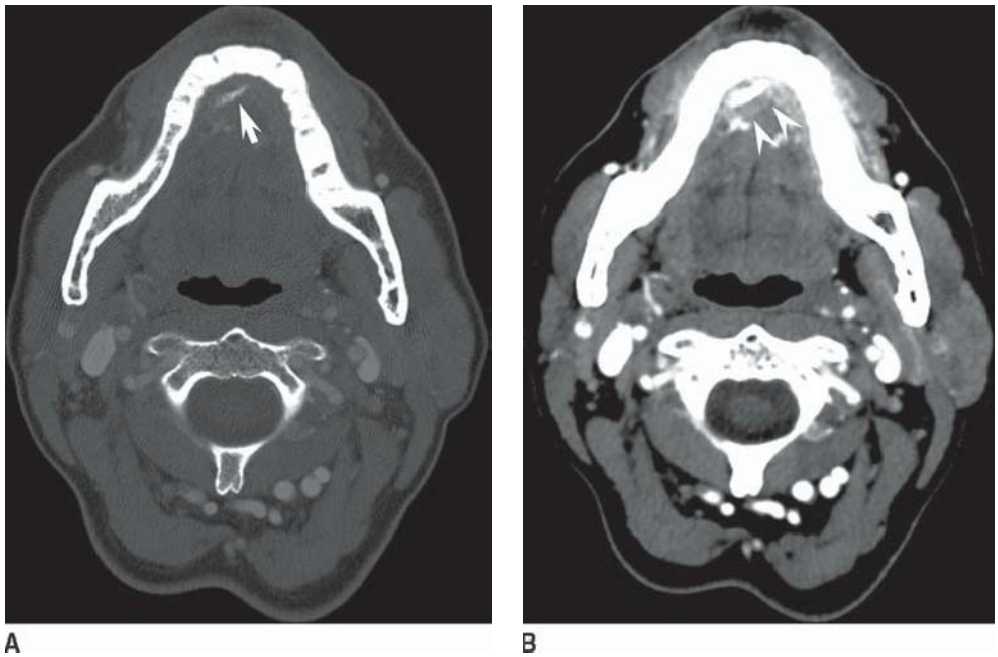


Figure 11.29 Right Wharton duct sialolith and floor of mouth squamous cell carcinoma. **A,B**: Axial contrast-enhanced neck CT. **A:** Bone windows demonstrate a tubular sialolith in the right sublingual space in the distal right Wharton duct (*arrow*). **B:** Soft tissue windows reveal an associated right floor of mouth enhancing squamous cell carcinoma (*arrowheads*) in the right sublingual space.



Figure 11.30 Plunging ranula. Coronal reconstruction from a contrast-enhanced neck CT. There is lobulated low attenuation cystic mass (*small arrows*) within the right submandibular space. The mass flattens the inferior margin of the right mylohyoid muscle. The normal left mylohyoid muscle is clearly seen (*asterisk*). A tubular portion of the mass (*large arrow*) extends from the right sublingual gland. This is a surgically proven plunging ranula.

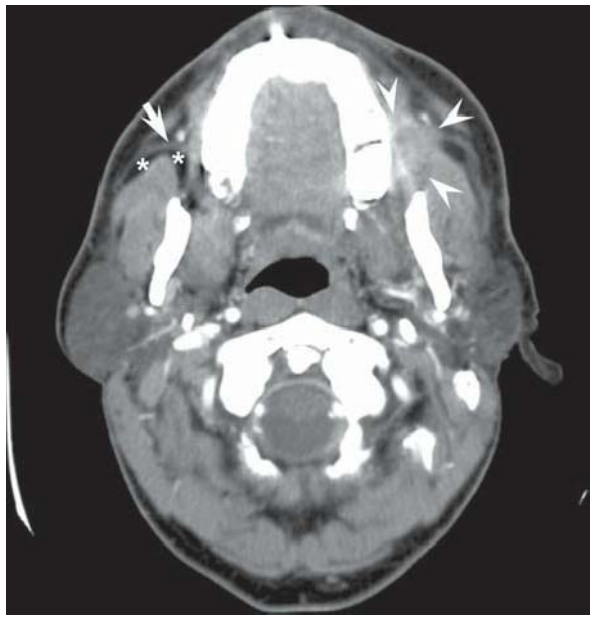


Figure 11.31 Left buccal carcinoma. Contrast-enhanced neck CT. There is a mass (*arrows*) arising from the left buccal mucosa that extends deep into the left buccal space, invading the left buccal fat pad and surrounding distal left Stensen duct. Compare this to the normal distal right Stensen duct (*arrow*) and right buccal fat pad (*asterisk*).

it communicates freely with the sublingual space at the free margin of the mylohyoid muscle. The submandibular space contains the superficial portion of the submandibular gland, level I lymph nodes, the facial artery and vein, branches of cranial nerve XII and the anterior belly of the digastric muscle (114). In adults, common pathology in the submandibular space includes lymphadenopathy, infection, sialolithiasis, and plunging ranula (Fig. 11.30). In children, a second branchial cleft cyst commonly occurs in this space.

Buccal Space

The buccal space consists mainly of adipose tissue and is interposed between the buccinator muscle medially, the superficial muscles of facial expression laterally, and the masticator space posteriorly. In addition to fat, the buccal space includes minor salivary gland tissue, parotid duct, lymph nodes, branches of cranial nerves V and VII, and facial vessels (115). Because it does not have fascia separating it distinctly from the adjacent spaces, infectious and neoplastic processes extend through the buccal space easily. Due to ectopic rests of minor salivary gland tissue, minor salivary gland tumors are a common cause for a primary buccal space mass. Other common pathologies in the buccal space include secondary involvement of squamous cell carcinoma and infection, facial lymphadenopathy and venous or venolymphatic malformation (Fig. 11.31).

Masticator Space

The masticator space is enclosed by the splitting of the superficial layer of the deep cervical fascia and includes the muscles of mastication, the posterior body and ramus of the mandible, the maxillary artery, the pterygoid venous plexus and V3 as it courses through the infratemporal fossa. The superomedial margin of the masticator space is the skull base, directly medial to foramen ovale. Consequently, neoplasms involving the masticator space can extend to the intracranial compartment via perineural spread of neoplasm along V3. Superolaterally, the suprazygomatic portion of the masticator space includes the attachment of the temporalis to the outer table of the calvarium. Inferiorly, the masticator space extends to the attachment of the medial pterygoid and masseter muscles to the mandible (114). In adults, the most common pathology affecting the masticator space is odontogenic infection, though involvement of the masticator space secondarily from metastasis, oropharyngeal and oral cavity squamous cell carcinoma and from skull base pathology are frequent as well (Fig. 11.32). Because much of the masticator space consists of the muscles of mastication, mesenchymal tumors occur in this space, particularly sarcomas in children.

Parapharyngeal Space

The parapharyngeal space extends from the skull base to the level of the angle of the mandible and consists of mostly fat and connective tissue. It lies lateral to the pharyngobasilar



Figure 11.32 Left hepatocellular carcinoma metastasis to the left masticator space. Axial contrast-enhanced neck CT. There is a large avidly enhancing mass (*arrow*) involving the left masseter and medial pterygoid muscles, eroding part of the left mandibular ramus. It displaces the parapharyngeal fat medially (*asterisk*) and extends into the left inferior alveolar nerve canal (*arrowhead*).

fascia surrounding the nasopharynx. There are numerous variations describing the boundaries of this space. It is subdivided into a prestyloid and poststyloid compartment by the tensor-vascular-styloid fascia, a fascia containing fibers from the tensor veli palatini (113). Posterior and medial to the fascial layer is the poststyloid parapharyngeal space, which is also referred to by some authors as the carotid space and contains the contents of the carotid sheath including the internal carotid artery (ICA), internal jugular vein, sympathetic chain, lymph nodes, and cranial nerves IX to XII in the suprahyoid neck (114). Anterior and lateral to the tensor-vascular-styloid fascia is the prestyloid parapharyngeal space, which contains primarily fat but also contains minor salivary gland rests. A small part of the deep portion of the parotid gland protrudes into the prestyloid parapharyngeal space via the stylomandibular tunnel.

MRI and CT can be used to differentiate prestyloid and poststyloid lesions by their position and displacement pattern of the parapharyngeal fat. Most lesions confined to the prestyloid parapharyngeal space are salivary in origin and may arise from the deep portion of the parotid gland or from salivary gland rests (113,116). If there is no fat plane between a prestyloid parapharyngeal space mass and the parotid gland, the mass is usually arising from the parotid gland. Prestyloid parapharyngeal space masses arising from the deep portion of the parotid gland will typically displace the parapharyngeal fat anteromedially toward the pharynx. Prestyloid lesions typically are anterior to the carotid artery and extend anterior to the styloid process. They may pass through the stylomandibular tunnel (Fig. 11.33).

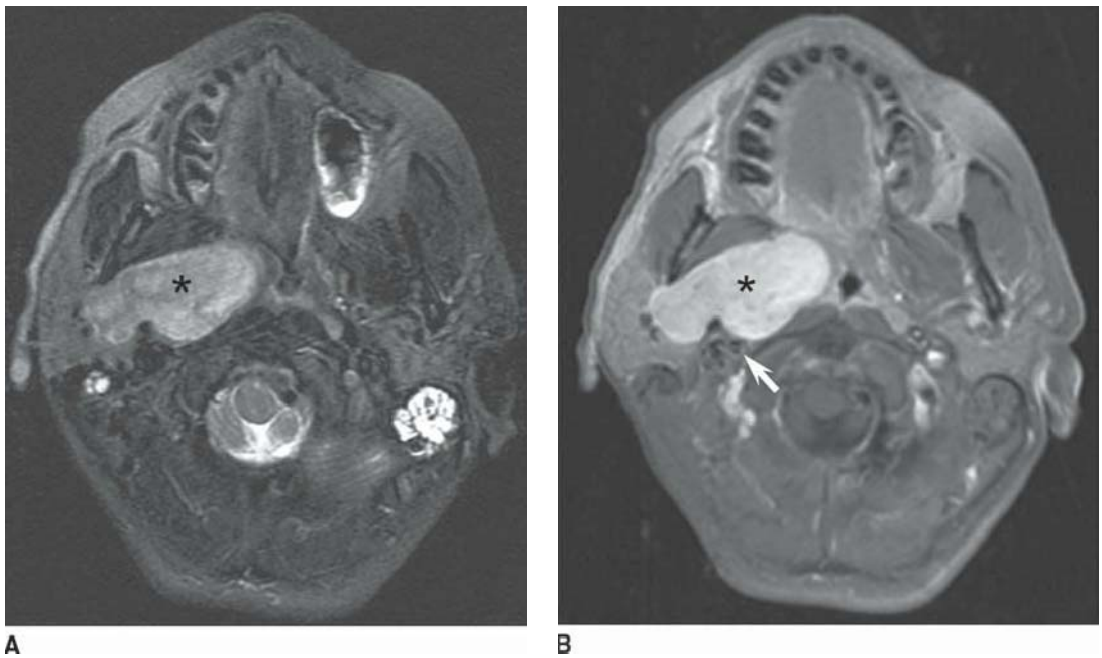


Figure 11.33 Pleomorphic adenoma. **A:** Axial T2 fat suppressed image. A T2 hyperintense pleomorphic adenoma (*asterisk*) arising from the deep portion of the right parotid gland extends through the stylomandibular tunnel into the prestyloid parapharyngeal space. There are incidental bilateral mastoid effusions. **B:** Contrast-enhanced axial T1-weighted image with fat suppression. The mass (*asterisk*) solidly enhances and the right ICA (*arrow*) is displaced posteriorly by the mass. *(conitnued)*



Figure 11.33 *(Continued)* **C:** Axial T1-weighted image. The prestyloid parapharyngeal fat (*arrowheads*) is displaced anteromedially by the mass (*asterisk*).

Poststyloid parapharyngeal space masses tend to displace the parapharyngeal fat anteriorly and laterally. Poststyloid lesions may have a small extension posterior to the styloid process. Similarly, poststyloid masses usually displace the ICA anteriorly (Fig. 11.34). Poststyloid lesions can extend through the jugular foramen. Lesions in the poststyloid parapharyngeal space arise from structures in the carotid sheath as discussed in the next section.

Carotid Sheath

The carotid sheath is an enclosed fascial space with various contributions from the layers of the deep cervical fascia. It traverses the suprahyoid and infrahyoid neck and extends from the skull base to the aortic arch. It contains the internal and common carotid arteries, the internal jugular vein, lymph nodes, fat, and the sympathetic chain. In the suprahyoid neck, the carotid sheath contains cranial nerves IX through XII. In the infrahyoid neck, it contains only cranial nerve X. There is debate in the radiology literature as to whether the suprahyoid portion of the carotid sheath containing the ICA should be included as part of the parapharyngeal space (referred to as the poststyloid parapharyngeal space) or should be designated a separate "carotid space" for the simplicity of a space-based differential diagnosis. The use of the term poststyloid parapharyngeal space referring to the contents of the carotid sheath in the suprahyoid neck is preferred because the tensor-vascular-styloid fascia serves as a surgical boundary between the prestyloid compartment (containing the deep portion of the parotid gland) and the poststyloid compartment (containing the carotid sheath) when approaching the parapharyngeal

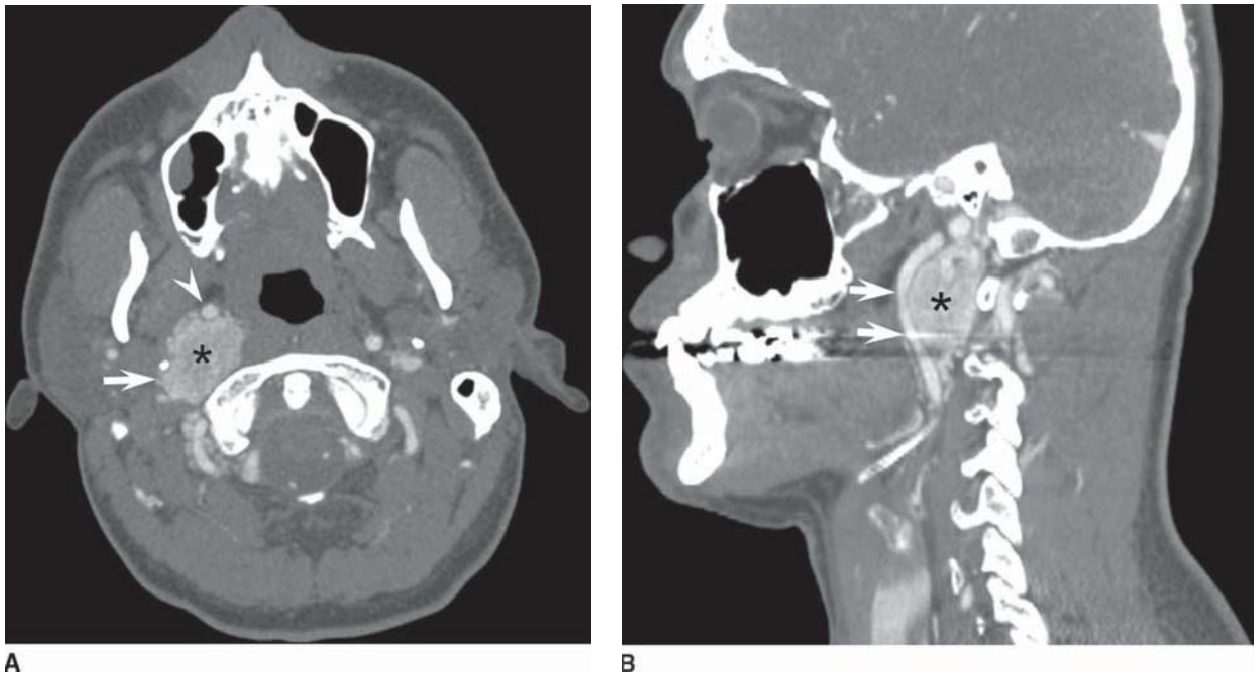


Figure 11.34 Right glomus vagale. **A:** Axial contrast-enhanced neck CT reveals a large avidly enhancing right poststyloid parapharyngeal space mass (*asterisk*) typical of a glomus vagale displacing the right cervical ICA (*arrowhead*) anteriorly. A small portion of the mass protrudes posterior to the right styloid process (*arrow*). **B:** Sagittal reconstruction from contrast-enhanced neck CT. There is anterior displacement of the cervical right ICA (*arrows*) along the anterior margin of the mass (*asterisk*). This is a pathologically proven paraganglioma.

space (117). Common pathology in the carotid sheath includes dissection, pseudoaneurysm, lymphadenopathy, schwannoma, and paraganglioma (Figs. 11.10 and 11.34).

Parotid Space

The parotid space contains the parotid gland as well as the facial nerve, intraparotid lymph nodes, the retromandibular vein, and parts of the external carotid artery (114). The intraparotid portion of the facial nerve is not well seen due to its small size but lies just lateral to the retromandibular vein. The majority of parotid space lesions are primary parotid neoplasms with the most common benign lesion being a pleomorphic adenoma. Inflammatory processes and lymphadenopathy are frequent in the parotid gland as well (Figs. 11.12 and 11.17).

Prevertebral Space

The prevertebral space is enclosed by the deep layer of the deep cervical fascia, which surrounds the vertebra and posterior paraspinal muscles. It attaches to the transverse processes, dividing it into anterior and posterior compartments. The anterior compartment includes the anterior vertebra, the prevertebral muscles and the vertebral vessels. The posterior compartment surrounds the posterior elements and also includes the paraspinal muscles and fat. In the infrahyoid neck, the scalene muscles, brachial plexus, and phrenic nerve are included in the anterior compartment. The majority of pathology arising in this space arises from the vertebra, discs and neural elements and commonly includes discitis/osteomyelitis, metastasis, and less commonly primary bone lesions (Fig. 11.35) (112).

Posterior Triangle (Cervical) Space

The posterior triangle space is between the superficial and deep layers of the deep cervical fascia in the posterior neck and has been referred to by numerous names including the posterior cervical space (118). It is between the sternocleidomastoid muscle anterolaterally and the paraspinal muscles posteromedially. Important structures in the posterior cervical space include cranial nerves XI, portions of the brachial plexus, cutaneous nerves, and level V nodes. Lymphadenopathy, vascular malformations, and lipomas are common in this space (Fig. 11.36).

The Visceral Space

The visceral space is the only space confined to the infrahyoid neck (114). It is circumscribed by the middle layer of deep cervical fascia and contains the thyroid, parathyroid glands, larynx, infrahyoid hypopharynx, trachea, cervical esophagus, paratracheal nodes, and recurrent laryngeal nerves. Pathology in the visceral space reflects the tissues in it and commonly includes squamous cell carcinoma, thyroid lesions, lymphadenopathy, and parathyroid adenoma (Figs. 11.13 and 11.24).

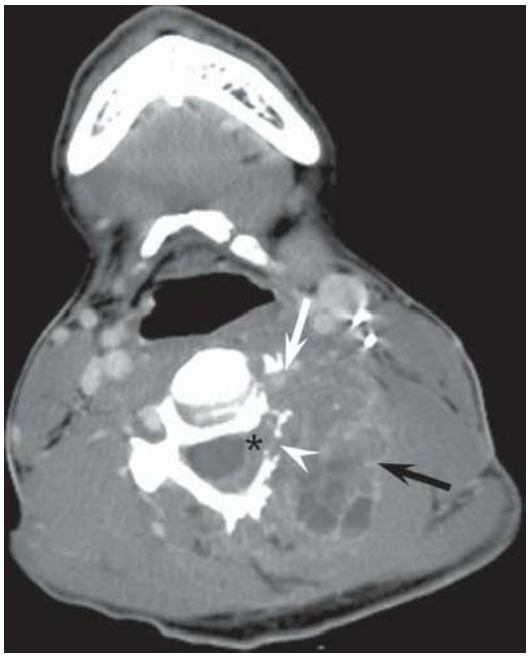


Figure 11.35 Metastatic melanoma. Axial contrast-enhanced neck CT. There is large enhancing mass (*large black arrow*) in the left posterior paraspinal soft tissues encasing part of the left vertebral artery (*white arrow*), eroding part of the vertebral body (*arrowhead*) and extending into the dorsolateral epidural space (*asterisk*). Surgical clips in the left neck are related to a prior neck dissection.

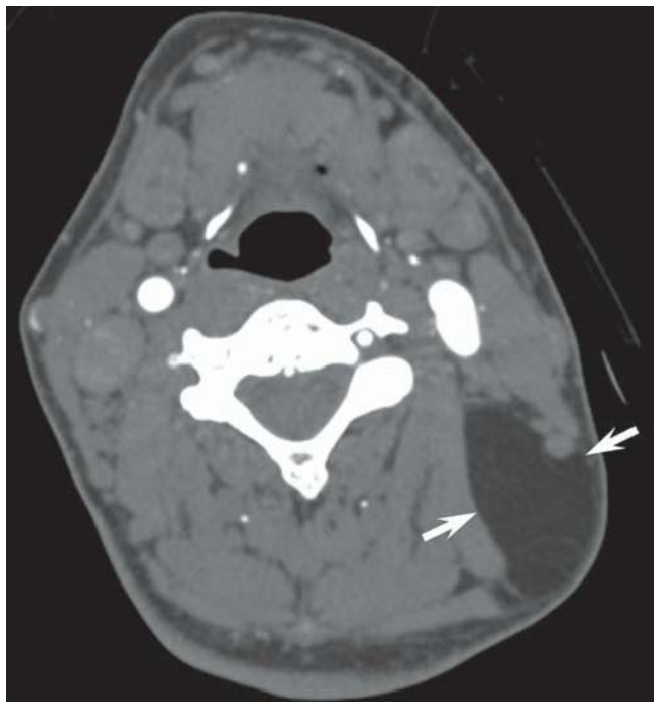


Figure 11.36 Posterior triangle lipoma. Axial contrast-enhanced neck CT. A well-circumscribed fat attenuation mass (*arrows*) in the posterior left triangle interposed between the paraspinal musculature and the left sternocleidomastoid muscle is consistent with a lipoma.

SUMMARY

Cross-sectional imaging plays an invaluable role in demonstrating the deep extent of mucosal lesions and characterizing pathology arising from the other spaces of the head and neck. CT and MRI are often complimentary, particularly in evaluating skull base pathology. Nuclear medicine studies provide complimentary functional and metabolic information, but lack good spatial resolution. The best choice of imaging modality and technique is dependent on the clinical question and emphasizes the importance of communication between radiologists and clinicians to provide the best care for the patient.

HIGHLIGHTS

- Contrast-enhanced CT is frequently the first study of choice for evaluation of an adult palpable neck mass. MRI offers better soft tissue contrast, but for practical reasons should be used to address specific questions or problem solve.
- Noncontrast neck CT is preferred for evaluation of sialolithiasis.
- CT and MRI are complimentary in the evaluation of skull base pathology. CT better demonstrates fine bony detail and MRI better characterizes marrow space disease, perineural spread of neoplasm, and intracranial extension of disease.
- Ultrasound is typically the first study of choice for evaluation of a palpable pediatric neck mass and for evaluating thyroid pathology. It is useful to evaluate for metastatic cervical lymph nodes in patients with thyroid cancer, characterize vascular lesions, differentiate cystic from solid lesions, and guide biopsies.
- PET/CT is the study of choice for staging patients with advanced HNSCC because it has greater sensitivity than conventional imaging modalities. It may be useful in cases of unknown primary neoplasm, radiation treatment planning, monitoring treatment response, and surveying for disease recurrence. It has a high negative predictive value for residual or recurrent disease in patients treated for HNSCC.
- In patients treated for differentiated thyroid carcinoma, whole body radioactive iodine scan, in conjunction with cross-sectional imaging of the neck, is useful to survey for recurrent or residual disease. PET/CT is reserved for patients with clinical evidence of disease recurrence and a negative posttreatment whole body I-131 scan.
- Ultrasound and parathyroid scintigraphy are currently the studies of choice for localization of parathyroid adenoma in patients with hyperparathyroidism. The sensitivity of ultrasound and parathyroid scintigraphy is suboptimal for multiglandular disease. 4-D-CT is a promising new tool for localization of hyperfunctioning parathyroid tissue, but currently is primarily used in cases of failed prior surgery or equivocal ultrasound and parathyroid scintigraphy results.

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12 Surgical Pathology in Otolaryngologic Practice

Matthew C. Miller *Christa L. Whitney-Miller*

A thorough understanding of pathology is essential to any surgical practice. Each day, the surgeon is faced with numerous scenarios that necessitate consultation with the pathology laboratory. The pathologist is consulted to interpret biopsies, to provide staging data, to assess surgical margins, to confirm clinical diagnoses, and, ultimately, to collaborate with the surgeon in a manner that allows for well-informed management decisions. Unfortunately the collaborative nature of this relationship is at times disregarded. As a consequence, our colleagues in pathology may be asked to make their assessment in a vacuum—devoid of potentially important clinical or surgical data. The degree to which the pathologist is informed of the clinical question can have a profound impact upon specimen preparation and interpretation. Conversely, if the surgeon does not have an understanding of specimen handling and preparation, he or she may unwittingly compromise the pathologist's ability to answer a given clinical question.

The aim of this chapter is to introduce the otolaryngologist to the general principles of anatomic pathology and to provide a framework for obtaining and interpreting pathologic data. Though the pathologic findings of specific diseases are discussed and exemplified in the text and accompanying atlas, this is in no way meant to be an exhaustive review of head and neck histopathology. A significant proportion of the materials herein are devoted to head and neck oncologic surgery as pathology plays a vital role in the management of head and neck tumors. However, the principles outlined are applicable to the other areas of otolaryngology as well.

BIOPSY TECHNIQUES

A common outpatient scenario involves the otolaryngologist evaluating a patient with a head and neck mass. Once the appropriate history and physical examination have been performed, the next step typically involves obtaining tissue for diagnosis.

The techniques employed for biopsy vary depending upon the site, size, and character of a particular mass. Atraumatic and meticulous technique is paramount and failure to properly handle a specimen can limit the quality and quantity of the data gleaned from the biopsy. This is true for samples procured from epithelial surfaces and from those obtained percutaneously.

Biopsy of Cutaneous and Mucosal Surfaces

In the context of a cutaneous lesion, incisional or excisional biopsies may be performed. Shave biopsies are generally not recommended as an accurate assessment of tumor thickness cannot be made using this technique. This is of particular importance with pigmented lesions since staging and subsequent therapy of malignant melanoma is dependent upon the depth of invasion (1). In addition, the dermatopathologist cannot differentiate between carcinoma *in situ* (CIS) and invasive carcinoma without evaluating the basement membrane—a feature that cannot be assessed on scrape biopsies.

The simplest and most efficient means of obtaining a skin sample is through the performance of a punch biopsy. A variety of skin punches are commercially available and typically range in size from 2 to 4 mm in diameter. These instruments are typically trephines attached to the end of a long plastic handle. The blade is inserted perpendicular to the skin and gently rotated through the epidermis and the dermis as to provide a full-thickness sample of the lesion in question. For all but the smallest lesions, punch biopsies are incisional rather than excisional. Thus a more definitive procedure will often be required once the diagnosis is confirmed. Alternatively, skin lesions may undergo incisional biopsy or, if small enough, be excised *en bloc* with a scalpel in the outpatient clinic. Care must be taken to orient

excisions within the relaxed skin tension lines within the face and neck.

When obtaining tissue from mucosal sites in the upper aerodigestive tract, through-cutting or cupped forceps are often employed. Using this method, a representative portion is grasped with the instrument and sharply divided or avulsed from the lesion in question. Though widely used, this forceps biopsy does have its drawbacks. The urologic literature suggests that this technique may result in inaccurate diagnosis due to limited sample size, distorted architecture, and crush artifact (2). In addition, the samples tend not to be full thickness. Consequently, the pathologist may not be able to differentiate *in situ* from invasive carcinoma. Conversely, incisional/excisional scalpel biopsies and punch biopsies allow for a more complete assessment of a mass, its interface with the surrounding tissue, and, in the context of malignancy, the depth of tumor invasion—a feature that has significant treatment implications for early-stage oral cavity tumors. Moreover, it has been demonstrated that when compared to other methods, oral biopsy samples obtained using a punch are significantly less prone to artifacts such as crushing, splitting, hemorrhage, and fracture—all features that might impede the pathologist's ability to make a complete and accurate assessment (3). Given all of this information, it is the authors' contention that punch biopsy be the first choice for mucosal biopsy in the upper aerodigestive tract and that the cup forceps should only be used when punch or scalpel biopsy is not technically feasible (i.e., due to inaccessibility because of the anatomic locale, trismus, or other factors).

Biopsy of Subcutaneous Masses

Neck masses are among the most common reasons for referral to otolaryngologist–head and neck surgeons. An understanding of percutaneous biopsy techniques is essential to their management. The most common method for obtaining tissue diagnosis in the context of a neck mass remains the fine needle aspiration (FNA) biopsy. FNA has long been central to the diagnostic algorithm for thyroid nodules. It has also assumed a prominent role in the evaluation of enlarged cervical lymph nodes, salivary masses, and other subcutaneous tissues. FNA is relatively simple to perform in the outpatient setting, it is safe and well tolerated by most patients without the use of local anesthesia, and is highly accurate when used appropriately. Indeed, a recent meta-analysis by Tandon et al. (4) revealed that the aggregate sensitivity, specificity, positive, and negative predictive values across all head and neck subsites were 89.6%, 96.5%, 96.2%, and 90.3%, respectively. Despite its benefits and widespread use, there is no consensus as to the optimal technique for specimen acquisition and preparation. In addition, most otolaryngology programs do not formally train residents to perform FNA—oftentimes leaving them unaware of the potential pitfalls in performing the procedure. This has likely contributed to the high rates of specimen inadequacy that have been observed in some contexts (4–7).

Failure to obtain adequate tissue for cytologic analysis remains a vexing problem in clinical practice. Several studies have addressed this issue and the means by which the rates can be improved. The process begins with using the appropriate equipment. It is recommended that either a 23 or 25-gauge needle of adequate length be employed for FNA (8). In the authors' experience, the 25-gauge needle is of sufficient caliber to obtain a specimen while at the same time minimizing patient discomfort. The authors use a modification of the technique described by Dusenberry (8): After decontaminating the skin with an alcohol wipe, the tip of the needle is passed into the center of the mass. A "series of short, staccato strokes" are performed while holding continuous suction on the plunger (among head and neck masses, active suction during aspiration appears to yield significantly higher rates of specimen adequacy when compared to needle strokes without suction (9)). The procedure is continued until material is observed within the hub of the needle. At this point, the aspiration should stop and the needle should be withdrawn from the skin. If a cystic lesion is encountered, it should be completely evacuated in order to reduce the risk of a false-negative aspiration—particularly when nodal metastasis is in the differential diagnosis. Once the sample is collected, a smear is made of the aspirate and it is prepared for the pathologist. If lymphoma is suspected, additional material should be placed into a specialized transport material and submitted for flow cytometry.

If sufficient material is available, a cell block may also be prepared. A cell block is a means of preparing an FNA specimen that allows it to be processed, sectioned, and stained as if it were a histology section. Cell blocks are prepared from small tissue fragments, blood clots, and mucus within the FNA needle. This material is then compacted into a "block" for further processing. Cell blocks can be made manually, with albumin or agar, and with or without the aid of centrifugation. The cell block is a valuable tool in that it can supplement the information gathered through cytologic smears. Additionally, special stains (including immunohistochemistry [IHC]) can be performed on cell blocks (10).

After aspiration and smearing, slides are allowed to air dry or are placed into 95% ethanol for Papanicolaou staining. Air-dried slides may be evaluated on-site using Diff-Quik staining. The Diff-Quik stain may be performed within minutes of specimen procurement and allows for immediate examination by the cytopathologist. On-site evaluation is not simply for establishment of an "on the spot" diagnosis. Rather its value is in the determination of specimen adequacy. The importance of this practice cannot be understated. In essence, it provides the physician with immediate confirmation that an appropriate amount of the desired material was collected—thereby decreasing

the likelihood that the patient will be subject to the discomfort, distress, and expense of rebiopsy. A 2010 report by Moberly et al. supports this notion. They found that both the rates of specimen adequacy and the ability to obtain a definitive diagnosis by FNA were improved by immediate cytologic analysis (7). Given these findings, it is recommended that whenever feasible, a cytotechnologist or cytopathologist be present during performance of an FNA so that they may assess the specimen for adequacy.

The addition of image guidance also appears to have a significant effect upon the success of FNA. Early experience with CT and ultrasound-guided biopsy yielded favorable results—with these techniques being utilized to improve needle placement and diagnostic yield during FNA, even in the presence of palpable disease. Due to the reduced cost, lack of radiation exposure, improved sensitivity, and widespread availability of ultrasound, it has to a great extent supplanted CT for use in image-guided biopsy. Indeed, office-based ultrasound is now employed by a growing number of otolaryngologists and is particularly useful for assisting with needle placement. When compared to the traditional palpation method of needle placement, ultrasound-guided FNA has been shown to reduce the number of false-negative biopsies (11) and improve the diagnostic accuracy and adequacy rates by 23% and 84%, respectively (12). Surgeon-performed ultrasound-guided FNA appears to yield similar results to those achieved by interventional radiologists and cytopathologists. A randomized controlled trial conducted by Robitschek et al. (6) found that the number of inadequate specimens decreased by nearly 30% when ultrasound was utilized to perform FNA in the otolaryngology clinic.

While FNA yields cellular material suitable for cytologic characterization, the technique does not preserve tissue architecture—a feature that may reveal additional clues as to the definitive diagnosis. Core biopsies, on the other hand, provide a more substantial and intact piece of tissue that may be fixed and stained for review by a surgical pathologist. Core biopsies are generally performed using larger bore needles (18 or 20 gauge) than those used for FNA. There are a number of commercially available devices for core needle biopsy. These typically consist of a spring-loaded mechanism that deploys the needle once a trigger is depressed. The needle enters the specimen and is rapidly withdrawn, taking with it a core of tissue that may subsequently be fixed and processed by the histology laboratory. Alternatively, core needle biopsy may be performed using a standard needle and syringe, making a single swift pass into and out of the lesion in question. Given the size of the needle, local anesthetic is often injected into the overlaying skin in order to minimize discomfort. A small skin incision may also be made to facilitate needle entry without contamination by the overlaying epidermis.

Though core biopsy is common in non–head and neck sites, it has yet to gain widespread popularity for our purposes. This may be due to concern regarding bleeding and trauma to structures such as the facial nerve and great vessels as these complications have been reported (13). However, larger studies specifically addressing head and neck biopsies have demonstrated complication rates similar to those reported for FNA (14–17). Another concern regarding head and neck core biopsy is that it may have the potential to seed tumor cells along the needle tract—though this has not been shown to be the case (18).

Moreover, Saha et al. (19) demonstrated that ultrasound-guided core needle biopsy was significantly more accurate than palpation-guided FNA at detecting cervical metastases (97% vs. 85%) and that seeding was not an issue. Among their series of 49 core biopsies and 50 FNAs, the nondiagnostic rates were 2% and 42%, respectively. The data is somewhat misleading given the fact that FNA was performed without ultrasound guidance. However, this and other similar studies do suggest that in skilled hands and with image guidance, core needle biopsy is a safe and useful tool in the evaluation of head and neck masses. It has been promoted as a less traumatic, less time consuming, and more easily performed alternative to open biopsy in the context of a neck mass. As such, core biopsy may be best suited as in an intermediate step between FNA and surgical exploration in patients with nondiagnostic or indeterminate cytology (14,15).

PATHOLOGY AND THE OPERATING ROOM

The appropriate management of surgical specimens within the operating room is a highly active and interactive process that involves the surgeon, operating room staff, laboratory personnel, and pathologist. In order to obtain meaningful information from the pathologist, surgeons must be intimately involved in this process both before and after the specimen leaves the back table. Implicit in this should be awareness that certain behaviors and operative maneuvers can have profound effects upon the pathologist's interpretation of the tissue being sent to them. Understanding these actions and the proper techniques for handling operative specimens will effectively minimize ambiguity in the interpretation of surgical margins, optimize the use of frozen sections, and maximize the accuracy of pathologic data.

Surgical Margins: Adequacy

In head and neck cancers (and in some benign diseases such as pleomorphic adenoma) margin status has long been known to affect subsequent treatment and ultimately prognosis. Both locoregional control and overall survival may be compromised in the context of grossly or microscopically positive margins. Using relatively nonstringent criteria for margin positivity (defined as frank carcinoma, CIS, or premalignant change at the margin), Loree and Strong (20) found that the incidence of

local recurrence increased twofold and that the survival rate was reduced by 13% in patients with positive surgical margins. The absolute distance from a margin is also of importance in head and neck cancers. Nason et al. (21) evaluated patients with margins that were 5 mm or more, 3 to 4 mm, 2 mm or less, and clearly involved. In their series of 277 patients with oral cavity carcinoma, there was a highly significant difference in overall and recurrence-free survival that varied with the size of the margin. After matching for stage and other confounding variables, patients with positive surgical margins had a 2.5-fold increase in risk of death at 5 years when compared to patients with negative but close (3-mm) margins. Patients with 3-mm margins had a 1.5-fold increase in risk of death compared to those with clear (greater than or equal to 5 mm).

Despite the findings of these and similar studies, there currently is no consensus in the literature as to what constitutes an adequate margin for head and neck squamous cell carcinomas (SCCs). Meier et al. surveyed members of the American Head and Neck Society in 2005. Of the 476 responses, the most common definition of a clear margin was greater than 5 mm. Though this was the most frequently used distance, it accounted for less than 50% of the total responses in the study—reflecting the significant diversity of definitions used throughout the literature and applied in clinical practice. This is further confounded by the fact that 14% of the participants considered CIS to be a negative margin while nearly 26% considered dysplasia to be a positive margin (22). Given the inconsistencies in the literature, it is imperative that individual cases be discussed at multidisciplinary tumor boards with consistent application of local standards and frequent re-evaluation of outcomes and practice patterns.

Surgical Margins: Orientation

Regardless of what standard is chosen, an understanding of how the pathologist evaluates margins will ultimately assist in clinical decision making. When a specimen is received, it is initially fixed in buffered formalin. The tissue is then examined grossly and measured. It is then marked at critical points and presumed margins with one of a variety of commercially available inks or dyes. These inks withstand the fixation and slide preparation process and are visible to the pathologist on light microscopy. Under the microscope, the distance between disease and ink is measured by the pathologist and reported. This essentially is how margins are assessed. However, procedures for specimen inking vary from institution to institution and from pathologist to pathologist. When coupled with the complexity of head and neck anatomy and the fact that excisions often do not obey true anatomic boundaries, the subjective nature of the inking process can confound margin interpretation. This makes communication between the surgeon and the pathology team paramount.

Along these lines, it is vital that the surgeon provide an adequate clinical history and description of the procedure. The pathologist may not have a detailed understanding of otolaryngologic procedures. For example, surgeries such as partial laryngectomy and tongue base resection can be quite foreign to nonsurgeons and involve three-dimensionally complex anatomy. The resulting specimens are often small and amorphous without any identifiable orienting landmarks or directionality. Large specimens such as composite resections or laryngopharyngectomies present another problem as it is not feasible to histopathologically examine the entire surface. In the absence of input from the surgeon, the pathologist must essentially make an educated guess as to what or where the true resection margin is in these cases. Hand delivering a specimen to the pathologist and orienting it for their team can help to minimize ambiguity in margin determination.

It may also be helpful for the surgeon to ink specimens himself or herself. This will ensure that the precise area of concern is being evaluated by the pathologist. Methylene blue is the author's preferred ink for this purpose as it is readily available in most operating rooms and can be easily applied using a cotton-tipped applicator. It should be noted that methylene blue is water soluble—hence the site must be reinked once it reaches the histology laboratory to avoid being washed away during processing. Though little has been written about surgeon-initiated inking in otolaryngology, the breast surgery literature suggests that it is indeed a valuable tool. Numerous studies have implicated surgeon inking as a means of reducing discrepancies and ambiguity in the identification of tumor margins. They have also detailed the shortfalls of suture orientation and the benefits of well-orchestrated specimen handoffs to the pathology team in this regard (23–25).

The inadequacies of contemporary margin procurement and analysis for head and neck surgery have been elegantly discussed by Black et al. (26). Framing this issue in the larger context of quality improvement in medicine, the authors applied a business model—governed by what are commonly known as the "Toyota" principles—to the process. Under this model, processes and production are subdivided into multiple steps with the ultimate goal of reducing redundancy, waste, and error. Each step is carefully regulated and a strong emphasis is placed upon the quality of "handoffs"—the points at which a product is transferred to another team member for performance of the next step. Black's paper highlights the fact that inconsistencies and discrepancies with respect to tumor margins can in large part be attributed to poor communication during handoffs. They contend that interdisciplinary communication must occur earlier in the overall process of margin determination—with the greatest benefit coming at the specimen orientation step. If the process fails at this step, then all subsequent steps and, eventually, the final pathology report, are jeopardized. With this in mind, it is again strongly advocated that the surgeon play an active role in specimen handoff and orientation.

Yet even when all of these measures are taken, we may still be left with a positive margin. However, surgeon-directed orientation—either by intraoperative inking or through a face-to-face handoff to the pathology team—should make the task of re-excision or targeted radiotherapy less daunting.

Surgical Margins: Shrinkage

Typically a head and neck resection is outlined on the tissue surface with a wide margin. However, it is not uncommon to see an assumedly appropriate cuff of normal tissue wither down to no more than a few millimeters once the specimen is excised. This margin may be even smaller by the time the pathologist reviews the slides and renders his or her report. While there may be multiple reasons for discrepancies between gross margins and those observed histologically, specimen shrinkage appears to play a major role. Most shrinkage appears to occur immediately after resection. It is thought to be the result of unopposed contractility in the submucosal musculature and release from surrounding supporting structures (27). In a 1996 study of canine oral mucosa, Johnson et al. demonstrated that specimen margins were reduced by 30% to 47% between the time of excision and the time of histologic review. The majority of shrinkage occurred after resection and before fixation (27). Subsequent to this, Mistry (28) presented a series of patients with SCC. In this report, 1 cm *in situ* margins were measured by the surgeon. Tumors were removed along this margin using monopolar cautery. The margin was subsequently remeasured on the specimen 30 minutes after resection. The overall mean margin shrinkage was 22.7%, with T1 and T2 tumors experiencing significantly greater rates of shrinkage than T3 and T4 tumors (25.6% vs. 9.2%). Similarly, Cheng et al. (29) demonstrated significantly increased shrinkage rates among T1 and T2 tumors as compared to T3 and T4 disease. This might have significant implications for adjuvant therapy as it is commonplace to use margin adequacy to guide adjuvant therapy—particularly in early-stage disease. Tumor location may also play a role in the degree of shrinkage, as the effects appear to be most marked in the buccal mucosa, mandibular alveolar ridge, and retromolar trigone (29). Knowing that significant shrinkage may be anticipated when resecting small tumors in these areas, the surgeon should—being mindful of the functional consequences—plan accordingly and design wider (i.e., greater than 1 to 2 cm) margins.

When discussing margin shrinkage, it is important to recall that prognostic statistics pertaining to margin status are based upon histopathologic data and not *in situ* or gross margins. Thus it is a fallacy to believe that because of shrinkage a close or positive margin may be disregarded as artifact in the context of a wide clinical margin.

Surgical Margins: The Influence of Surgical Technique

The choice of surgical instruments may also influence the pathologist's interpretation of margins. While "cold steel" has for generations been the standard for surgical incisions and excisions, a number of new technologies and instruments—such as the monopolar cautery pencil, the CO_2 laser, and the harmonic scalpel—have been introduced for this purpose. These have been variably touted for their improved hemostasis, reduced operative time, and positive effects on wound healing and postoperative pain (30,31). However, what is often lost in these discussions is the fact that each technique can impart artifactual changes to the tissues. As these artifacts can interfere with the interpretation of margins, it is helpful to inform the pathologist about which technique was used for the resection. Monopolar cautery can induce significant thermal injury and has been shown to induce a wider area of tissue damage when compared to CO_2 laser excision (31,32). Both monopolar and laser techniques result in vacuolar degeneration and nuclear elongation. The nuclei may appear pyknotic and distorted—features that can be confused with dysplasia or even overt carcinoma. If the laser is used, the thermal effects may be reduced using the pulse-wave mode. Likewise, the harmonic scalpel results in fewer artifacts than monopolar cautery, but significantly more than cold steel technique. In comparing these methods, Kakarala et al. showed that harmonic scalpel resulted in significantly less tissue fragmentation and nuclear change than the monopolar. However, the scalpel was superior to both with respect to margin distortion (30). Though the histologic benefits must be weighed against other factors such as bleeding, it is recommended that any surface being evaluated as a resection margin be incised using cold sharp technique.

PRACTICAL USE OF FROZEN SECTIONS

Frozen section is a technique in which a small portion of tissue is frozen, allowing for it to be cut, stained, and analyzed without the time-consuming fixation/dehydration process that is required for routine specimens. Using this method, a small tissue sample can typically be prepared and interpreted within 20 minutes from time of receipt in the surgical pathology laboratory. The rapidity and accuracy of intraoperative consultation allows for immediate changes in patient management. In the head and neck, it is a useful tool for establishing a definitive diagnosis, determining margin adequacy, differentiating between benign, malignant, and nonneoplastic masses, evaluating lymph nodes for the presence of metastatic disease, determining the adequacy of a tissue sample, establishing the need for special tissue handling—as in the case of lymphoma, granulomatous, or infectious disease, and for verifying the identity of organs such as the parathyroid glands

(33). Patterns of frozen-section usage are highly variable and are dependent upon the surgeon and the procedure. Nearly all respondents to a recent survey of the American Head and Neck Society reported using frozen sections to evaluate resection margins for oral cavity and oropharyngeal tumors (97% and 91%, respectively). Among this same group of surgeons, fewer than half obtained frozen sections during parotidectomy, thyroidectomy, or sinonasal/skull base resections (22). These patterns are likely to reflect differences in training and local customs. Each individual otolaryngologist's practice should be commensurate with his or her training and the expertise/experience of the surgical pathologist.

Perhaps the most frequent application of frozen section in otolaryngology is in the evaluation of surgical margins. This is evidenced by the fact that 99% of respondents in the American Head and Neck Society survey utilize the test for this purpose (22). The method for procuring margins varied among those polled. Though most reported obtaining samples from the resection bed, 24% took frozen samples from the primary specimen at least part of the time. The advantage of taking frozen-section specimens from critical areas of the resection bed is that it allows for more precise localization of the sample site in the event of a positive margin. And while there is no standard method for obtaining frozen-section samples, there is likewise no standard method for margin analysis by pathologists. This again underscores the need for open communication between the surgeon and the pathologist. The pathologist must be made aware of the surgeon's practices and preferences with respect to margin procurement. Without this interaction, there are likely to be discrepancies between what the surgeon and the pathologist believe to be the status of the margins (26).

Regardless of the sampling method, it appears that frozen section is highly sensitive, specific, and accurate for the determination of tumor margins in the head and neck. In the largest series examining frozen section for this purpose, DiNardo et al. (34), found that the test was 88.8% sensitive, 98.9% specific, and 98.3% accurate in identifying a positive resection margin. However, in an era of medical cost containment, it follows that frozen section should be reserved for circumstances where there is a significant likelihood that it will alter intraoperative management.

Handling of Cervical Lymph Node Specimens

Cervical lymph node excision is one of the most common procedures performed by otolaryngologists. Whether this is in the context of a diagnostic biopsy or a neck dissection, the quality and quantity of information in the pathology report can be significantly affected by specimen handling in the operating room. This is perhaps no more evident than in the context of a suspected lymphoma. If a lymphoproliferative disorder is in the differential diagnosis, the lymph node (or Waldeyer ring tissue) should not be placed into a fixative solution. Instead, it should immediately be sent to the surgical pathology laboratory "fresh"—with the concern for lymphoma clearly indicated on the requisition. The fresh tissue should be hand delivered to the laboratory immediately as fixation, time, and heat will result in protein denaturation. If target antigens denature, the accuracy of flow cytometry may be limited. Furthermore, flow cytometry requires that specimens be separated into individual cells. This allows them to freely flow through the analyzer during characterization. The fixation process makes it difficult to separate the cells from one another—thus making flow cytometry an impossibility. It is important to remember that most flow laboratories only operate during business hours (i.e., Monday to Friday day shift). Specimens that are allowed to sit all weekend or even overnight may significantly degenerate and produce less than optimal results. Hence the surgeon must make the pathology team aware if such a biopsy is being performed at night or on weekends. Many hospitals have established "lymphoma protocols" whereby the specimen cup is explicitly labeled as a possible lymphoma. This initiates the above-mentioned cascade of procedures in an attempt to systematically reduce misadventures in processing.

Neck dissection presents different challenges with regard to specimen handling. In the context of head and neck cancers, a great deal of prognostic information may be derived from histologic evaluation of the cervical lymph nodes. Data such as the number of involved nodes, their location (i.e., level), and the presence or absence of extracapsular extension are used to determine whether or not a patient would benefit from adjuvant therapy and, in some cases, what that therapy might consist of (35,36). Knowing the precise level(s) of involvement may also point to the origin of an unknown primary tumor (37). The absolute number of lymph nodes collected and evaluated also appears to be important. During selective neck dissection for early-stage disease, the likelihood of identifying cervical metastases increases when the total nodal yield is in excess of 20 (38). A 2011 report by Ebrahimi et al. takes this one step further—finding that a nodal yield of less than 18 during elective neck dissection for oral cavity cancers resulted in a significant reduction in overall survival. Though the study does not detail the patterns of failure, a plausible explanation is that these patients were initially understaged at the nodal level and hence undertreated. The authors argue that the minimum number of lymph nodes evaluated during selective neck dissection be 18 (39). This points to the fact that the pathology report should be carefully scrutinized after neck dissection with attention to the total node count. If the 18 lymph node benchmark is not reached, additional therapy may be warranted. In addition, the pathologist should be asked how nodes are counted in their laboratory as this varies from institution to institution. In most, nodes are grossly identified and removed from the fibrofatty tissue after the specimen is received. They are then counted, submitted into individual cassettes,

embedded in paraffin, and analyzed under the microscope. The remaining tissue is typically submitted separately for histologic examination—allowing for the identification of microscopic lymph nodes.

The American Head and Neck Society and American Academy of Otolaryngology–Head and Neck Surgery have convened a task force with a primary goal of standardizing neck dissection classification and nomenclature. This has become increasingly important in the era of selective neck dissection. In recognizing the ambiguity of certain terminology and the difficulties associated with reorienting a nodal packet once it reaches the pathology laboratory, the task force has established guidelines for specimen submission. They recommend that neck contents be divided into levels and sublevels by the surgeon in the operating room immediately after the specimen is removed from the patient. Each level should be carefully placed into a separate container and labeled appropriately. Using this methodology, the risk of misidentifying the neck levels should be minimized (40).

THE PATHOLOGY LABORATORY

To many otolaryngologists, the pathology laboratory is a "black box"—a specimen is sent and sometime later (never fast enough) the results appear in the patient medical record. However, pathology departments are typically among the largest and busiest in both community and academic hospitals. Pathology departments typically consist of two main divisions—anatomic and clinical pathology. Anatomic pathology divisions deal with tissue diagnoses while the clinical pathology laboratory deals with testing of nontissue specimens (i.e., blood chemistry, coagulation testing, etc.) Most anatomic pathology divisions have subdivisions including surgical pathology and cytopathology; some may also have neuropathology, medical (autopsy) pathology, and even molecular pathology laboratories. Many departments also have a separate hematopathology division, which may be part of anatomic or clinical pathology. In addition to the pathologists, there are numerous layers of professional staff and technicians working to prepare and analyze specimens. It is helpful for surgeons to familiarize themselves with the structure and personnel within their local pathology department. This can facilitate the transfer of information and will most certainly promote collegiality and collaboration.

Specimen Handoff and Processing

The importance of communication between surgeon and pathologist has been outlined above and need not be further belabored here. For most routine specimens, this communication may be in the form of an appropriately completed requisition. One should view the pathology requisition as they would any other consultation request. It should pose a clinical question and provide any supporting data or information that might facilitate the expert opinion of the consultant. As such, the clinical history should include the patient's symptoms, differential diagnosis, any prior diagnoses, and/or treatment. Though we expect objective and unbiased assessments, it is important to remember that clinical information helps to frame the pathologist's interpretation of the tissue that they are examining. It may also lead him or her to perform special stains or other tests that they might otherwise not pursue. For instance, clinical suspicion for lymphoma should be clearly stated so that the appropriate tests may be performed. If infectious processes are suspected, this should also be explicitly indicated. This will facilitate use of the appropriate culture media and will serve to warn the pathology team of any potential exposure risks so that they may take the appropriate precautions (as in the case of *Mycobacterium tuberculosis*, for instance).

Prompt placement into fixative is of considerable importance (provided infection and hematologic malignancy are not under consideration). Tissue that is not fixed promptly may show marked drying or degenerative changes, making accurate diagnosis difficult or even impossible. Fixation is a chemical process which prevents this decay and increases the mechanical strength and stability of the tissues (10). The most commonly used fixative in today's surgical pathology laboratories is neutral buffered formalin (NBF). NBF is 3.7% formaldehyde in phosphate buffered saline. The formaldehyde acts by cross-linking proteins. NBF is inexpensive and compatible with most special stains, including IHC (41). The volume of NBF should be at least 10 times that of the tissue sample, and the sample should be completely surrounded by fixative (specimens that float and sink should be wrapped in Telfa or gauze to ensure that they are completely submerged and fixed evenly). Formalin penetrates at a rate of approximately 1 mm/h and tissue must be fixed through before it can be processed. In small biopsy specimens, this will happen in a matter of hours and the specimen can be processed later that day or the next. Larger specimens benefit from additional cuts into the tissue in order to allow for quicker penetration and fixation. The largest most complex specimens (such as laryngectomies and composite resections) may require multistep dissection with interval fixation. Those that contain bone will require decalcification, which can take several days itself, depending on the thickness of the bone. Fixed specimens are subsequently embedded into paraffin blocks. The blocks are sectioned into wafer-thin slices (typically a few microns in thickness) on a microtome. These slices are affixed to glass slides and stained so that they may be viewed under the microscope. The entire process may take several days, but must be completed before the pathologist can render a histologic diagnosis.

The College of American Pathologists (CAP) does allow for some specimens to be examined grossly without histopathologic examination. Which specimens may be handled in this manner is up to the discretion of individual departments (42). However, in most institutions foreign

bodies, tonsils, and adenoids fall under the "Gross evaluation only" umbrella. This is an important point to remember if tonsillectomy is being performed for diagnostic purposes as in the case of lymphoma or carcinoma. Again, if the requisition indicates a specific clinical concern rather than simply stating "Enlarged tonsil," the pathologist will be alerted and will perform the necessary steps for a more thorough analysis.

Reporting Standards

There are no specific guidelines for the reporting of benign disease. At a minimum, reports should include a definitive diagnosis and a statement regarding the status of the margins. Conversely, there are a number of organizations that issue publications related to the reporting of malignancy. For example, the World Health Organization periodically issues the Classification of Head and Neck Tumors as part of a series on classification of tumors from all sites (43). The American Joint Committee on Cancer (AJCC) and the International Union for Cancer Controls collaborate to maintain the staging systems used worldwide, with the AJCC leading these efforts in the United States (1). To help pathologists provide useful reports, the CAP publishes reporting guidelines for cancer (44). In fact, as part of the inspection process for accreditation, CAP reviews random reports to ensure they include the appropriate information.

HEAD AND NECK HISTOPATHOLOGY

The ability to recognize the histologic features of commonly encountered diseases and to understand the language of pathology reports are important skills for any surgeon to possess. Obviously surgeons cannot be expected to be expert diagnostic pathologists and a comprehensive review of head and neck histopathology is well beyond the scope of this chapter. Such an endeavor would itself require an entire textbook to be complete. Individual organ systems and diseases are discussed in the context of their associated pathologic findings elsewhere in this book. Consequently, the remainder of this chapter focuses on a few key concepts that will assist in interpreting pathology images and reports as they pertain to otolaryngologic diseases. To assist in this, we have also included an "atlas" containing a number of common epithelial neoplasms and their histopathologic description. All photos are stained with hematoxylin and eosin (H&E) unless otherwise noted (Figs. 12.1 to 12.25).

Special Stains

In reviewing pathology reports, one should pay attention to the stains used in slide preparation. Most commonly, this will be H&E. This mixture is universally employed for routine staining of tissues. Hematoxylin is a blue nuclear stain, while eosin is a pink counterstain that highlights cytoplasm as well as collagen. H&E staining allows specimens to be characterized morphologically. In many cases, a definitive diagnosis can be made based upon H&E alone. In others, however, the interpretation may not be so straightforward. Diseases may have overlapping microscopic features and may not be readily distinguished from one another. For instance, a benign paraganglioma can be morphologically similar to a medullary thyroid carcinoma on H&E staining. Despite their similar appearance, they have widely disparate clinical behaviors and treatments. Another more commonly encountered scenario involves diseases that are obviously malignant on H&E staining, but are too poorly differentiated to determine the cell of origin. For the pathologist to make a definitive diagnosis, additional testing is necessary. This testing is most often in the form of special stains.

A variety of special stains are available to aid the surgical pathologist. These take advantage of a cell's chemical makeup and may reveal features that are not otherwise discernable on H&E. They are most often used to highlight substances (mucin, amyloid, elastic), microorganisms (bacteria, fungi), or pigments and minerals (hemosiderin, iron, calcium). A list of histochemical stains that are frequently employed for head and neck specimens is provided in Table 12.1 (10).

IHC is another technique commonly used by surgical pathologists. IHC uses the principles of immunology to help determine the nature of a lesion (benign vs. malignant), prognosticate (HPV status), and establish site of origin. During this process, monoclonal antibodies directed at specific antigens are applied to the specimen. A second antibody is then bound to the targeted antibody. These are typically enzyme labeled (alkaline phosphatase, horseradish peroxidase) and produce a visible indicator in the presence of the antigen. The results are then qualitatively or semiquantitatively interpreted by the pathologist (10). Numerous commercially prepared antibodies are available and scores of these have relevance to otolaryngology.

A summary of commonly used IHC stains is provided in Table 12.2 (45).

SQUAMOUS CELL CARCINOMA AND ITS VARIANTS

A great deal of emphasis in otolaryngologic pathology centers around malignant diagnoses—the vast majority of which are SCC. Consequently, it is important that the otolaryngologist recognize some of the common features of SCC, its histologic variants, and its precursor lesions. In its native state, the surface of the upper aerodigestive tract is almost entirely covered by stratified squamous nonkeratinizing and respiratory epithelium.

(Text continued on page 194)

BENIGN NEOPLASMS

Salivary Gland Type Adenomas

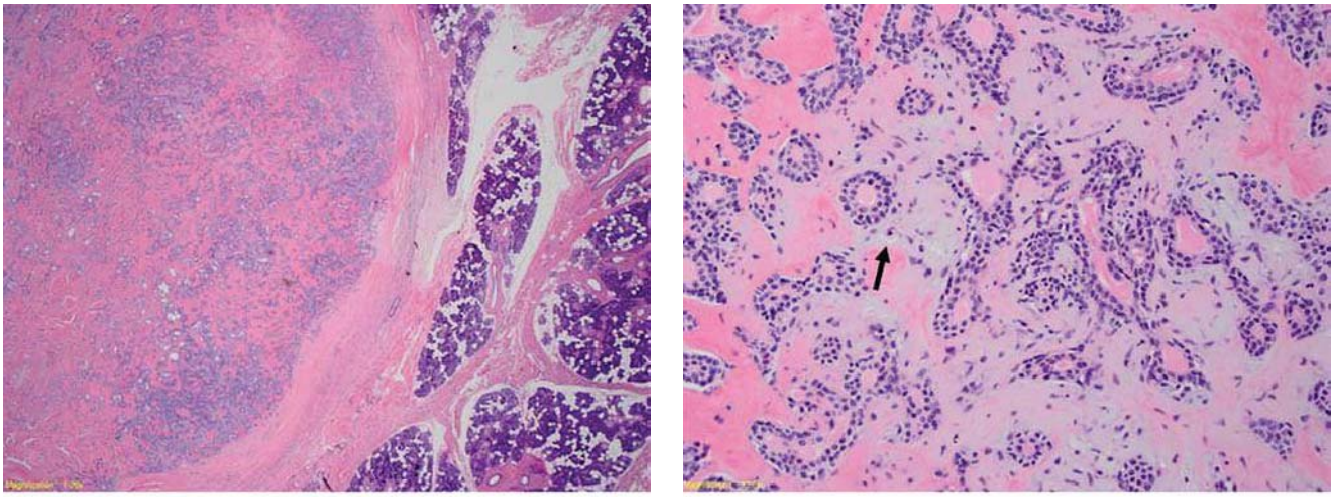


Figure 12.1 Pleomorphic adenoma. **A:** In the low-power photo (20×), the interface of the pleomorphic adenoma with the normal salivary gland may be seen (the latter is on the right hand side of this image). The lesion is encapsulated; this is one of the essential components of a pleomorphic adenoma. **B:** The intermediate-power photo on the right shows the other essential components: stromal elements, epithelia, and myoepithelial cells. At the center of this photo, mesenchymal cells with cartilaginous differentiation are evident (*arrow*). The duct-like structures show epithelial and myoepithelial cells (200×).

Sinonasal Papillomas

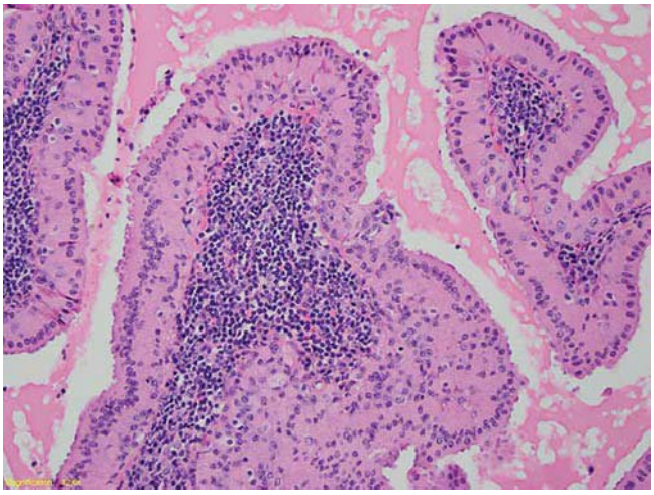


Figure 12.2 Warthin tumor (papillary cystadenoma lymphomatosum), with fibrovascular cores containing prominent lymphoid tissue. The epithelial lining is bilayered, with columnar oncocytic luminal cells and cuboidal basal cells. There are sometimes cystic areas that typically contain eosinophilic secretions (seen here); they may also contain crystals and laminated bodies (200×).

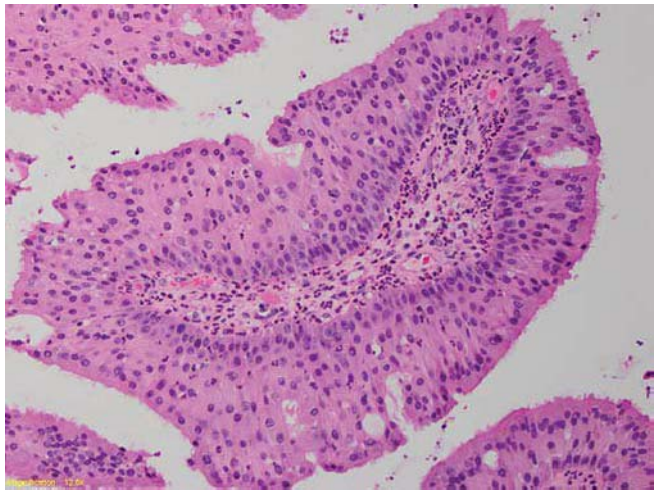


Figure 12.3 Exophytic Schneiderian papilloma, with a fibrovascular core covered by thickened respiratory and transitional epithelium and occasional clear mucus cells. Neutrophils are conspicuous (200×).

Squamous Precursor Lesions

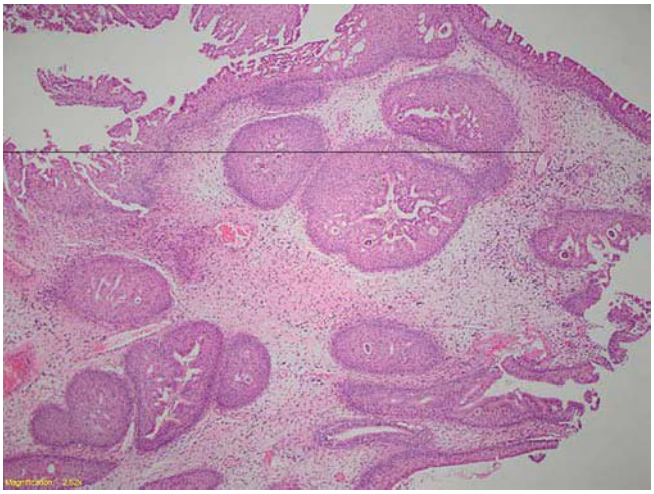


Figure 12.4 Inverted Schneiderian papilloma, with hyperplastic ribbons of transitional epithelium growing endophytically into the underlying stroma. The epithelium also contains occasional clear mucus cells (40×).

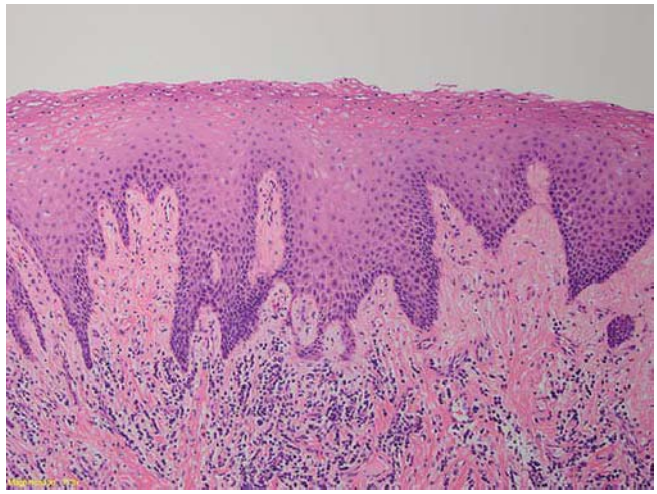


Figure 12.6 Squamous hyperplasia with increased epithelial thickness that remains orderly and without atypia (100×).

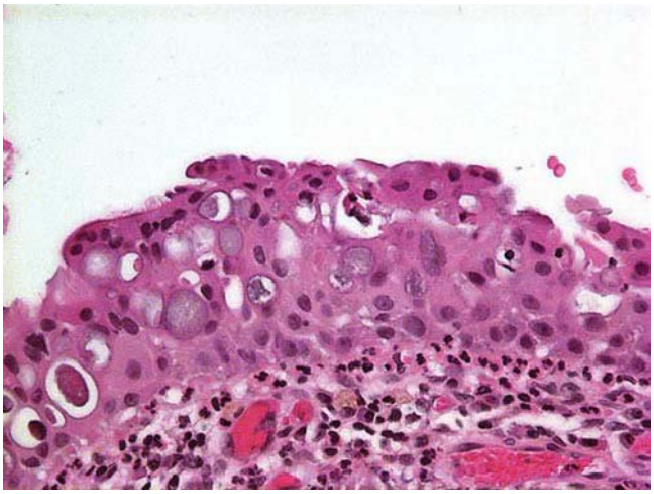


Figure 12.5 Oncocytic Schneiderian papilloma. The epithelium is composed of tall columnar cells with finely granular cytoplasm, reminiscent of oncocytes. Numerous microcysts and neutrophils are present (400×).

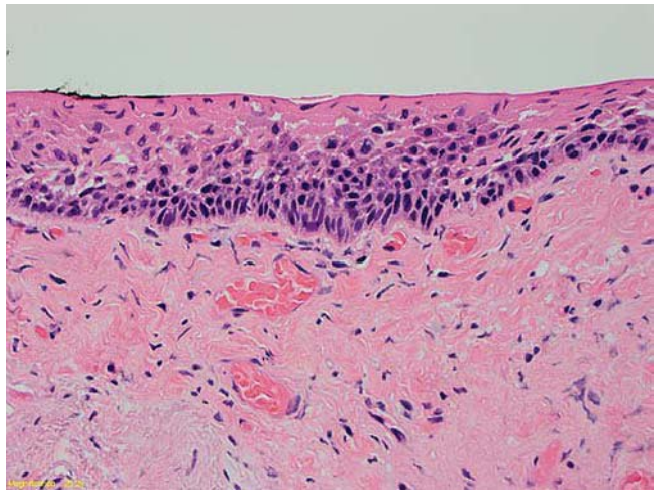


Figure 12.7 Mild squamous dysplasia. Architectural disorder (irregular stratification) with associated cytologic atypia (increased nuclear:cytoplasmic ratio, prominent nucleoli) confined to the lower third of the epithelium (400×).

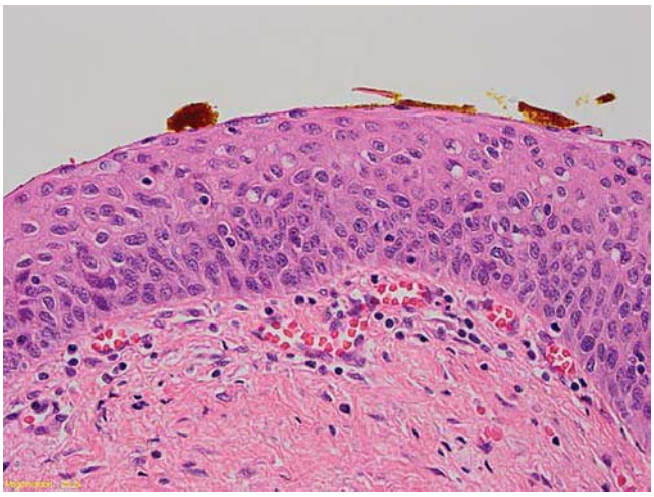


Figure 8 Moderate squamous dysplasia. Architectural disorder (irregular stratification) extending into the middle third of the epithelium with associated cytologic atypia (pleomorphism, increased N:C ratio, prominent nucleoli) (400×).

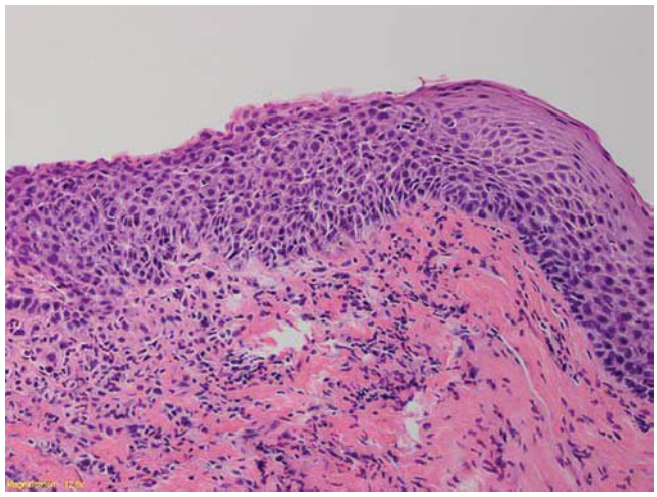


Figure 12.10 Severe squamous dysplasia on the left, with architectural irregularity and cytologic atypia extending to the top, with mild to moderate dysplasia on the right, where the irregularity and atypia is confined to the lower portions of the epithelium (200×).

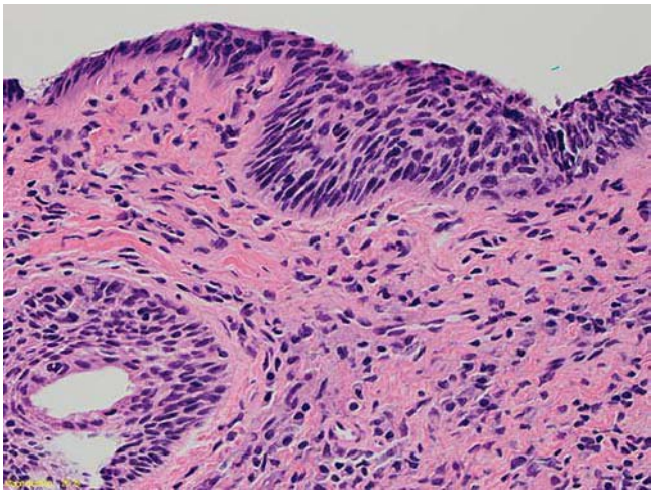


Figure 12.9 Severe squamous dysplasia. Architectural disorder (irregular stratification) extending into the upper third of the epithelium with associated cytologic atypia (pleomorphism, increased N:C ratio, prominent nucleoli). The specimen was previously frozen and shows resulting artifact. The dysplasia is also evident in a duct in the lower left of the photo (400×).

MALIGNANT NEOPLASMS

Squamous Cell Carcinoma and its Variants

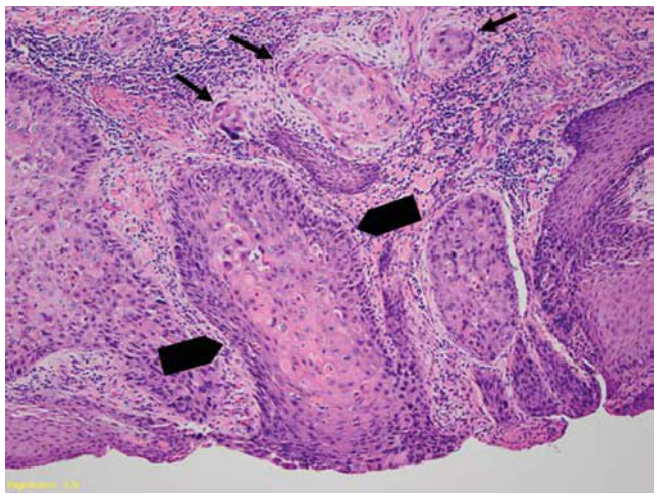


Figure 12.11 Invasive and *in situ* SCC. There is *in situ* carcinoma in the bottom middle of the photo (*arrowhead*). Deep to that (toward the top of the photo, *arrows*), are cohesive nests of large atypical cells with intercellular bridges, which incite a desmoplastic (or dense fibrotic) reaction, characteristic of invasive SCC (100×).

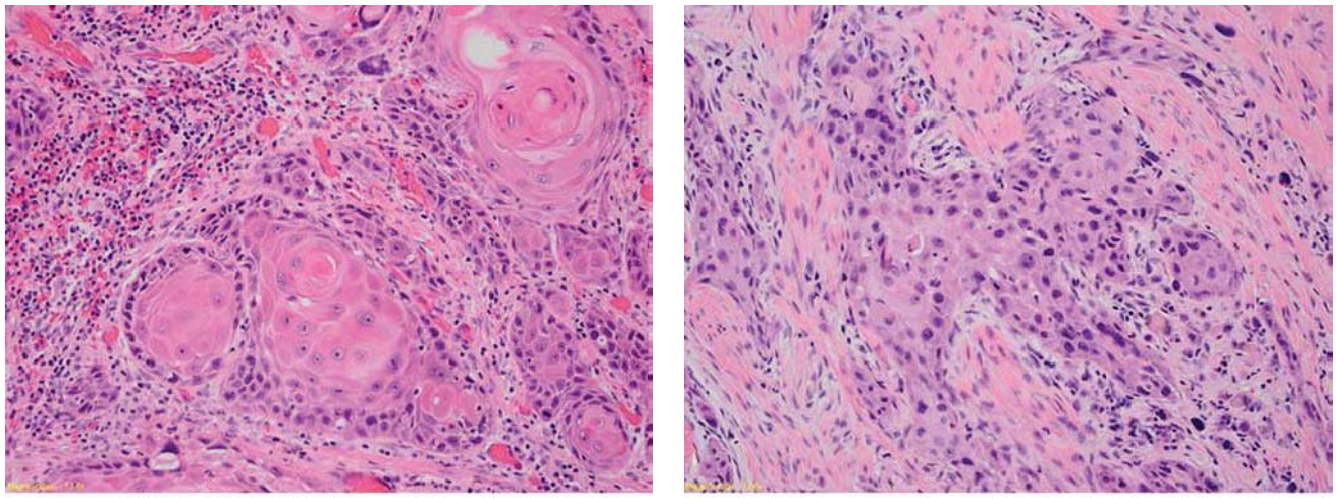


Figure 12.12 SCC, well (Panel A) and moderately differentiated (Panel B). **A:** The carcinoma in the photo is clearly invasive, but also displays obvious evidence of keratinization. **B:** The lesion demonstrated here is also invasive and has some evidence of keratinization (intercellular bridges and dyskeratotic cells), but to a lesser extent than is seen in the well-differentiated SCC (both images 200×).

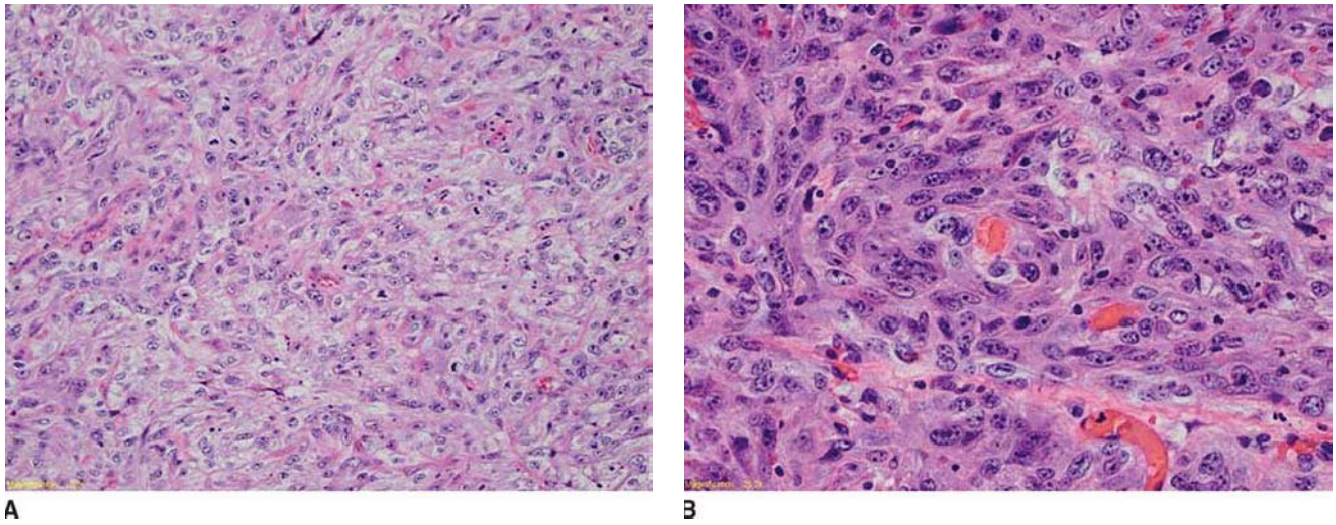


Figure 12.13 SCC, poorly differentiated. **A:** The photo depicts an obviously malignant neoplasm with little evidence of squamous differentiation (200×). **B:** The tumor seen here is also poorly differentiated, but with spindle cell features. This particular variant shows some residual evidence of squamous differentiation in the form of intercellular bridges. Some spindle cell carcinomas may be so poorly differentiated as to resemble sarcomas, requiring immunohistochemical or even electron microscopic evidence of epithelial differentiation for diagnosis (400×).

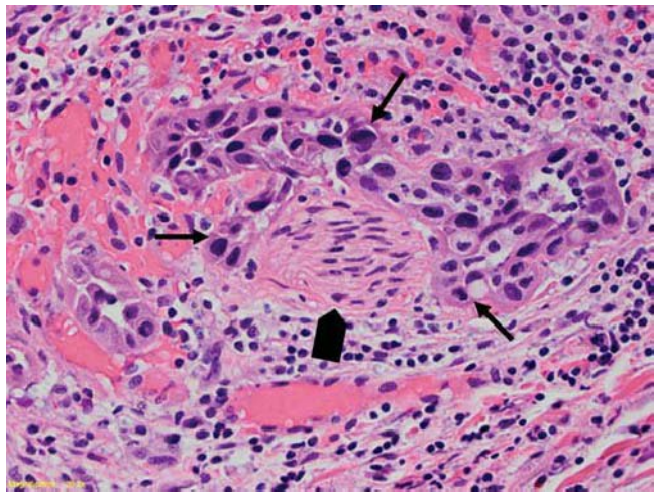
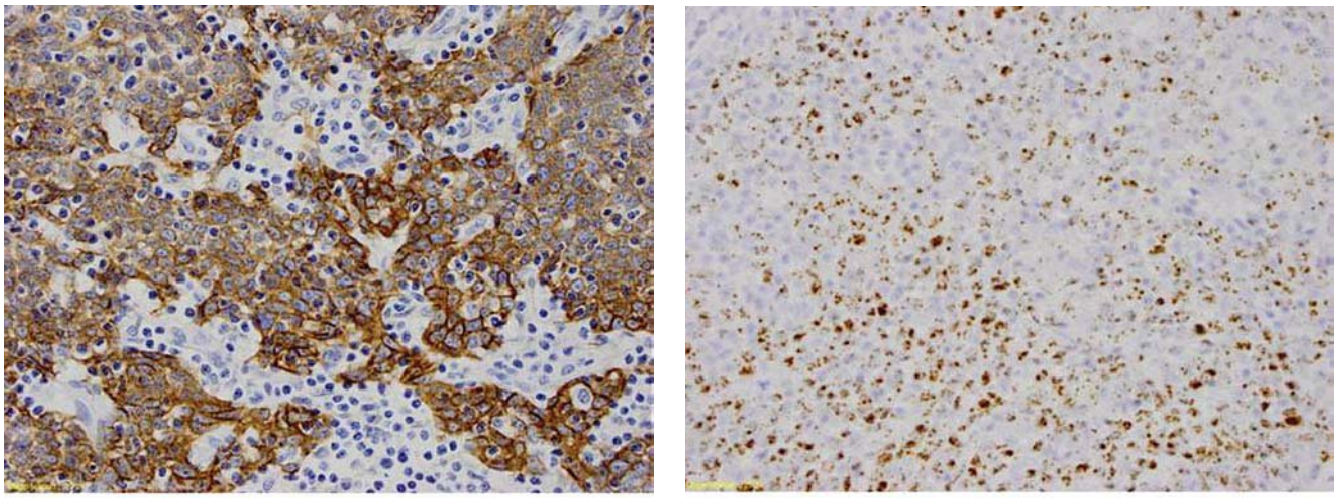


Figure 12.14 SCC with perineural invasion. The small structure in the center with wavy nuclei is a nerve (*arrowhead*). Malignant epithelial cells are evident immediately above the nerve (*arrows*). (400×).



A B

Figure 12.15 **A:** IHC for epidermal growth factor receptor showing strong diffuse staining. **B:** ISH assay demonstrating HPV+ carcinoma (both photos 400×).

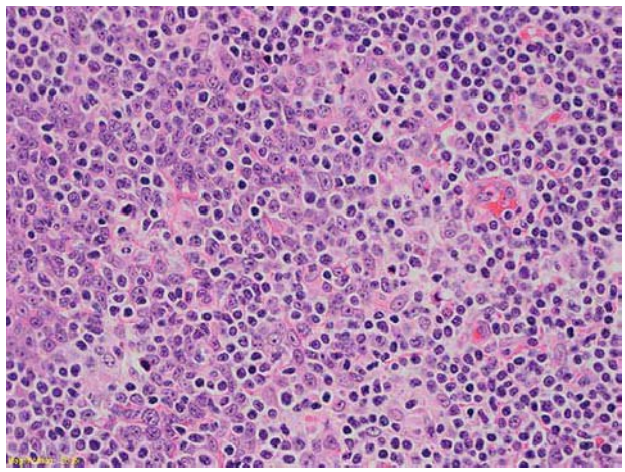
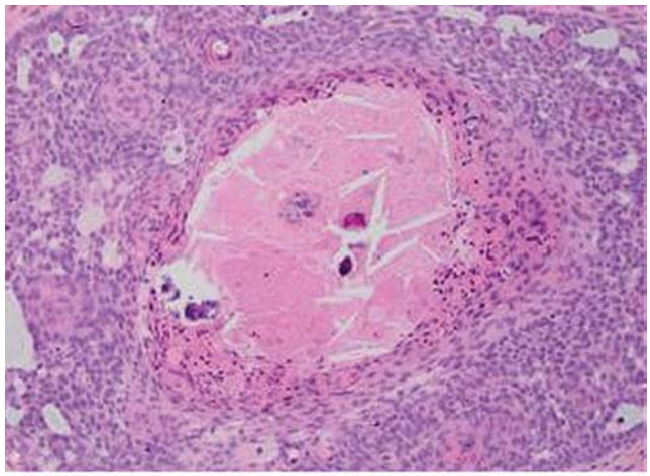
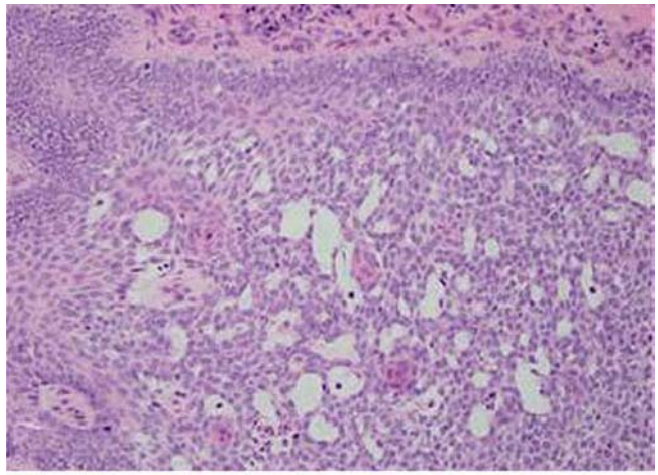


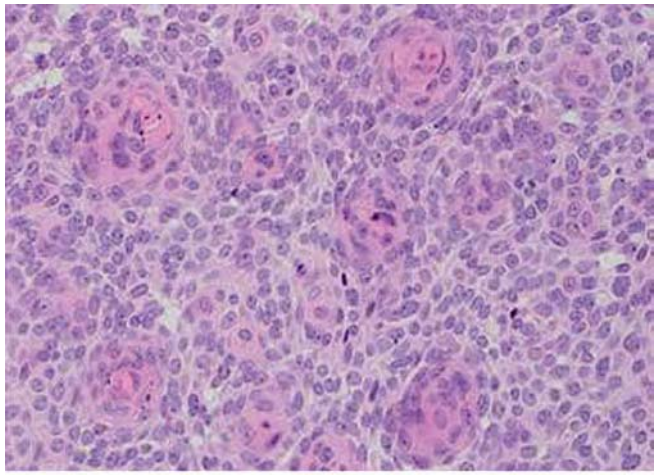
Figure 12.16 Lymphoepithelial carcinoma showing sheets of cells with indistinct cell borders imparting a syncytial appearance. Nuclei are vesicular with prominent nucleoli. Infiltrating lymphocytes are conspicuous (400×).



A



B



C

Figure 12.17 Basaloid SCC. **A:** Demonstrates the basaloid component, with small cells with scant cytoplasm and hyperchromatic nuclei, growing in solid sheets, with comedo-type necrosis. (200×). **B:** The cells exhibit peripheral palisading—the nuclei of the outer layer of cells are lined up perpendicular to the surface. Also evident in this photo are small cyst-like spaces. Both peripheral palisading and these cyst-like spaces are distinctive features of BSCC (200×). **C:** Foci of squamous differentiation within basaloid tumor island. BSCC have both basaloid and conventional SCC components (400×).

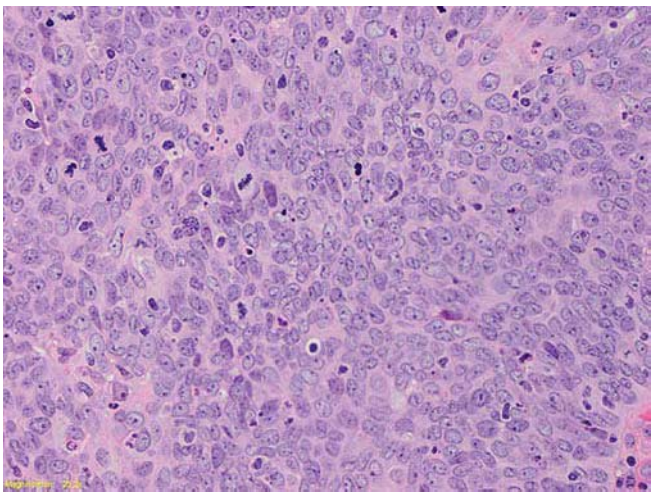


Figure 12.18 Nasopharyngeal carcinoma. The undifferentiated subtype pictured here shows large tumor cells growing in syncytial sheets. The cells are crowded and have oval vesicular nuclei with prominent nucleoli. The differentiated subtype, which is of no clinical significance and often coexists with the undifferentiated subtype, shows cells with well-defined borders and more (though still minimal) evidence of squamous differentiation. Numerous mitoses are present in this photo, as well as occasional lymphocytes (400×).

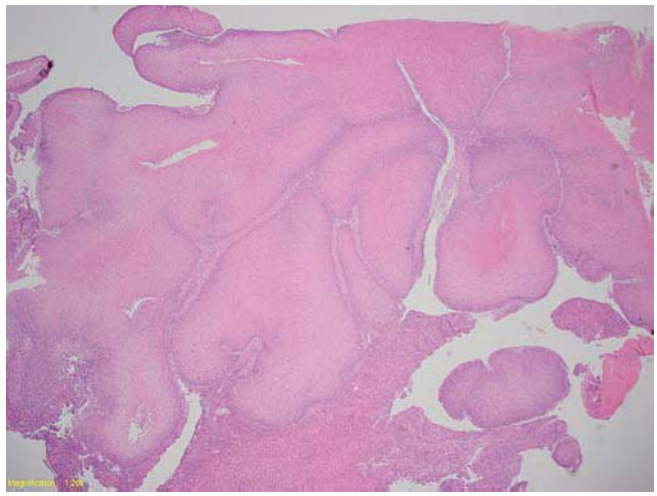


Figure 12.19 Verrucous carcinoma, low power showing well-differentiated epithelium without significant atypia invading into the stroma with pushing borders. The cells are typically larger than those seen in typical SCC (20×).

Salivary Gland-Type Carcinomas

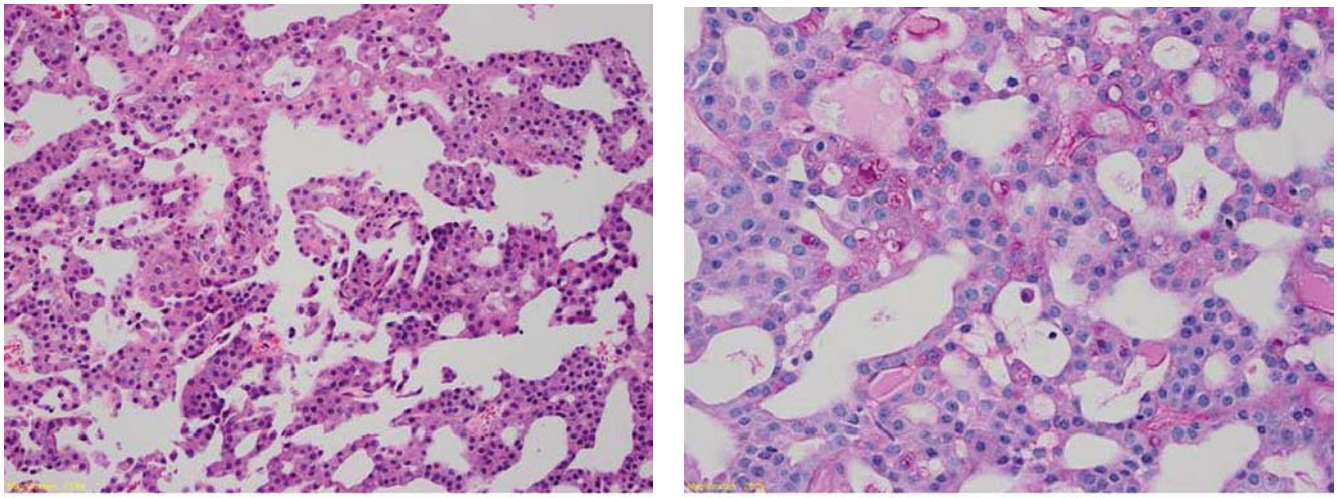


Figure 12.20 Acinic cell carcinoma. **A:** Demonstrates the typical polygonal cells with round eccentric nuclei, growing in sheets and lobules (200×). **B:** Periodic acid-Schiff (PAS)+ diastase resistant globules—another feature of acinic cell carcinoma (400×).

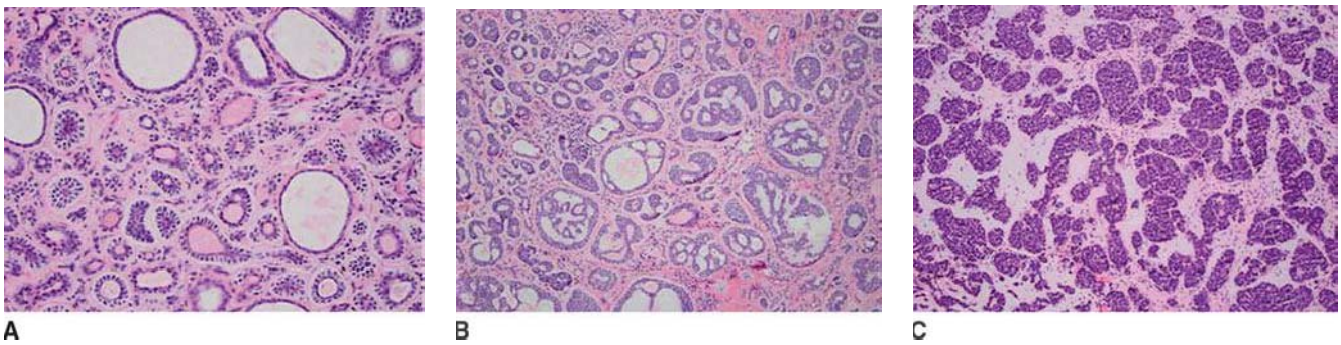


Figure 12.21 Adenoid cystic carcinoma. **A:** Well-formed ducts and tubules with central lumina, characteristic of the tubular pattern. (200×). **B:** Nests of cells containing microcystic spaces, characteristic of the cribriform pattern (100×). **C:** Sheets of uniform cells which lack tubules or cyst formation, characteristic of the solid pattern. (100×).

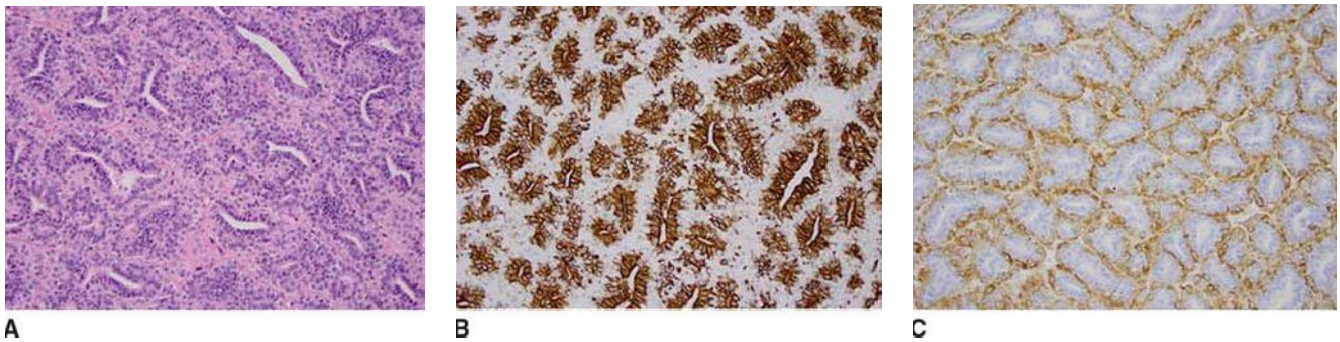


Figure 12.22 Epithelial–myoepithelial carcinoma. **A:** Duct-like structures with inner cuboidal cells with dense finely granular cytoplasm and outer polygonal cells with clear cytoplasm. **B:** Keratin IHC highlighting the inner layer of cells. **C:** Smooth muscle actin IHC highlighting the outer layer of cells (all photos 200×).

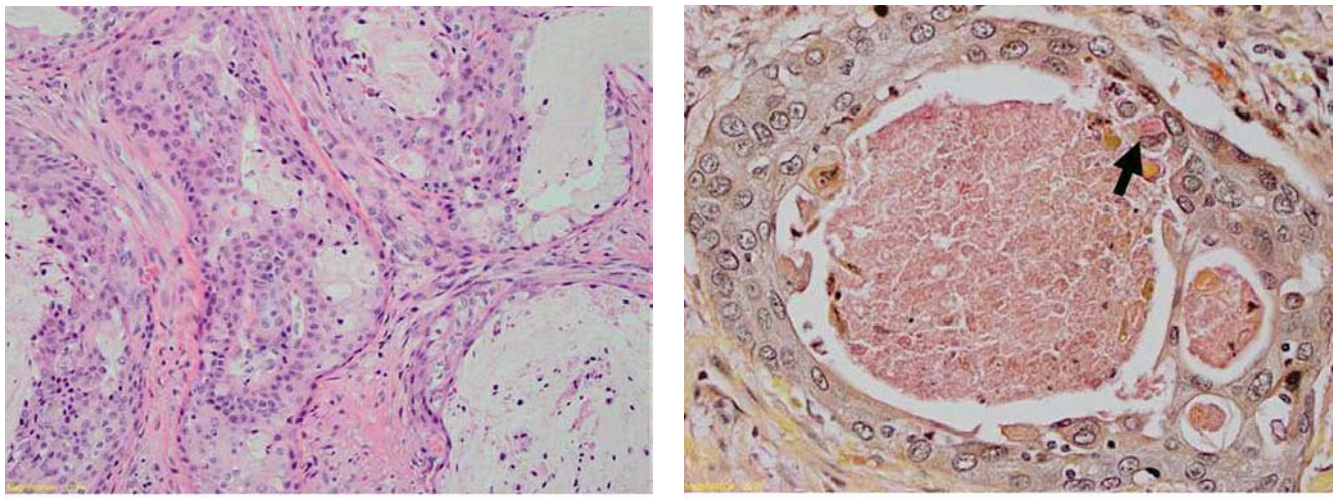


Figure 12.23 Mucoepidermoid carcinoma. **A:** Low grade, with squamoid (epidermoid) cells, mucus producing cells, and intermediate cells. The polygonal epidermoid cells and cuboidal intermediate cells predominate in this photo. Composition varies between tumors and even within a tumor (200×). **B:** High grade. There is necrosis in the middle of the photo, which is unusual in mucoepidermoid carcinoma. This mucin stain was performed to highlight rare mucus cells, one of which is evident at approximately 2 o'clock (*arrow*) (400×).

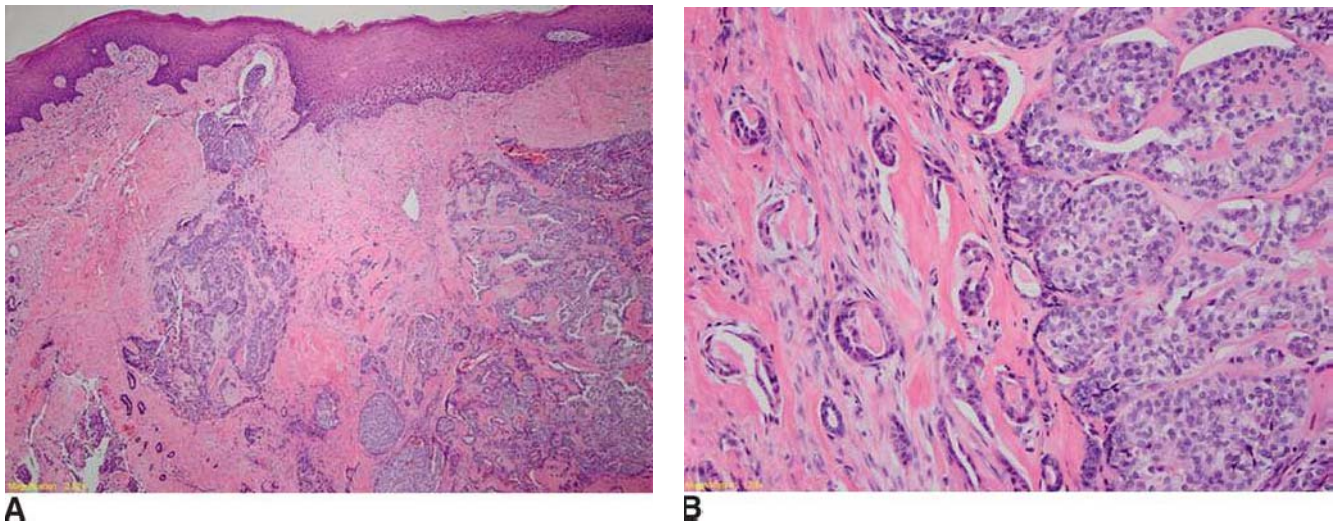


Figure 12.24 Polymorphous low-grade adenocarcinoma. **A:** Low power, showing infiltrative growth (40×). **B:** Demonstrates cytologic uniformity with small relatively bland cells. PLGA has morphologic variability: there are duct-like structures in panel A and more solid lobular growth in panel B. Other patterns include papillary and cribriform (200×).

Uncertain Histogenesis

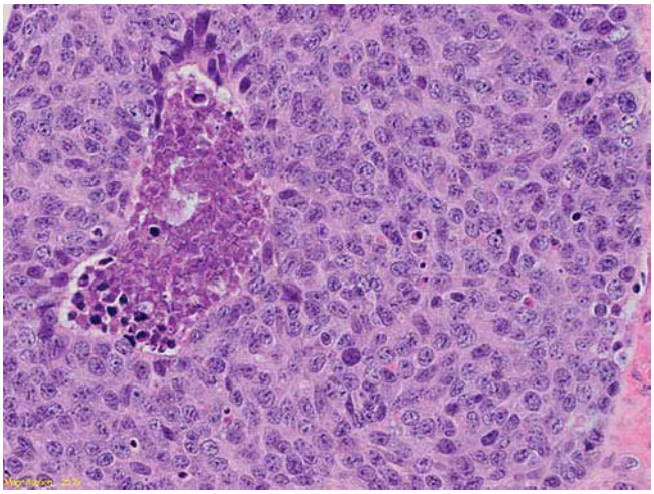


Figure 12.25 Sinonasal undifferentiated carcinoma, with sheets of medium-sized cells with scant cytoplasm. The nuclei have one or more prominent nucleoli. Tumor necrosis is evident, as are apoptotic cells (400×).

Dysplasia

Squamous mucosa is slowly but continuously replaced—with a gradual maturation of cells as they progress from the basement membrane to the surface. If this orderly transition is disrupted and less mature cells are present in the superficial layers of the mucosa, the tissue is said to be dysplastic. Dysplasia is defined as disordered growth with atypia (variations in size, shape, and nuclear appearance). The term is usually applied to changes within an epithelial lining. Dysplasia is by default a precancerous condition, though not all dysplastic lesions will progress to frank carcinoma. Dysplasia can represent a spectrum of changes between normal mucosa and invasive cancer. By convention, dysplasia is graded as mild, moderate, and severe. The risk of progression to malignancy does to some extent correlate with the grade of dysplasia, with the risk of severe dysplasia near 40% (46). Currently, there is no widely accepted grading system for head and neck dysplasia. As a result, significant inter- and intrarater variability exists (46–49). Despite the subjectivity, a general rule of thumb is that mild dysplasia occurs when there is minimal cytologic atypia confined to the lower third of the epithelium. Moderate dysplasia involves extension of the atypical changes into the middle third of the epithelium. In severe dysplasia, atypical changes extend into the top third of the epithelium and/or major cytologic atypia is present (48). When dysplasia involves the full thickness of the epithelium, it becomes known as a CIS. Invasive carcinoma is present when the basement membrane is breached by the disease.

Histologic Variants of Squamous Cell Carcinoma

Invasive SCC may be well, moderately, or poorly differentiated—depending upon the degree to which squamous cell morphology is maintained. It may be present as one of a variety of subtypes. Given the potential treatment and prognostic implications, three of these—spindle cell, basaloid, and verrucous carcinoma—merit particular attention.

Basaloid squamous (basosquamous) carcinoma is a high-grade variant of squamous carcinoma that is characterized by basaloid and squamous components. The basaloid cells tend to cluster at the periphery of the tumor while the squamous cell populations may be found near the center (50,51). Basosquamous carcinoma may involve any head and neck site, but it tends to be more common in the oropharynx, supraglottis, and hypopharynx. It is thought to be more aggressive than conventional SCC (46,50,52). However, a subset of these tumors are now believed to be related to the human papillomavirus (HPV) (51,53).

TABLE 12.1 HISTOCHEMICAL STAINS COMMONLY USED IN HEAD AND NECK PATHOLOGY

Histochemical Stain	Target	Otolaryngology Applications
Mucicarmine, Kreyberg, PAS	Intracellular mucin	Confirming adenocarcinoma:, Differentiating mucoepidermoid and squamous carcinoma
Gomori methenamine-silver	Fungal elements	Mucormycosis and actinomycosis
Acid-fast bacilli	Mycobacteria	Tuberculosis and atypical mycobacterial infections
Ziehl-Neelsen	Mycobacteria	Tuberculosis and atypical mycobacterial infections
Warthin-Starry Silver	Spirochetes, Bartonella	Syphilis Cat-scratch disease
Fontana-Masson	Melanin	Melanoma
Congo red	Amyloid	Amyloidosis

TABLE 12.2 IMMUNOHISTOCHEMICAL STAINS COMMONLY USED IN HEAD AND NECK PATHOLOGY

Stain Family	Specific Example	Positive	Examples/Uses
Keratins	Cam5.2; AE1-3; specific keratins (CK7, CK19 etc)	Epithelial cells	Carcinoma; Can sometimes be used to help determine site of origin (ex: colon cancer is CK7−/CK20+; breast Cancer is CK7+/CK20−)
Squamous	p63; CK5/6	Squamous cells	Confirm squamous differentiation in poorly differentiated carcinomas.
S-100	S-100	Neural crest derivatives; chondroid, fat and myoepithelial cells	Melanoma; schwannoma
HMB-45	HMB-45	Immature melanosomes	More specific than S-100 for melanoma; Also positive in angiolipoma, tuberous sclerosis and rarely carcinomas
Lymphoid markers	LCA (CD45); CD3; CD5; CD20; CD79a	White cells (LCA); T cells (CD3, CD5); B cells (CD20, CD79a)	Lymphoma
Actins	SMA; MSA	Smooth muscle/myoepithelial cells	Leiomyoma (SMA); rhabdomyosarcoma(MSA)
Vascular	FVIII, CD31	Endothelial cells, megakaryocytes, platelets	Hemangioma; hemangioendothelioma; confirmation of vascular invasion
Neuro-endocrine	NSE, chromogranin, synaptophysin, CD56	Neuroendocrine cells	Paragangliomas, carcinoid, small cell carcinoma
Neural	GFAP; CD57 (Leu-7)	Intermediate filaments (GFAP) and glycoproteins (CD57) of Schwann cells	Differentiate schwannoma from other spindle neoplasms
Cell proliferation Marker	Ki-67	Cells not in G0	Burkitt lymphoma
Tissue specific	TTF-1; thyroglobulin Calcitonin; Melan-A	Lung and thyroid (TTF-1); Thyroid Follicular Epithelium (thyroglobulin); Thyroid C-cells (Calcitonin); MART-1 antigen (Melan-A)	Confirm a primary thyroid or lung carcinoma. Confirm presence of medullary thyroid carcinoma. Confirm the diagnosis of melanoma (Melan-A)

Despite identical morphology, HPV positivity is indicative of a highly significant survival advantage when compared to HPV-negative basaloid squamous carcinoma (51).

Histologically, the spindle cell variant (sometimes referred to as carcinosarcoma) is a cytologically malignant proliferation of fusiform cells that are intimately associated with obvious elements of SCC. Confirmation of a squamous cell origin is typically made immunohistochemically. Spindle cell tumors are most often seen in the larynx—with the true vocal folds involved more often than the supraglottis (46). Though the body of literature pertaining to these tumors is somewhat limited, they are widely thought to be more aggressive than conventional SCC (46,52). Given the apparent negative prognostic implications, aggressive multimodal therapy is typically recommended.

Verrucous carcinomas, on the other hand, are low-grade malignancies. They are commonly identified in elderly patients and are named for their verrucous, or wart-like, appearance—both grossly and histologically. Given its appearance, a viral etiology has been proposed, though no definitive evidence has been uncovered to date. On light microscopy, these tumors appear as uniform groups of cells without significant dysplastic features. They demonstrate marked surface keratinization and broad pushing borders without evidence of infiltration (46). These lesions have a relatively indolent course, but can be locally destructive if left unattended. They are readily treated with surgical excision. Their principal import rests in the fact that verrucous carcinoma has long been considered to be a contraindication to radiotherapy. Early reports indicated that these tumors were not sufficiently radiosensitive and that they were prone to anaplastic transformation after definitive radiation therapy. Subsequent studies of larger and more controlled patient populations have failed to demonstrate any cases of anaplastic transformation. These studies did confirm that local control rates for verrucous carcinoma are better with surgery than with radiation. The ultimate local control and survival statistics after surgical salvage are comparable, however (54). In essence, the evidence seems to indicate that while this disease is most appropriately treated with surgery, it should not be considered a contraindication to radiotherapy.

Adverse Pathologic Features in Squamous Cell Carcinoma

Given the potential therapeutic implications, reporting of SCC should not only include a description of tumor grade and subtype but also a description of histologic features of known prognostic significance. We have already discussed resection margins and their significance in detail. However, the presence or absence of a number of other findings must be noted by the pathologist if a report is to be considered complete. Primary tumors should be evaluated for perineural and lymphovascular invasion. It has been repeatedly demonstrated that perineural spread is an independent risk factor for locoregional recurrence and mortality (55,56). This holds true even for minor (less than 1-mm diameter) nerve involvement. It is therefore imperative that the pathologist pay careful attention to this feature and make the appropriate comments in his or her report. Though somewhat less pronounced than perineural invasion, lymphovascular invasion also has deleterious effects upon locoregional control and survival (56). The depth of tumor invasion also appears to bear prognostic significance in oral cavity cancers. Depth of invasion has been correlated to an increased risk for occult nodal disease in early-stage tongue and floor-of-mouth cancer (57,58). A 2009 meta-analysis confirmed this and concluded that early-stage tumors greater than 4-mm-thick require elective treatment of the neck (59).

In recognizing the importance of perineural spread, lymphovascular invasion, and tumor thickness, CAP now recommends that they be included in all reports. Unfortunately, as evidenced in a recent study by Goodman and colleagues, a majority of pathologists still do not comment on depth of invasion or mode of spread (56). Reporting of this information should be the rule rather than the exception. If these features are not described, it is appropriate to ask the pathologist to review the case and issue an addendum. It is also an opportunity to request that all reports be updated to reflect CAP standards.

Identification of Human Papillomavirus–Related Squamous Cell Carcinoma

HPV-related oropharyngeal cancers are increasing in incidence at an alarming rate (60). Despite the fact that they are squamous carcinomas, HPV-related cancers are clinicopathologically unique from conventional SCC. Patients with HPV-related SCC are typically younger, they have distinct risk factor profiles, and their prognosis is improved when compared to cohorts with HPV-negative tumors (61–63). The prognostic advantages of HPV-related SCC are limited to oropharyngeal tumors and have not been consistently demonstrated for other subsites (64). The biology and clinical behavior of these tumors are described in detail elsewhere in this text. HPV now accounts for the largest percentage of new head and neck cancers in the United States and it is important to discuss some of the pathologic features that assist in making the diagnosis of an HPV-related SCC.

HPV is a DNA virus that preferentially infects basal epithelia. Several high-risk subtypes have been identified, but HPV16 is the most frequently implicated in head and neck cancers (63). In the oropharynx, it most likely gains entry via the specialized epithelium located at the base of tonsillar crypts (65). Once inside the cell, the viral DNA integrates with the host and encodes a number of proteins. Tumorigenesis is largely dependent upon the production of the E6 and E7 viral proteins. These structures are capable of inactivating the tumor suppressors p53 and pRB and, consequently, promoting unchecked cell growth (66).

While many HPV-related tumors may appear similar to conventional SCC on light microscopy, the evidence suggests that these are more likely to be poorly differentiated or basaloid in nature (61,65,67). Poorly differentiated and basaloid SCC are also observed in HPV-negative cancers, and the presence of these variants are not sufficient to establish HPV as a cause. As noted above, when there is overlap of light microscopic features, special stains and tests are often necessary to confirm a tumor's origin, or, in this case, its etiology and prognosis. A number of assays for the detection of HPV are now commercially available. The gold standard remains polymerase chain reaction (PCR). PCR is highly sensitive and specific and can detect a single copy of viral DNA. This technique is of limited clinical utility due to its high cost and the lack of widespread availability (68). Alternative methods include *in situ* hybridization (ISH) for HPV DNA and immunohistochemical staining for p16, a protein that is upregulated by viral E6 and is widely considered to be a surrogate for the presence of HPV infection. Both methods are widely available, relatively inexpensive, and easily interpreted. p16 is highly sensitive for the detection of HPV, but lacks specificity. HPV ISH, on the other hand, is a very specific test that lacks sensitivity (63,65,68,69). Using the area under receiver operating curves as a measure of overall test performance, Schlect et al. (69) found that p16 IHC was superior to ISH in confirming the presence of HPV in SCC. Interestingly, the authors also found that p16 staining intensity was inversely correlated to the degree of keratinization on light microscopy. Knowledge of an oropharyngeal cancer patient's HPV status carries with it tremendous prognostic and counseling implications. Ultimately, it may also affect management decisions. It is thus advocated that all oropharyngeal carcinomas be screened using one of the above-mentioned methods—with preference given to p16 IHC if it is available.

HIGHLIGHTS

- Communication between the otolaryngologist and pathologist is of paramount importance.
- Preferred biopsy techniques of epithelial lesions include incisional, excisional, and punch. Shave biopsies should be avoided, especially in pigmented lesions.
- FNA is a safe, well-tolerated, useful technique of sampling thyroid and salivary gland nodules, as well as enlarged lymph nodes. Its accuracy and diagnostic yield may be improved using image guidance.
- Margin assessment is most accurate when there is a well-orchestrated handoff between the surgeon and the pathology team. Surgeon-directed specimen orientation and inking are critical to this process.
- Intraoperative frozen section provides accurate information, but its use should be restricted to situations where the results will change operative management.
- Reporting of head and neck malignancies should be standardized, with explicit attention to the tumor subtype and the presence or absence of adverse pathologic features.

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Neurology in Otolaryngology

13

Rachel E. Roditi *Benjamin T. Crane*

Many neurologic disorders present with symptoms in the head and neck region. Thus, it is important for the general otolaryngologist to recognize these neurologic disorders in order to initiate management or arrange for proper and prompt referral to the appropriate physician. Further, since otolaryngologists are most familiar with head and neck anatomy and physiology, they may play an active role in the multidisciplinary care of patients with primary neurologic disorders. Thorough understanding of the cranial nerves, neurologic examination, and the neurologic diseases frequently presenting with head and neck symptomatology is of utmost importance. A screening neurologic examination is helpful in detection of neurologic diagnoses affecting the head and neck. This provides a quick method for evaluating mental status, cranial nerves, the motor system, gait, balance and coordination, reflexes, and sensation. This chapter addresses many of the most common and important issues in neurology for the otolaryngologist to understand.

ANATOMY AND CRANIAL NERVE FUNCTIONS

When neurologic diseases involve the head and neck region, cranial nerve deficits are important to recognize. Understanding of cranial nerve anatomy and function, as well as the ability to perform a proper cranial nerve examination is key (Figs. 13.1 and 13.2). Table 13.1 outlines the cranial nerves and examination findings.

CEREBROVASCULAR DISEASE

Abnormalities of blood flow to the central nervous system (CNS) are a common cause of morbidity and mortality across the world. In the United States, cerebrovascular disease is the third leading cause of death and the primary cause of long-term disability (1). Stroke can be either hemorrhagic or ischemic in nature, with ischemic strokes being far more common and making up approximately 87% of all cerebrovascular events (1). Clinical presentations and functional deficits can be quite variable depending on the area of the CNS involved. Permanent losses typically result from complete arterial occlusion or from hemorrhagic infarction. Transient effects may accompany arterial stenosis, vascular spasm, inadequate perfusion pressure, or reversed arterial flow with shunting such as subclavian steal syndrome.

The blood supply to the inner ear, brainstem, and cerebellum arises from the vertebrobasilar system, thus vertigo is a common manifestation of cerebrovascular disease and can be caused by occlusion of any of the three major circumferential branches of the vertebral or basilar arteries: the posterior inferior cerebellar artery (PICA), the anterior inferior cerebellar artery (AICA), and the superior cerebellar artery (SCA) (Fig. 13.3).

Vertebrobasilar Insufficiency

Vertebrobasilar insufficiency is a significant cause of vertigo in individuals over age 65 (2). Vertigo due to vertebrobasilar insufficiency has a sudden onset, usually lasts several minutes, and is often associated with nausea and vomiting. Because of the presence of vertigo symptoms, the otolaryngologist may be called upon to make this diagnosis; however, vertigo symptoms alone are extremely uncommon and occur in less than 1% of patients (3). Usually, multiple symptoms suggestive of central etiology are present which often include headache, diplopia, ataxia, numbness, weakness, or oropharyngeal dysfunction (4). Repeated episodes of vertigo without other symptoms suggest another diagnosis.

Atherosclerosis of the subclavian, vertebral, or basilar arteries is often the underlying cause of vertebrobasilar insufficiency. The distribution of atherosclerosis differs according to race and gender (5). European men tend to have

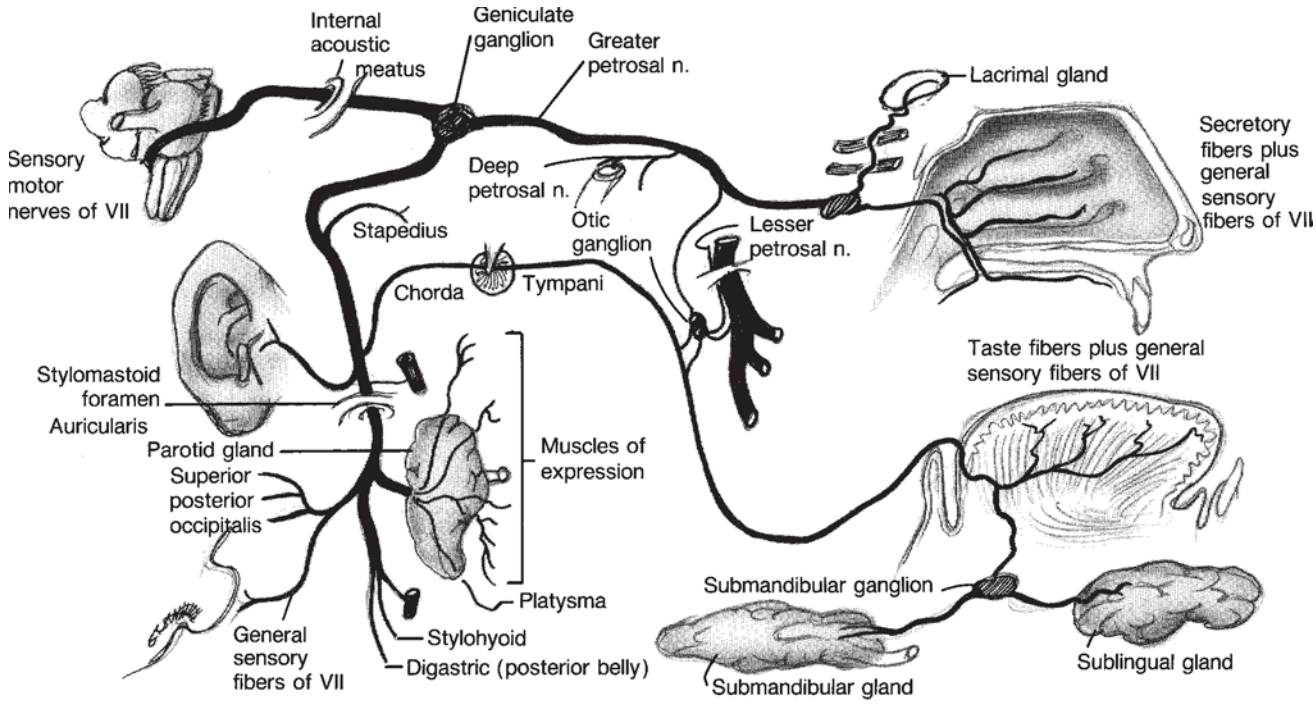


Figure 13.1 Facial nerve.

atherosclerosis at the origin of the vertebral arteries near the subclavian. Intercranial large-artery atherosclerosis is more common among African Americans, Asians, and women. Hypertension increases the risk of lipohyalinotic thickening of these vessels, which increases the risk of infarction.

If a patient is suspected to have had a stroke, a computed tomography (CT) scan without IV contrast should be ordered to rule out the possibility of a hemorrhagic event. Patients with ischemic strokes who present within three hours of the onset of symptoms should be considered for administration of intravenous tissue-type plasminogen activator (6). However, recommendations in this area are rapidly evolving, and a neurologist familiar with stroke should treat acute patients.

In most patients with nonacute presentation, treatment consists of controlling risk factors such as diabetes, hypertension, and hyperlipidemia. In patients with symptomatic intracranial stenosis of 50% to 99%, aspirin is the treatment of choice. Anticoagulation with warfarin should be considered if the patient has previously had an embolic stroke, which is cardiac in origin (2). Stenting of vertebral artery stenosis has been attempted with mixed results. Endarterectomy for extracranial vertebral artery disease has also been successfully performed, but indications for such procedures are still evolving.

Lateral Medullary Syndrome

Lateral medullary syndrome (Wallenberg syndrome) is caused by an infarction involving a wedge of the dorsolateral medulla just posterior to the olive (Fig. 13.4). The syndrome usually results from occlusion of the ipsilateral vertebral artery and rarely from occlusion of the PICA (7). Classic presentation includes sensory deficits affecting the trunk and extremities on the opposite side of the infarct and sensory and motor deficits affecting the face and cranial nerves ipsilateral to the infarct. Characteristic symptoms include vertigo, ipsilateral facial pain, diplopia, dysphagia, and dysphonia. Neurologic examination may reveal an ipsilateral Horner syndrome, ipsilateral dysmetria, dysrhythmia, spontaneous nystagmus, and contralateral loss of pain and temperature sensation. Hearing is not preserved because the lesion is caudal to the cochlear nerve entry zone and cochlear nuclei.

Lateral Pontomedullary Syndrome

Occlusion of the AICA results in infarction of the dorsolateral pontomedullary region and the inferolateral cerebellum (8). The middle cerebellar peduncle is typically the core of the affected territory (Fig. 13.5). Because the labyrinthine artery originates from the AICA in 80% of patients, infarction of the membranous labyrinth is a common accompaniment. Severe vertigo, nausea, and vomiting are common initial symptoms. Other symptoms include ipsilateral hearing loss, tinnitus, facial paralysis, and cerebellar asynergy. Spontaneous nystagmus is common. Contralateral loss of pain and temperature sensation may be caused by crossed spinothalamic fibers. Onset of symptoms is acute followed by gradual improvement. Vertigo may persist longer than would be expected from a pure vestibular lesion due to damage of the central compensation mechanisms.

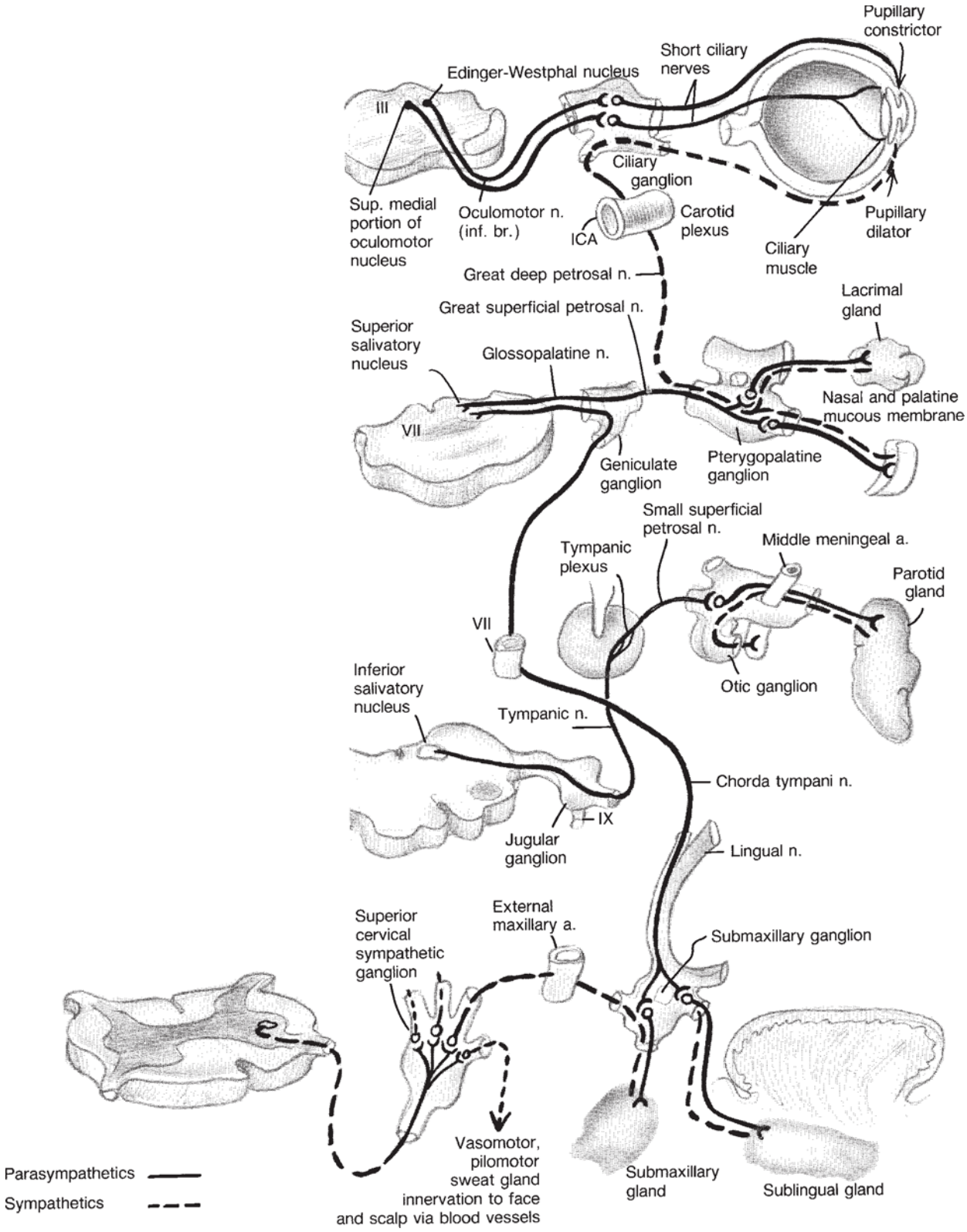


Figure 13.2 Cranial nerve autonomic ganglia. The parasympathetic nervous system (*solid lines*) has ganglia close to the structure being innervated. The sympathetic nervous system (*dashed lines*) originates from three cervical ganglia. The superior cervical ganglion communicates with cranial nerves IX, X, and XII supplying the pharyngeal plexus, carotid sinus, and carotid body. The middle cervical ganglion is often small or absent. The inferior cervical ganglion is often fused with the first thoracic ganglion to form the stellate ganglion to provide sympathetic input to the upper limb.

TABLE 13.1 CRANIAL NERVES AND RELATED CLINICAL FINDINGS

Cranial Nerve	Clinical Relevance	Typical Lesion	Abnormal Findings
I	Smell	Fracture of cribriform	Anosmia, CSF leak.
II	Vision	Fracture involving optic canal	Visual field defect
III	Ocular motility	Cavernous sinus thrombosis	Dilated pupil, ptosis, eye turns down and out
IV	Superior oblique innervation	Damaged cutting of the tentorium during middle fossa approach to large tumor	Inability to look down and in
V	Facial Sensation Motor to muscles of mastication (V3)	Pressure on trigeminal ganglion from intracranial tumor	Loss of pain and touch sensation. Deviation of mandible to the side of the lesion when it is opened.
VI	Abduction of the eye	Cavernous sinus thrombosis	Diplopia, failure of eye to move laterally
VII	Facial motion Taste sensation to anterior 2/3 of the tongue.	Facial laceration Bell palsy Fracture of temporal bone	Paralysis of facial muscles As above + loss of taste
VIII	Hearing and Balance	Vestibular schwannoma	Unilateral hearing loss, tinnitus, loss of balance function
IX	Taste to posterior tongue, palate elevation	Brain stem lesion	Loss of taste, palate sensation, and elevation.
X	Parasympathetics, Vocal cord mobility	Injury during thyroidectomy	Hoarse voice, aspiration, vocal cord paralysis
XI	Lifting of the shoulder	Injury during neck dissection	Paralysis of trapezius, poor shoulder elevation
XII	Protrusion of the tongue	Tumor involving floor of mouth	Tongue deviates toward the side of the lesion, dysarthria.

Midbrain Syndromes

Occlusion of the posterior cerebral artery (PCA) or its more distant branches can result in several brainstem syndromes that may present with cranial neuropathies (Fig. 13.6). *Paramedian midbrain syndrome (Benedikt syndrome)* involves the oculomotor fascicle, red nucleus, medial lemniscus, and dentatothalamic tract. An ipsilateral oculomotor nerve paresis with contralateral chorea or tremor secondary to red nucleus involvement is seen. *Weber syndrome* similarly affects the oculomotor fascicle, but also involves the medial midbrain. Here, penetrating branches of the PCA supplying the cerebral peduncle are affected, leading to defects in the corticospinal and

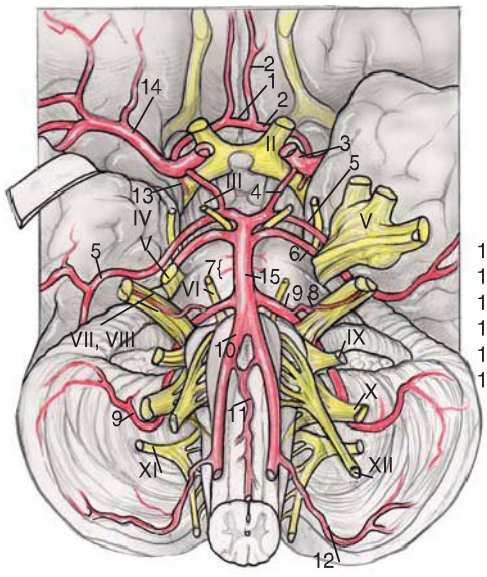
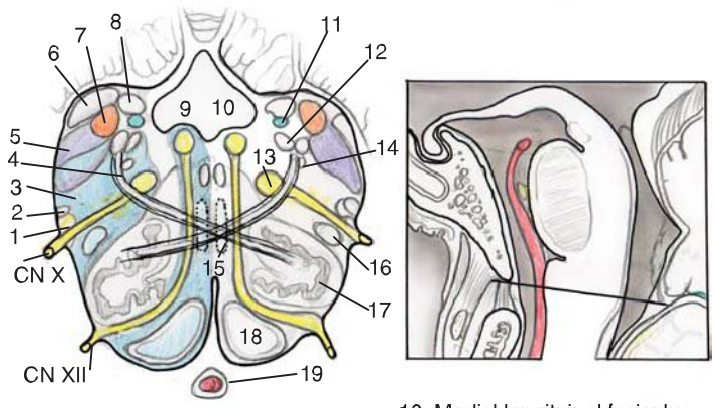


Figure 13.3 The blood vessels supplying the brain. The brainstem is supplied by branches of the vertebral arteries and basilar artery. Note that while this figure shows the internal auditory artery arising directly from the basilar artery, it is commonly a branch off of the anterior inferior cerebellar artery (AICA) instead. (Adapted from Kandel ER, Schwartz JH, Jessell TM. *Principles of neural science*. New York: McGraw-Hill, 2000:1303.).



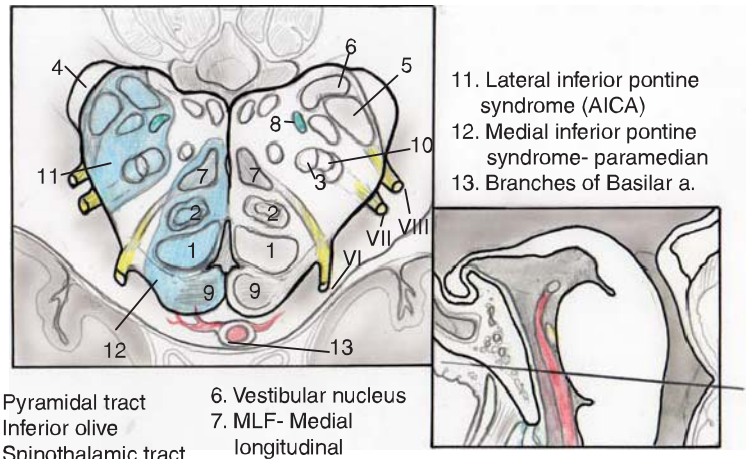
1. Dorsal spinocerebellar tract
2. Ventral spinocerebellar tract
3. Lateral medullary syndrome
4. Olivocerebellar fibers
5. Spinocerebellar tract
6. Inferior cerebral peduncle
7. Lateral Cuneate nucleus
8. Vestibular nucelus
9. Nucelus of CN XII
10. Medial longituinal fasiculus
11. Tractus solitarius
12. Descending tract CN V
13. Nucleus ambiguous
14. Descending sympathetic tract
15. Medial lemniscus
16. Ventral spinocerebellar tract
17. Inferior olive
18. Pyramid

Figure 13.4 Medulla cross-section with anatomic structures labeled on the right and vascular lesions on the left. (Adapted from Kandel ER, Schwartz JH, Jessell TM. *Principles of neural science*. New York: McGraw-Hill, 2000:1303.)

corticobulbar tracts, which manifest as contralateral hemiparesis. Dorsal midbrain infarction leads to *Parinaud syndrome* resulting in a tetrad of findings: (a) loss of upward gaze (with loss of smooth pursuit and saccades but with vestibuloocular reflex preservation), (b) large pupils with loss of light reflex, (c) convergence–retraction nystagmus, and (d) lid retraction. Parinaud syndrome is due to lesions affecting the posterior commissure and pretectal region, and can often be identified in an asymptomatic patient on physical examination.

Cerebellar Infarction

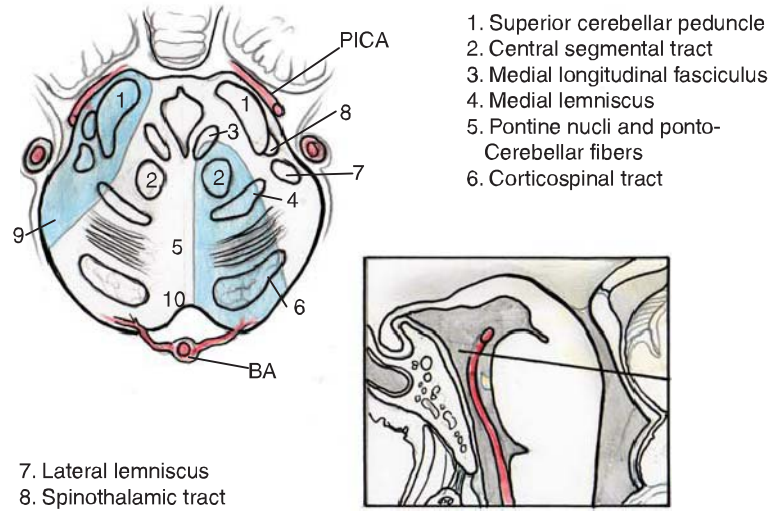
Initial symptoms of cerebellar infarction are often nonspecific and many include severe vertigo, vomiting, and ataxia (9). This may be caused by occlusion of the vertebral artery, the posteroinferior cerebellar artery, the anterior inferocerebellar artery, or the SCA. Lack of typical brainstem signs may cause an incorrect diagnosis of an acute peripheral labyrinthine disorder. The key to the diagnosis is the presence of prominent cerebellar signs such as gait ataxia and paretic gaze nystagmus. An early CT scan will often miss posterior fossa ischemia. The diagnostic procedure of choice is magnetic resonance imaging (MRI, Fig. 13.7). After a latent interval of 24 to 96 hours, some patients develop progressive brainstem dysfunction caused by compression by a swelling cerebellum. Progression to quadriplegia, coma, and death may follow, and early surgical decompression should be considered.



11. Lateral inferior pontine syndrome (AICA)
12. Medial inferior pontine syndrome- paramedian
13. Branches of Basilar a.

1. Pyramidal tract
2. Inferior olive
3. Spinothalamic tract
4. Inferior cerebellar peduncle
5. Dorsal cochlear nucleus
6. Vestibular nucleus
7. MLF- Medial longitudinal fasciculus
8. Solitary tract and nucleus
9. Pontine nuclei and ponticerebellar fibers
10. Spinal tract and nucelus of CN V

Figure 13.5 Lower pons cross-section with anatomical structures labeled on the right and vascular lesions on the left. (Adapted from Kandel ER, Schwartz JH, Jessell TM. *Principles of neural science*. New York: McGraw-Hill, 2000:1303.).



1. Superior cerebellar peduncle
2. Central segmental tract
3. Medial longitudinal fasciculus
4. Medial lemniscus
5. Pontine nuclei and ponto-Cerebellar fibers
6. Corticospinal tract
7. Lateral lemniscus
8. Spinothalamic tract
9. Lateral superior pontine syndrome
10. Medial superior pontine syndrome

Figure 13.6 Upper pons cross-section with anatomic structures labeled on the right and vascular lesions on the left. (Adapted from Kandel ER, Schwartz JH, Jessell TM. *Principles of neural science*. New York: McGraw-Hill, 2000:1303.)

Cerebellar Hemorrhage

Hemorrhage into the cerebellum causes neurologic symptoms that often rapidly progress to coma and death (10). The initial symptoms include severe vertigo, vomiting, and ataxia. Similar to cerebellar infarction, brainstem signs may not initially be present, which may cause the condition to be confused with a peripheral vestibular problem. Rapid diagnosis can be made with CT or MRI. Mortality with this condition remains near 25%, with a poor neurologic outcome in many who survive (11). Better initial neurologic status at presentation is highly correlated with a favorable eventual outcome. The value and indications for surgical intervention remain controversial and likely depend on the size and location of the hematoma as well as the patient's symptoms (12).



Figure 13.7 Cerebellar infarction on T2 MRI.

Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) frequently occurs in young and middle-aged adults. Eighty-five percent are caused by aneurysms, most commonly saccular (berry) aneurysm rupture within the Circle of Willis (13,14). Cigarette smoking, age, hypertension, and genetic factors have all been associated with increased risk. Most cases occur before age 55. Presenting symptoms include a sudden explosive headache ("worst headache of one's life"), nuchal rigidity, decreased consciousness, photophobia, meningismus, nausea, and vomiting. The fatality rate is near 50% with many dying prior to arrival at the hospital (14), The seriousness of the condition necessitates a high clinical suspicion to ensure rapid diagnosis and management. Early CT scan is the diagnostic test of choice and may detect subarachnoid blood in 95% of patients if performed within 24 hours from time of rupture (15). If CT is negative and clinical suspicion is high, lumbar puncture should be pursued. Cerebrospinal fluid (CSF) analysis classically shows xanthochromia. If SAH is present, cerebral angiography should be completed with management focused on eliminating the aneurysm from the circulation, which is often addressed using intravascular techniques. Subarachnoid blood is associated with high risk of seizure development, and early seizure prophylaxis should be considered.

Evaluation and Management

Acute spontaneous vertigo is a frequent reason for referral to an otolaryngologist. The possibility of a stroke must be considered, particularly if the patient has vascular

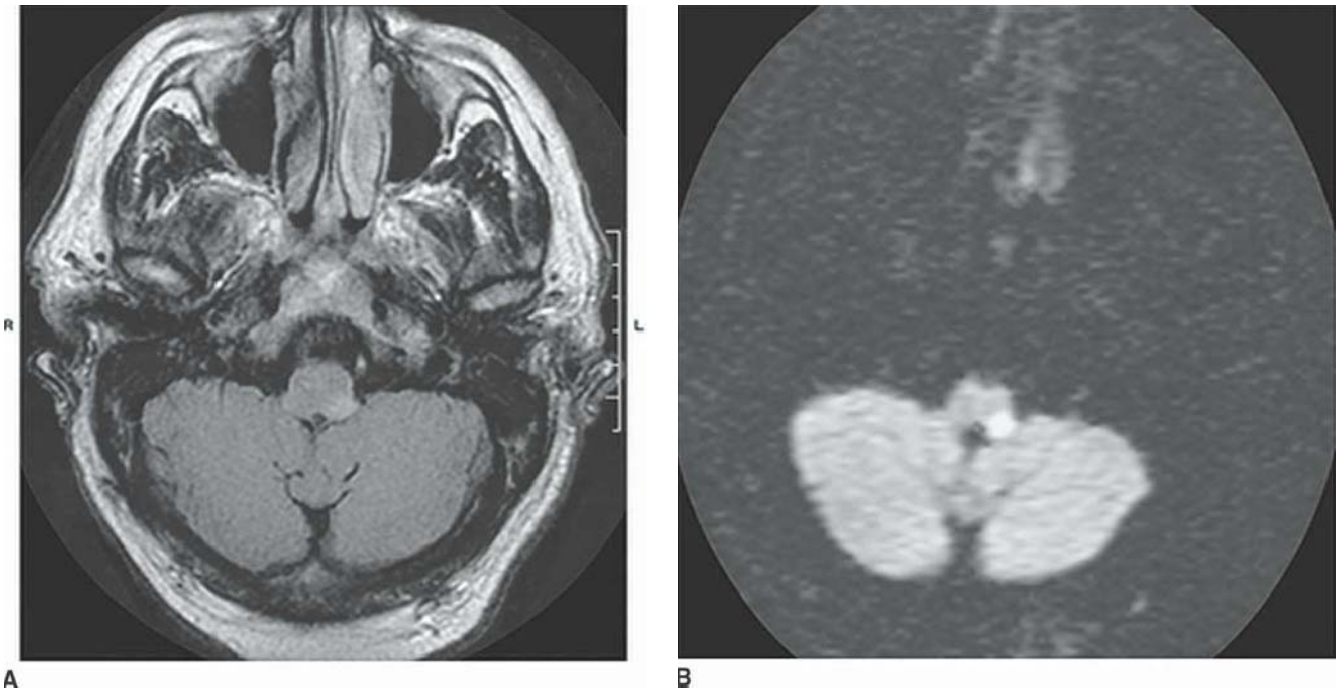


Figure 13.8 MRI of a lateral medullary infarction. **A:** The FLAIR. **B:** Diffusion-weighted images. Both show changes of an acute infarction involving the left dorsolateral medulla. (Courtesy of KD Flemming.)

risk factors or other cranial neuropathies. If the history and examination suggest a vascular disorder, immediate neuroimaging is recommended. CT of the brain without contrast is often the first imaging test because it is widely available and shows intraparenchymal or subarachnoid blood. Hemorrhage can mimic any of the ischemic stroke syndromes and must be excluded with thin-section CT through the cerebellum, brainstem, and fourth ventricle. MRI and MRA are superior to CT for visualizing the vertebrobasilar vessels and their supplied structures since CT is often normal with cerebellar or brainstem infarction. MRI, on the other hand, detects ischemic strokes in the brainstem and cerebellum early on, as well as edema. Diffusion weighted imaging with MRI can now detect infarcts within the first hour of ischemia (Fig. 13.8). MRA has begun to replace conventional angiography in certain circumstances. Vertebral artery dissection and vertebral or basilar stenosis/occlusion can generally be identified with MRA of the cervical vessels (Fig. 13.9).

MIGRAINE

Migraine is understood by the general public to be a headache disorder but the symptoms commonly extend beyond headache. Headaches are usually recurrent and associated with nausea, vomiting, hypersensitivity to light, sound, and smell (16). Neurologic aura is present in a third of migraine patients. Dizziness and pain in the sinus distribution are frequent presentations, making migraine diagnosis important to otolaryngologists. It affects 16% of the population but is much more common in women than men (17). In the prepubertal period, boys with migraine slightly outnumber girls, but at puberty, migraine decreases in boys and increases in girls so that a 2:1 female preponderance is established by adulthood. Migraine typically begins in young adulthood with symptoms developing after age 40 in only 10% of sufferers.

The diagnosis and classification of migraine and other headache disorders has been a controversial issue. The most recent effort of the Headache Classification Committee of the International Headache Society (IHS) (16) sets criteria that allow meaningful comparisons of patients between centers. The IHS classifies the most common type of migraine disorder as migraine with and without aura (Table 13.2). There are also other classified types of migraine, but this is out of the scope of this chapter as they will only rarely be encountered by the otolaryngologist.

Vertigo manifestations are common in migraine patients, and classically are characterized by chronic low-grade dizziness. The definition of migrainous vertigo has also been controversial. Neuhauser et al. (18) proposed criteria for definite migrainous vertigo as (a) episodic vestibular symptoms (rotational vertigo, other illusory self or object motion, positional vertigo, head motion intolerance) of at least moderate severity, (b) migraine according to IHS criteria, (c) at least one of the following migrainous symptoms during at least two vertiginous attacks: migrainous headache, photophobia, phonophobia, visual or other auras, and (d) other causes ruled out by appropriate investigations. Probable migrainous vertigo was chosen for patients

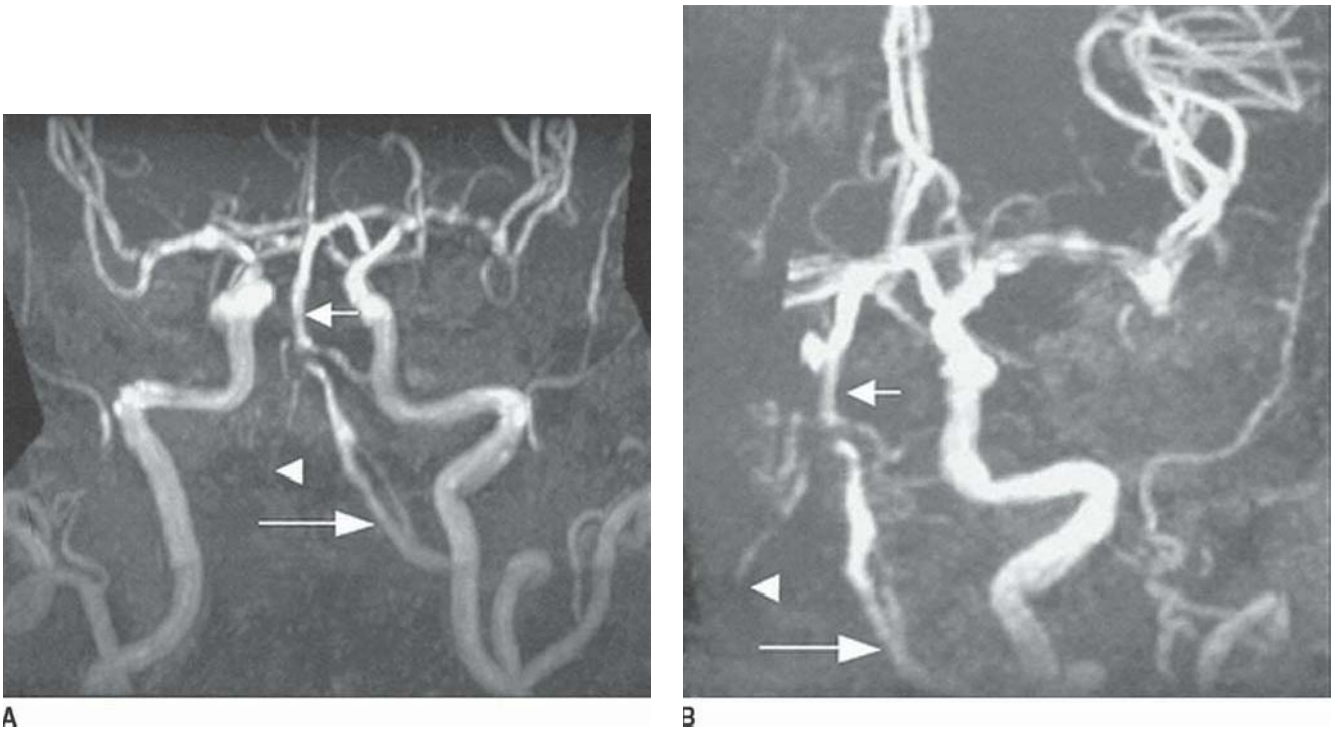


Figure 13.9 **A:** Frontal. **B:** Lateral. Magnetic resonance angiogram showing a severe stenosis at the junction of the left vertebral artery (*long arrow*) and the basilar artery (*short arrow*). The right distal vertebral artery is also occluded (*arrowhead*). (From Lee H. Sudden bilateral simultaneous deafness with vertigo as a sole manifestation of vertebrobasilar insufficiency. *J Neurol Neurosurg Psychiatry* 2003;74:540.)

who did not meet definite criteria but were still believed to have migrainous vertigo as the most likely diagnosis. This requires criteria a and d from the list, plus at least one of the following: migraine according to IHS criteria, migrainous symptoms during vertigo, migraine-specific precipitants of vertigo (e.g., specific foods, sleep irregularities, hormonal changes), or response to antimigraine drugs.

TABLE 13.2 INTERNATIONAL HEADACHE SOCIETY CLASSIFICATION OF MIGRAINE

Migraine without aura

A. At least 5 attacks fulfilling B–D.
B. Headache lasting 4–72 h when untreated.
C. Headache has at least two of the following characteristics: unilateral location, pulsating quality, moderate or severe intensity, aggravation by physical activity.
D. During the headache either nausea and vomiting or photophobia
E. Not attributed to another disorder

Typical aura with migraine headache

A. At least two attacks fulfilling B–D.
B. Fully reversible visual, sensory, or aphasic aura symptoms with no motor weakness
C. At least two of the following: homonymous positive features or unilateral sensory symptoms, at least one symptom develops gradually over more than 5 min, each symptom lasts 5–60 min.
D. Headache follows aura with a free interval of <60 min.
E. Not attributed to another disorder

Vestibular Symptoms

Nonspecific dizziness occurs frequently in patients with either tension or migraine headaches and in itself, does not differentiate between the two groups, although dizziness is more common and severe in migraine sufferers.

Vertigo is extremely common in patients with migraine and occurs in at least a quarter of patients, much higher than the less than 10% prevalence in patients with tension headache. Awareness of the temporal relationship of vertiginous spells to migraine headaches is important. Vertigo does not usually present as an aura immediately preceding the headache. Rather, vertigo is often present without headache symptoms, even though the patients usually have a history of migraine headache.

Motion sickness is common in migraine patients (17,19). Severe motion sickness is approximately five times more common in patients who suffer from migraine. Adult-onset motion sickness should be considered migraine until proven otherwise. A subset of migraine patients experience disabling motion sickness with the need to minimize their head motion, which limits their daily activities. Vestibular stimulation can trigger migraine headaches. Caloric responses in these patients tend to be symmetric and very brisk, often culminating in emesis. If treatment

provides a dramatic response, patients are often surprised at how much they have restricted their lifestyle. Neither the patient nor their physician typically suspects that migraine had any relationship to the other symptoms since patients often only discuss the vestibular symptoms and ignore or discount any symptoms of the underlying problem. Prophylactic migraine therapy often yields dramatic improvement.

Auditory Symptoms

Migraine patients are frequently sensitive to loud sounds, which may trigger or exacerbate headache or vertigo symptoms. Auditory symptoms such as hearing loss and tinnitus are occasionally present and are more prominent in patients with basilar migraine.

Migraine Associated with Neurologic Symptoms

The coexistence of migraine with neurologic symptoms suggestive of brainstem pathology defines basilar migraine (20), which is due to presumed ischemia in the distribution of the basilar artery (21). This subtype of migraine is similar to classic migraine in that it consists of an aura followed by a severe headache; however, vertigo symptoms are usually present.

Migraine can be diagnosed in the absence of headaches. Patients sometimes develop typical headaches later in life, or have auras that are only intermittently related to headaches. A history of motion sickness, premenstrual clustering of attacks, or headaches associated with some attacks is frequently present. Personal or family history of migraine is also helpful in diagnosing these patients.

Etiology

Current theory of the genesis of migraine implicates a neural origin with spreading of depression activity (22), although the neurophysiology is far from completely understood.

Family history of migraine is present in approximately 40% to 90% of affected individuals. When migraine patients with and without aura are examined separately, patients who have migraine with aura are more likely to have affected family members. In twin studies, the concordance of migraine is only 10% to 34% depending on the country, suggesting that both genetic and environmental factors play a role (23).

Familial hemiplegic migraine (FHM) is a rare type of migraine affecting only 0.01% of the general population (24). However, the underlying cellular cause is relatively well understood. Unlike most migraine, FHM has a clear autosomal dominant pattern of inheritance. So far, mutations have been found in three different genes that determine neuronal excitability.

Management

Migraine treatment has traditionally been dominated by management of headache symptoms and can be divided into symptomatic and prophylactic management strategies. Symptomatic interventions are useful in ameliorating the acute attack, while prophylactic interventions are designed to reduce the frequency or severity of attacks. Symptomatic management includes analgesics, antiemetics, antivertiginous drugs, sedatives, and vasoconstrictors. In many patients, over-the-counter analgesics (such as ibuprofen, aspirin, or acetaminophen) and rest are sufficient to relieve headache symptoms.

Nutrition may play a significant role in the frequency and severity of migraine headaches and migraine-associated dizziness. Riboflavin (vitamin B_2) and high-dose magnesium have been shown to have a therapeutic effect on migraine. Suggested mechanisms include inhibiting platelet aggregation, counteracting vasospasm, stabilizing cell membranes, and anti-inflammatory effects.

Food sensitivity may be a migraine trigger in a significant number of patients with migraine symptoms (25). Although some patients have observed that consuming a certain food will reliably provoke a headache, the effect of diet is often more subtle. Foods, which should be avoided include red wine, aged cheeses, beer, chocolate, caffeine, and yogurt (26). Dietary modification may be considered as first-line therapy for migraine prophylaxis (Fig. 13.10.)

Vestibular migraine symptoms are often continuous and not directly related to the headache symptoms; however, treatment of vestibular migraine mirrors that of traditional migraine prophylaxis. Because migraine-associated dizziness is often much more frequent than the headaches, symptomatic treatment effective for headaches is usually not effective for dizziness.

Sumatriptan (Imitrex), a 5HT1D receptor-agonist, has become the principal drug to abort severe migraine headache. Initial trials indicate that in 90% of cases the drug effectively aborts migraine headache symptoms within an hour of onset when used subcutaneously and 70% to 85% may be aborted if used within 2 hours. Despite efficacy in relief of early migraine headaches, breakthrough is common and the drug has limited efficacy for concurrent vestibular symptoms.

Propranolol (Inderal) is the most common drug for preventing migraine episodes. The medication is contraindicated in patients with asthma, congestive heart failure, peripheral vascular disease, diabetes, and hypothyroidism. Principal side effects include fatigue, lethargy, and orthostasis. Side effects are minimized by slowly increasing the dose from a low starting level. Because of these side effects, the medication is poorly tolerated in patients who do not have preexisting hypertension.

Tricyclic antidepressants are currently the mainstay of migraine prophylaxis. Amitriptyline is perhaps the most studied drug in this category with several studies showing

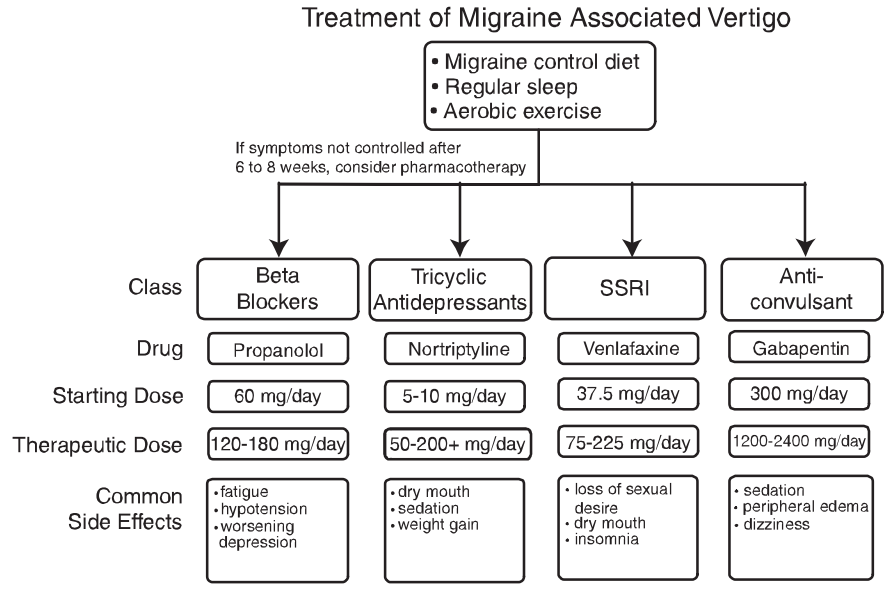


Figure 13.10 Flowchart of suggested migraine treatment. Lifestyle modification is usually a good first option since it is not associated with side effects and will provide symptomatic improvement in most patients. Pharmacotherapy should be considered if more conservative measures fail.

its efficacy (27). However, the newer drug nortriptyline is usually better tolerated due to the milder side effect profile. Starting doses are usually 10 to 25 mg, which is usually given at bedtime to minimize sedation and anticholinergic activity. Weight gain is a side effect that limits compliance with therapy in some patients. Therapeutic doses are usually 50 to 100 mg, with some patients who also suffer from depressive symptoms requiring doses of up to 200 mg.

Use of selective serotonin reuptake inhibitors (SSRIs) for treatment of migraine remains controversial. However, in patients with chronic subjective dizziness as their primary symptom, SSRIs have some efficacy (28).

Gabapentin (Neurontin) has been effective at dosages of 1,200 to 2,400 mg/d (29), which is usually divided into three daily doses. Dizziness, peripheral edema, and somnolence are common side effects, which limit their use.

NEUROMUSCULAR DISORDERS

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease of undetermined etiology. In the United States, ALS is often referred to as Lou Gehrig disease after the well-known baseball player who was diagnosed with the disease in 1939. Gehrig had been known as the "The Iron Horse" for his well-rounded play and durability. However, with decreased strength and difficulties with coordination and stamina, the world watched as this illness affected the strongest of men.

Disease incidence in the United States is approximately 2 per 100,000 with a prevalence rate of 6 per 100,000. Men are more often affected than women. While the sporadic form is most common, an autosomal dominant inheritance pattern is identified in 5% to 10% of patients with ALS, and this form of the disease is referred to as familial ALS. In this disease subtype, mutations in an enzyme called copper/zinc superoxide dismutase (SOD1) have been identified in up to 20% of patients and have been the focus of many research efforts. In the sporadic form, many neurologists and researchers have identified a link between disease and glutamate toxicity due to decreased glutamate transport, leaving the neurons at risk for increased calcium influx and subsequent cell toxicity and apoptosis.

ALS affects both the upper and lower motor neurons of the CNS. It leads to progressive muscle atrophy as well as spasticity. Though the illness typically begins in an area of contiguous peripheral muscles (upper extremity > lower extremity), manifestations in the head and neck can be the first signs of illness in up to 28% of patients (30). This, bulbar-onset form of the disease may present with slurred speech, inability to project the voice, hoarseness, or dysphagia, and is associated with a more rapid progression (31). Tongue atrophy and fasciculations are commonly seen and may be first noticed by the otolaryngologist who can assist in diagnosis. Extraocular muscles are usually spared, and if weakness is noted, other diagnoses should be pursued. Unlike the classic form of ALS, bulbar-onset ALS has a slight female predominance.

Aspiration is a common and significant symptom of ALS that can lead to infection and further respiratory compromise. Thus, prevention of aspiration is one of the mainstays of therapy. Weakness of the cervical muscles is also a common manifestation that can result in worsening dysphagia, sialorrhea, and more-pronounced head-droop. Dysphagia and reduced caloric intake hastens general muscle atrophy, and, a focus on maintenance of nutritional status is quite important with consideration of gastric feeding if necessary. Diaphragmatic and respiratory muscle weakness often results in the need for ventilator support, and respiratory failure is the most common cause of death.

TABLE 13.3 SYMPTOMATIC TREATMENT OF HEAD AND NECK MANIFESTATIONS OF ALS

Symptom	Pharmacotherapy	Other Therapy
Jaw cramps	Benzodiazepines	Botox injection of masseters
	Quinine sulfate	PT
	Baclofen	Massage
	Vitamin E	
Pseudobulbar affect	Tricyclic antidepressants	
	SSRIs	
	Carbidopa/levodopa	
	Lithium	
	Venlafaxine	
	Quinidine/dextromethorphan	
Sialorrhea	Glycopyrrolate	Botox injections of salivary glands
	Carbamazepine	Parotid radiation
	Diphenhydramine	Reassurance
	Scopolamine patch	Suction machine
	Hyoscyamine sulfate	
	Tricyclic antidepressants	
	Atropine	
Thick secretions	Guaifenesin	Cool mist humidifier
	Nebulized *N*-acetylcysteine	Oscillation therapy
	Nebulized saline	
	Propranolol	
Aspiration	Motility agents	Tracheostomy
		Modification of diet
		Swallow therapy
		Tracheal diversion
Voice disturbance	Antireflux medications	Tracheostomy if obstruction
	Sublingual lorazepam	Communication boards
		Morse code
		Use of computer systems
		Use of infrared eye movement
		Voice therapy
Respiratory failure	Morphine sulfate	Noninvasive positive-pressure ventilation
	Bronchodilators	Tracheostomy w/ventilation

Prognosis of ALS is dismal with an average 5-year survival rate of 22% and 10-year survival of 9.4%. Median survival is 2 to 3 years (32). Treatment is focused primarily on supportive care and symptom management (Table 13.3). Riluzole (Rilutek) and other antiglutamatergic agents are pharmacologic therapies that are often used as they have been the only agents shown to impact survival. Studies have shown increased survival in patients taking Riluzole compared to placebo, but the survival benefit is small and is more often seen in patients with bulbar-onset disease. A recent Cochrane meta-analysis showed that 100 mg of Riluzole daily was associated with a 9% increase in probability of surviving 1 year (33). Because of the complexity of care and the many systems involved, treatment by a multidisciplinary team has been highly regarded. This includes physicians, nutritionists, speech pathologists, dietitians, and occupational therapists to name a few of the participants. Treatment in multidisciplinary ALS clinics has been associated with decreased hospital admissions and longer survival (1,080 vs. 775 days, $P = 0.008$) (34), and therefore should be strongly considered in management of patients with ALS.

Pseudobulbar Palsy

Pseudobulbar palsy, also called spastic bulbar palsy, is a disease affecting the corticobulbar tracts bilaterally. The corticobulbar tracts help control the motor nuclei of CN V, VII, IX, and XII, which play a role in deglutition, mastication, and speech. Thus, patients may experience hyperreflexia and spasticity of the pharynx, larynx, lips, tongue, and palate. The voice may sound spastic or strained (not unlike spasmodic dysphonia) and speech may be slow and effortful. Emotional lability is also a feature of this illness that can be embarrassing for many patients as they may demonstrate pathologic laughter, grimaces, or crying. Treatment is typically supportive. Baclofen has been used for spasticity, and SSRIs as well as tricyclic antidepressants

have had some effect on decreasing emotional outbursts. A combination of dextromethorphan and quinidine agent is under investigation as it did decrease emotional outbursts in patients with ALS, and was therefore thought to be helpful in pseudobulbar palsy (35). Pseudobulbar palsy must be differentiated from bulbar palsy, which affects the lower motor neurons of these motor nuclei directly.

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is an acute inflammatory demyelinating polyradiculoneuropathy (AIDP) that, in its most common form, has been linked to upper respiratory or gastrointestinal infection. *Campylobacter jejuni* is the bacteria most often identified in relation to GBS; however, several viral agents have also been implicated. GBS is characterized by symmetrical motor weakness, paresthesias, and areflexia that begin in the lower extremities and ascend to affect the upper extremities, oropharyngeal structures, and respiratory muscles. This progression can occur within hours to days, and if it continues for over 4 weeks is considered subacute (4 to 10 weeks) or chronic (greater than 10 weeks) AIDP (subacute IDP, chronic IDP). Sensory impairment is minimal and is usually limited to distal loss of vibratory sense. Cranial nerves are commonly affected with up to 50% of patients experiencing bilateral facial paresis. Areas of demyelination have been found on the peripheral nerves leading to slowed conduction time on electromyography. This conduction deficit, in addition to the CSF findings on lumbar puncture (high protein with otherwise decreased cellularity of the fluid), aids in diagnosis. The proportion of patients with severe respiratory failure requiring ventilation ranges from 12% to 30% (32) and seems to increase in age. Plasma exchange and high-dose IVIG therapy have been shown to be equally effective in reducing the harmful effects of autoantibodies and shortening recovery time (36). Corticosteroids have not shown a significant benefit and are not recommended. Treatment is most effective when started within 2 weeks of disease onset. Most patients do recover from the illness with 70% showing full recovery in 1 year and 82% at 2 years; however, some patients do have residual sequelae and others may recur (recurrence rate = 5%) Improvements in critical care and ventilator use have decreased the mortality rate of this disease from 33% to 5% to 10% (32).

Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the CNS that affects younger patients, especially women in their 20s to 40s. The female to male ratio of those affected is approximately 1.7:1. The etiology of MS is still unclear, though the current theory is that the etiology is multifactorial with a genetic predisposition needing an environmental trigger to activate the disease process leading to a continued autoimmune process. Several HLA types have been correlated with MS, with some related to increased risk of disease (DRB1*15 and DRB1*03) and others offering a potential protective role (DRB1*14 and DRB1*07) (37). That viral infection plays a role in development of MS has been speculated; however, studies looking to identify a viral genome have not been successful and therefore much controversy surrounds this topic. Other environmental triggers have been evaluated, and geographic studies have provided some interesting findings, namely that disease prevalence seems to increase with distance from the equator. Migration studies demonstrate that when moving from a high-risk to low-risk area during adulthood, the original risk is maintained. However, when immigrating in childhood, the risk profile takes on that of the newly inhabited area. These studies offer evidence that environmental factors are certainly involved in MS development.

MS is characterized by demyelination of white matter areas within the CNS with relative axonal sparing, leading to slower conduction times of action potentials. Myelin basic protein (MBP) is a candidate for the target of T cells attack; however, other protein components of myelin may also be involved. As demyelination occurs in a particular area, the threshold for conduction is altered, leading to transient symptoms (i.e., Uhthoff phenomenon—blurring of vision during times of strenuous activity or increase in temperature). Similarly, de novo action potentials from mechanical activation of demyelinated areas can lead to electric shock-like sensations with muscle flexion (Lhermitte phenomenon). Completely spontaneous action potentials in these areas may contribute to trigeminal neuralgia, which is commonly seen in MS patients.

Symptom development and the clinical course of MS are quite variable, and several forms of the disease exist; however, the relapsing–remitting form is the most common. This pattern demonstrates acute exacerbations with periods of remission where the symptoms resolve either partially or completely. A hallmark of MS is that symptoms are "disseminated in both time and space" (i.e., more than one area of the CNS is involved and at more than one time point). Both motor and sensory systems are involved, and head and neck manifestations are plentiful, with cranial neuropathies often representing brainstem lesions. Optic neuritis (an episode of decreased visual acuity with associated pain [especially with eye movement], alterations in color perception, and afferent pupillary defect [Marcus-Gunn pupil]) is a common initial presentation of MS in approximately 17% to 19% of patients (38). Nystagmus, saccadic eye movements, loss of smooth pursuit, oscillopsia, and internuclear ophthalmoplegia (loss of ability to link the nuclei of CN III and CN VI together during lateral gaze due to lesions in the medial longitudinal fasciculus) are other common ocular manifestations of MS. The nystagmus seen in MS patients is called acquired pendular nystagmus and is characterized by small-amplitude oscillations. Impairment of facial sensation including trigeminal neuralgia, facial myokymia (wave-like twitching of facial

muscles), hemifacial spasm, and facial paresis may also be seen. Vertigo affects 30% to 50% of patients and hearing loss is usually unilateral, but is an uncommon finding (32). Lower cranial nerve involvement typically presents only in late-stage disease and displays an upper motor neuron–type defect leading to dysarthria and dysphagia.

MS affects many areas outside of the head and neck. Cerebellar dysfunction presents with dysmetria, ataxic gait, intention tremor, lack of upper extremity coordination, and slurred speech. Charcot triad represents the combination of nystagmus, scanning speech, and intention tremor seen in many MS patients. Motor involvement with paraparesis, spasticity, and exaggerated deep tendon reflexes is often seen. Various other systems are also affected throughout the body including bowel/bladder control, heat intolerance, fatigue, cognitive impairment, affective disorders, pain, and difficulties with memory and coordination.

Because of the variable range in presentation of MS, diagnosis is often delayed and can be quite difficult. The diagnosis of MS is made clinically with assistance from laboratory studies and neuroimaging. The McDonald criteria, which were recently revised in 2010, help clarify diagnosis by combining clinical, laboratory and imaging parameters (39). MRI of the brain and spinal cord depicts areas of demyelination and edema as seen on T2 imaging and "black holes" representing axonal loss on T1 imaging. MS plaques are seen in characteristic areas within the periventricular white matter and corpus callosum (Dawson fingers). Gadolinium enhancement can be used to demonstrate more acute lesions. Aside from neuroimaging, CSF analysis, as well as evoked potential testing, can assist in diagnosis of MS. CSF is often normal in patients with MS, but the presence of a lymphocytic predominance, elevated immunoglobulin, or oligoclonal bands is a helpful adjunct to MS diagnosis. Electrical conduction studies such as evoked potential testing (brainstem auditory, visual, or somatosensory) are not specific for MS but can show increased latencies consistent with demyelination. They are particularly helpful for detection of subclinical disease.

Management of MS focuses on treatment of acute exacerbations, reduction in lasting sequelae, decreasing the number of relapses, and supportive care. In the acute setting, corticosteroids are the mainstay of therapy. For overall disease management, the "ABCs" of immunomodulating therapy are often used, which include Avonex (interferon beta-1a), Betaseron, and Copaxone (glatiramer acetate). The first interferon approved by the FDA for treatment of MS in 1993 was Betaseron (interferon beta-1b), which decreased the rate of relapses by 34% after 2 years (32). Copaxone differs from the interferons, but is another first-line therapy shown to decrease relapse rate by simulating MBP and acting as a decoy for the body's immune system. Novantrone (Mitoxantrone) is a chemotherapeutic agent used in the progressive form of the disease. The newest agent, now approved as single-agent therapy for relapsing-remitting MS, is Tysabri (Natalizumab), a monoclonal antibody directed against a4 integrin adhesion molecules. This inhibits trafficking of lymphocytes from the blood into the CNS, and has been shown to decrease the relapse rate as well as to slow disease progression. A few cases of progressive multifocal leukoencephalopathy were associated with Tysabri treatment (concurrent with interferon therapy) leading to the product being pulled from shelves. It is been reapproved as monotherapy for patients who have failed or not tolerated ABC therapy. Other agents can be used to target symptoms directly and the use of a multidisciplinary team including occupational therapists, psychiatrists, physical therapists, and speech pathologists among others has also been recommended.

Autoimmune Neurologic Diseases

Many autoimmune diseases may manifest as head and neck pathology. A comprehensive description of these illnesses is beyond the realm of this chapter; however, we will touch on several of the most common pathologies to introduce the reader to this interesting discussion.

Myasthenia Gravis

Myasthenia gravis (MG) is a progressive autoimmune disorder and is the most common primary disorder of neuromuscular transmission. The highest incidence is seen in women in their 20s and 30s and men in their 60s. The pathogenesis of this disease relates to the development of autoantibodies to nicotinic acetylcholine (Ach) receptors affecting the neuromuscular junction of striated muscles. Detection of these autoantibodies in the serum of patients is 80% to 90% sensitive for diagnosis of MG. Sensation and reflex movements are not impaired.

Symptoms of MG usually begin with small muscle groups, especially the ocular muscles. In fact, 90% of patients have some ocular involvement, and the medial rectus muscle is most affected. Approximately, 20% of patients demonstrate ocular myasthenia that never progresses to limb muscles and affects ocular muscles alone (40). With either form of disease, patients usually report diplopia, eye fatigue, ptosis, and blurred vision that worsen as the day progresses. Symptoms are further worsened during times of eye strain (i.e., watching television, bright sunlight, driving). Other head and neck muscles are also affected, including the pharyngeal muscles among others. For example, jaw muscle weakness and a sad facial appearance due to facial muscle weakness may also be noted. Cricopharyngeal involvement resulting in dysphagia and velopharyngeal insufficiency has also frequently been described. Symptoms are more pronounced after repetitive use of the particular muscle group. Respiratory dysfunction is atypical, except in the context of anti-MuSK antibody–positive myasthenia, which mimics motor neuron diseases (41).

Diagnosis of MG can be made by a combination of methods including antibody detection, edrophonium challenge, and electrodiagnostic studies. Even so, diagnosis is often delayed due to the fluctuation of symptoms. An Edrophonium challenge test acts to increase Ach in the neuromuscular junction by inhibiting acetylcholinesterase, thus allowing prolonged interaction with the Ach receptor. Weakness that improves after acetylcholinesterase inhibitors can be seen in patients with MG, but can also be present in other disease entities such as Lambert-Eaton syndrome. Patients with ocular myasthenia show decreased rates of response to edrophonium challenge compared to patients with generalized myasthenia; therefore. Other methods of detection are important to address. As discussed above, serum assay for autoantibodies to the acetylcholine receptor along with clinical symptoms can confirm the diagnosis. However, the lack of these antibodies can be seen early in the disease, and thus, should be retested 6 to 12 months after symptom onset if the initial testing is negative. Ocular cooling, or the "ice pack test" has been shown to improve lid ptosis after application for 2 minutes. This test shows 89% sensitivity and is helpful for detection of ocular myasthenia, particularly in the context of a normal edrophonium challenge (42). Finally, electrodiagnostic testing includes repetitive nerve stimulation (RNS) with comparison of the amplitude of the compound action potential from the first stimulus to the fourth or fifth stimulus. A 10% decrease in amplitude over this period is reliable in diagnosis. Single-fiber electromyography can be performed when RNS is negative but a high clinical suspicion for a neuromuscular junction disorder is present. This more sensitive test shows increased jitter in at least one muscle in almost all patients with MG. Sensitivity is higher with generalized myasthenia compared to ocular myasthenia alone, but specificity remains high (40).

Thymic hyperplasia (affecting 70% of patients) and thymoma (affecting 10% of patients) have been associated with MG and play a role in disease management. Increased activity suggests an ongoing immune response. Most thymomas are benign, though malignancy has been described. Thymectomy improves the clinical course of MG, though this has not been clearly shown in prospective controlled trials. Despite this, current recommendations include thymectomy for patients with MG whose symptoms began before the age of 60, except in the case of purely ocular myasthenia. Younger women show the best response after thymectomy; however, overall response is variable especially in those with ocular myasthenia or thymoma.

Other therapeutic measures to control MG include cholinesterase inhibitors (including pyridostigmine and neostigmine), corticosteroids, immunosuppressants (e.g. azathioprine), plasma exchange, and IVIG. With the current treatment recommendations, mortality rate of myasthenia approaches zero, and patients lead near-normal lives with adequate treatment.

Susac Syndrome

Susac syndrome was first described in 1979 by John Susac and consists of a triad of branch retinal artery occlusion (BRAO), encephalopathy, and hearing loss. Young women (age 20 to 40) are most commonly affected, but this entity has been described throughout a wide age range (age 7 to 72). Susac syndrome has been characterized as a small-vessel autoimmune endotheliopathy. The precapillary arterioles of the brain, cochlea, semicircular canals, and retina are affected leading to arteriolar occlusion with subsequent microinfarction of the involved end organs.

Symptoms of this disorder include headache (often with migrainous characteristics), bizarre behavior changes, cognitive changes, memory loss, confusion, tinnitus, vertigo, sensorineural hearing loss, and visual defects. Two subsets of the disease have been described: (a) the encephalopathic form and (b) the recurrent BRAO form. The encephalopathic form is the most common and more easily recognized subtype in which encephalopathic symptoms are the dominating clinical features. These patients often develop BRAO and/or hearing loss as well; however, these need not be present at the initial time of diagnosis. This form is often self-limited, but active disease duration ranges from 2 months to almost 20 years. However, several studies have described late manifestations and residual deficits. Thus, this disorder cannot be taken lightly, and early treatment is recommended to prevent sequelae. The recurrent BRAO subtype is less severe, though more often a chronic disorder with a fluctuating clinical course. It is characterized by repeated episodes of retinal vasculopathy that can range from symptomatic occlusive disease to asymptomatic arteriolar wall hyperfluorescence. Symptoms of ocular symptomatology include black spots within the visual field and scintillating scotoma. Hearing loss is typically sensorineural in nature. The onset of hearing loss is quite variable and can manifest acutely or follow an insidious or even fluctuating course. A loss of wave I on brainstem auditory-evoked response testing may be seen indicating cochlear infarction. Low tones are affected first and the resulting hearing loss can be severe or even profound.

Diagnosis of Susac syndrome is often difficult, especially when the full triad of symptoms is not present. Both MRI and retinal fluorescein angiography are helpful in diagnosis. Due to the predominance of white matter changes and similarities of MRI findings, it is often misdiagnosed as MS or acute disseminated encephalomyelitis. The corpus callosum is always involved in Susac syndrome. Sagittal T1 and T2 FLAIR images depict microinfarctions of this area that are described as "snowballs" or "holes" by some (43) (Fig. 13.11) There is a predilection for the central areas and the roof of the corpus callosum to be involved in this syndrome. This helps differentiate Susac syndrome from MS, which tends to involve the periventricular areas. A new MRI finding described in 2010 by Rennebohm et al. is a "string of pearls" seen best on diffusion weighted



Figure 13.11 Sagittal T1 MRI image demonstrating microinfarction in the corpus callosum.

axial MRI, representing microinfarctions along the internal capsule. Unlike patients with MS, grey matter or cortical changes can be seen in as many as 70% of patients with Susac syndrome (44). Fluorescein angiography (FA) is helpful to evaluate for retinal vasculopathy and can help identify even subtle changes that affect only the periphery or asymptomatic lesions. Further, serial FA has been used to help determine treatment response and clinical course.

Treatment of Susac syndrome should be initiated early to help prevent development of residual sequelae. Immunosuppression is the key to disease management with corticosteroids being the first-line therapy. IVIG and cyclophosphamide have also been utilized with a clear clinical response in severe cases. Recent descriptions of monoclonal antibody therapy, specifically anti-TNF-alpha therapy (infliximab), have shown dramatic effects; however, no adequate clinical trials have yet been conducted. Other therapies targeting the vasculature have been described including aspirin, calcium-channel blockers, and anticoagulants. Given the rarity of this disease entity, few trials have been conducted to compare various therapeutic regimens with sound evidence-based methodology. Symptoms-specific management targeting visual changes or hearing loss have been attempted. Hyperbaric oxygen therapy was shown by Li et al. (45) to reverse visual loss in a patient. Cochlear implantation may be a treatment option for patients who have significant bilateral hearing loss.

NEOPLASMS

Space-occupying lesions can induce otolaryngologic symptoms by compressing or by destroying neural tissue within the temporal bone, in the cerebellopontine angle, or intra-axially within the brainstem and cerebellum. Symptoms can also be produced or increased by vascular compression.

Vestibular Schwannomas (Acoustic Neuromas)

Vestibular schwannomas are slow-growing benign neoplasms most often seen at the cerebellopontine angle (Fig. 13.12). They can present asymmetric hearing loss, tinnitus, and with vertigo. Although, vertigo is present in less than 20% of patients with vestibular schwannomas (46). It can be disabling (47). These tumors can also present with hyperventilation-induced vertigo in the absence of hearing loss (48). Discussion of the diagnosis and treatment of vestibular neuromas is covered in depth elsewhere in this text.

Brainstem Neoplasms

Gliomas of the brainstem usually grow slowly and infiltrate the brainstem nuclei and fiber tracts, producing progressive symptoms and signs. Astrocytoma is the most common form of glioma. The typical history is relentlessly progressive involvement of one brainstem center after another, often causing death with the destruction of the vital cardiorespiratory centers of the medulla. These tumors are 5 to 10 times more common in children than adults. Vestibular and cochlear signs and symptoms occur in about half of patients but the spectrum of findings makes a brainstem origin clear. In the modern era, imaging studies such as



Figure 13.12 A T1 MRI with gadolinium contrast demonstrating a 2.2 cm vestibular schwannoma in the left internal auditory canal and cerebropontine angle.

CT or MRI are usually obtained when the first symptoms present, making the diagnosis obvious.

Tumors originating in the fourth ventricle can compress the vestibular nuclei producing vestibular symptoms. An attack of headache, vertigo, vomiting, and visual loss may result from a change in head position, producing transient CSF obstruction (Bruns syndrome). Positional vertigo and nystagmus may be the presenting symptom and sign. Other fourth ventricular tumors that produce similar clinical pictures include ependymomas, medulloblastomas, papillomas, teratomas, epidermoid cysts, and cysticercosis. The diagnosis of a fourth ventricular mass is made readily with MRI and CT scanning, but frequently the exact nature of the tumor cannot be determined prior to surgical exploration and biopsy. Complete removal of tumor should be achieved when possible. Medulloblastomas are particularly sensitive to radiotherapy (49).

Cerebellar Neoplasm

Dizziness is a common clinical manifestation of a posterior fossa tumor occurring in 81% of patients (50). Half of patients with posterior fossa tumors have spontaneous nystagmus, and a third lack caloric responses. Other common symptoms of cerebellar tumors include tinnitus, hearing loss, headache, nausea/vomiting, and ataxia. Gliomas of the cerebellum may be relatively silent until they become large enough to obstruct CSF circulation or compress the brainstem. Positional vertigo is occasionally the initial symptom of a cerebellar tumor (51). Paroxysmal positional nystagmus, when present, is atypical because it can be induced in several different positions and is nonfatigable. Tumors that can produce these signs and symptoms include gliomas, teratomas, hemangiomas, and hemangioblastomas. Each of these tumors has a characteristic appearance on MRI and CT scanning, although occasionally, the exact tumor type cannot be determined before surgical biopsy.

CHIARI MALFORMATION

Chiari malformations are characterized by herniation of the contents of the posterior cranial fossa through the foramen magnum. They can be divided into two forms: Chiari types I and II.

Chiari type I is more mild and common. Symptoms are usually delayed until age 25 to 35 years. Affected individuals often have subtle neurologic symptoms that are not associated with other developmental defects. Diagnosis is made through CT scan or MRI reconstructed in the sagittal plane, which may demonstrate deformation of the cerebellar tonsils more than 5 mm caudally through the foramen magnum (Fig. 13.13). Symptoms often include upper extremity weakness, sensory loss, and pain. Occipital headaches, which are exacerbated by coughing, sneezing, bending over, or lifting, are also common. Dizziness is also frequently described and nystagmus may be present.



Figure 13.13 Magnetic resonance image of a patient with Chiari type I malformation, with cerebellar tonsils (*arrow*) below foramen magnum.

Patients can also present to an otolaryngologist with dysphagia, aspiration, or hoarseness due to involvement of the lower cranial nerves (CN IX, X, and XII).

Chiari type II manifests in the first few months due to associated hydrocephalus and other CNS malformations such as meningomyelocele.

NORMAL-PRESSURE HYDROCEPHALUS

Idiopathic normal-pressure hydrocephalus classically presents with the triad of dementia, urinary incontinence, and gait or balance disturbance. However, these symptoms represent the more severe end of the clinical spectrum, and more subtle cases can present with only mild gait or balance symptoms (52); thus an otolaryngology consultation may be requested. Cognitive symptoms are also common, but may be mild. Patients usually become symptomatic after age 60. Diagnosis requires an imaging study demonstrating nonobstructive ventricular enlargement disproportionate to cerebral atrophy.

HIGHLIGHTS

- Many neurologic disorders present with symptoms in the head and neck region, and a screening neurologic exam can help to identify some of these disorders.
- The cranial nerves contain fibers involved in sensation, motor function, and the special senses and are an integral part of the head and neck examination.

- Neurologic conditions can have a wide variety of manifestations in the head and neck leading to symptoms of dysphagia, vertigo, dysphonia, hearing loss, and other cranial neuropathies.
- Cranial neuropathies can be a sign of cerebrovascular disease. The deficits reflect the territory of blood supply to the affected area, which aids in diagnosis.
- Migraine is more than just a headache and can present to the otolaryngologist with various symptoms including vertigo.
- Management of migraine is complex and includes dietary and lifestyle modifications as well as a variety of pharmacotherapeutic agents including beta-blockers, tricyclic antidepressants, SSRIs, and other drugs.
- ALS is a progressive neuromuscular disorder that involves both upper and lower motor neurons and may present with bulbar symptoms including dysphagia and tongue atrophy and fasciculations.
- The otolaryngologist should be aware that MS, GBS, MG, and Pseudobulbar Palsy commonly have symptoms that involve the head and neck. The otolaryngologist may play a role in symptom management in patients with these disorders as part of a multidisciplinary medical team.
- Susac syndrome is rare and symptoms include the triad of retinal artery occlusion, hearing loss, and encephalopathy.
- Neoplasms of the CNS may induce otolaryngologic symptoms by compressing or destroying neural tissue within the temporal bone, in the cerebellopontine angle, or intra-axially within the brainstem and cerebellum or by vascular compression.
- Disorders of the craniovertebral junction may present as vertigo with patient's seeking initial consultation by an otolaryngologist.
- It is important for the general otolaryngologist to recognize key features of common neurologic disorders in order to initiate management or arrange for proper and prompt referral to the appropriate physician.

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Ophthalmology

14

Jean Edwards Holt *G. Richard Holt*

Abnormalities of the ocular structures produce visual dysfunction, altered appearance, pain, or systemic symptoms. Many persons believe vision to be the most important and comprehensive of the senses. Decreased visual acuity can indicate a blinding eye disease that can be controlled with restoration of vision, a systemic disease that can endanger life if not detected and managed, a tumor or other disorder of the central nervous system that can threaten vision and life, or a simple refractive error, correction of which simplifies the patient's life. Ocular symptoms bring the patient rapidly to the physician because the eyes are the focus of a patient's perception, and alterations in these structures usually are not ignored.

The otolaryngologist–head and neck surgeon often joins the ophthalmologist in a team approach to care for a patient with congenital or acquired abnormalities of the orbit, adnexa, and periorbital structures. Appreciation of the fundamental concepts of vision, ocular anatomy and physiology, and local and systemic disorders is essential to direct care or assist in caring for a patient with ophthalmic problems (Fig. 14.1). Consultation with an ophthalmologist is mandatory for many disorders and such a joint approach is beneficial to patient care. This chapter highlights the most common disorders seen by otolaryngologist–head and neck surgeons, which have orbital, adnexal, and ocular implications. Also discussed are the best diagnostic studies for the identification of ophthalmologic and orbital disorders, trauma, and tumors.

THE EYE EXAMINATION

The three indications for performing an ocular examination include:

1. Presenting symptoms clearly related to ocular structures, such as pain in the eye and decreased vision
2. Presymptomatic screening to detect controllable eye disease, such as amblyopia and glaucoma
3. Evaluation or diagnosis of systemic disease mirrored in the eye, such as retinopathy and neuropathy in diabetes

With these goals in mind, it is obvious that testing the function of the visual system and examining the eyes should be part of any complete head and neck examination (1).

An eye examination begins with obtaining a history related to the symptoms. Relevant areas are chronology, eye history, family history, concurrent systemic diseases, present use of medications, and existence of allergies. Ocular symptoms usually can be classified into three groups—altered visual function, abnormal sensation, or altered appearance. Abnormalities in visual functioning generally reduce vision, cause superimposed visual phenomena, or produce diplopia. Abnormal sensation in or around the eye can take many forms—deep pain, which signifies intraocular or orbital inflammation; foreign-body pain related to trauma; superficial pain of mild conjunctivitis; vague discomfort known as *asthenopia*, or eyestrain, with prolonged, intensive use of the eyes; headache related to neurologic disease or tension; or photophobia or ocular pain with exposure to light, most commonly related to corneal abnormalities. *Altered appearance* usually refers to eyelid abnormalities, orbital deformities, motility disturbances, or redness of the eyeball.

Visual Acuity

An eye examination begins with determining the visual acuity of each eye, with the other eye completely covered. Although measurements are obtained at a distance and near, with and without refraction (glasses), the most important determination of general eye condition is the best-corrected-distance visual acuity, usually assessed with a Snellen chart (which has been in clinical use for 150 years). Examination of children often requires pictures or individual E charts. Each line on the chart is meant to

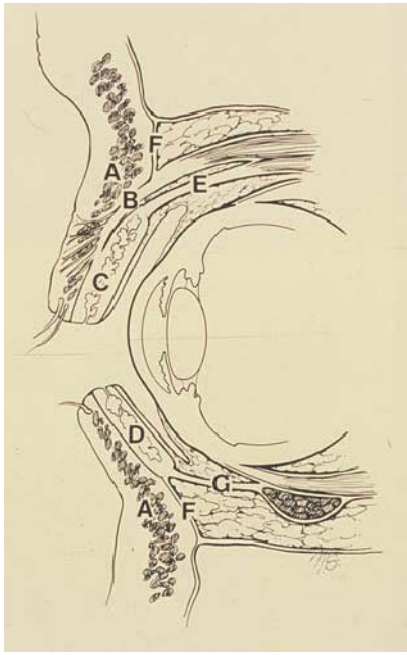


Figure 14.1 Cross-sectional anatomy of the orbital adnexae and globe: (*A*) orbicularis oculi muscles, (*B*) levator aponeurosis, (*C*) upper tarsal plate, (*D*) lower tarsal plate, (*E*) Mueller muscle, (*F*) orbital septum, and (*G*) lower eyelid retractors. Courtesy of the American Academy of Otolaryngology-Head and Neck Surgery, Inc. From: Holt JE, Holt GR. *Ocular and orbital trauma* 1983:10.

be read by a person with normal vision at 20 feet (6 m). The largest letter should be seen at 200 feet (60 m) by a person with normal vision. If a patient can see that letter at a distance of 20 feet and is unable to see any of the smaller letters, vision is 20/200. If the line read by a person with normal sight can be seen at 20 feet, and the patient is 20 feet from the chart, the vision is 20/20. If the patient is unable to read the largest letter on the chart, the distance at which he or she can count fingers accurately is recorded. If the patient cannot count fingers, the distance at which hand movements are perceived is determined. If this is not possible, whether the patient can perceive light is documented. Table 14.1 compares visual acuity with visual ability or disability. Vision is not a true fraction. In other words, 20/40 vision does not mean 50% of normal vision but that the patient can see at 20 feet what a person with normal sight can see at 40 feet (12 m). If the patient can see the 20/20 line by wearing glasses, his or her functional vision is probably just as good as that of someone who sees the line without glasses.

The ophthalmologist uses the process of refraction to determine the refractive error of the eye or the lenses needed for the eye. The need for refraction is determined with a pinhole test. The patient views a chart through a 1-mm pinhole, which reduces the blur of the image on the retina and appreciably increases visual acuity if it is decreased owing to a refractive problem. This test helps to rule out retinal or optic nerve dysfunction as a cause of decreased vision. Measurement of best-corrected visual acuity is an important concept. Often, patients say they are "blind" without their glasses. They should be informed that vision can be physiologically abnormal without pathologic consequence.

Peripheral vision, or side vision, can be evaluated with visual field testing. This test can be performed with various instruments, but it is commonly performed with the confrontation technique. The patient is asked to fix on the examiner's nose with one eye and to cover the other eye. A test object or finger is brought in from the side until the patient reports it is being seen. The visual field is approximately 90 degrees on the same side but only 50 degrees on the opposite side of testing. Abnormalities of peripheral vision often are detected only through examination because patients report loss of central vision, but loss of peripheral vision is not easily detected. Performing this test for each eye is a good screening method for many neurologic diseases. Ophthalmologists will use a more sophisticated perimeter test to obtain a graphic representation of each visual field to identify and follow visual field defects.

External Inspection and Pupil Examination

Inspection of the external eye structures includes the eyelids, eyelashes, lacrimal apparatus, cornea, conjunctiva and sclera, anterior chamber, and iris, as well as the general symmetry of the face and orbits. Much information can be obtained with this examination, which often reveals the presumptive diagnosis. Particular notice should be taken of abnormal alignment of the eyelids (ptosis or lid retraction), the position of the eyelids against the globe (entropion or ectropion), and abnormal direction of the eyelashes (trichiasis). Swelling in the medial canthal area can indicate a block of proper lacrimal drainage. Proptosis always is an important finding (Fig. 14.2). The causative factor may be orbital, periorbital, or systemic disease. Specific abnormalities in the color and contour of the conjunctiva, cornea, and sclera are discussed later with "red eye." Of particular importance is an estimation of the depth of the anterior chamber in detecting an important form of glaucoma known as "angle-closure" glaucoma. This test can be performed with side illumination using a penlight. If the anterior chamber is of normal depth, the entire surface of the iris is illuminated. If the anterior chamber is shallow, the iris on the opposite side of the pupil is in shadow.

Examination of the iris usually centers on assessing the pupillary response. When light is shined into the eye, a normal pupil constricts and then redilates after the stimulus is removed. This is the *direct light reflex*. The opposite pupil constricts as well with the stimulus, and this is known as the *consensual light reflex*. These reflexes should be brisk and approximately equal. Pupillary constriction is also part of the "near-vision complex" associated with the process of accommodation. If the pupil

TABLE 14.1 CORRELATION OF VISUAL IMPAIRMENT WITH VISUAL DISABILITY

Visual Impairment	Visual Disability
20/12–20/25	Healthy young adults average better than 20/20 acuity Normal vision
20/30–20/70	Nearly normal vision Causes no serious problems but should be evaluated for potential improvement or possible early disease
20/80–20/160	Moderately low vision Strong reading glasses or magnifiers usually provide adequate reading speed.
20/200–20/400 or CF 10 feet (3 m)	Severely low vision (legal blindness in the United States) Gross orientation and mobility generally adequate but difficulty with traffic signs, bus numbers, etc. Reading requires high-power magnifiers. Reading speed and endurance reduced.
CF 8 ft (2.4 m) to CF 4 feet (1.2 m)	Profoundly low vision Increasing problems with visual orientation and mobility. Long cane useful to explore the environment. Highly motivated and persistent persons can read visually with extreme magnification. Others rely on nonvisual means: braille, talking books, radio.
<CF 4 feet (1.2 m)	Near blindness Vision unreliable except under ideal circumstances. Must rely on nonvisual aids
NLP	Total blindness. No light perception. Must rely on other senses entirely

CF, counts fingers; NLP, no light perception.

reacts to accommodation but not to light, it is the classic Argyll Robertson pupil, often associated with syphilis. A Marcus Gunn pupil is an important physical sign in the evaluation for neurologic disease. It is elicited with the swinging flashlight test. Light is shined in one pupil for 2 or 3 seconds and then rapidly swung back and forth between eyes. Prompt constriction should appear if each pupil is normal. If optic nerve disease or injury is present in the affected eye, the pupil gradually dilates, indicating a decreased direct light reflex. With an impaired neural connection in the affected eye, the examiner will observe a diminished pupillary response in both eyes when the normal eye is stimulated. Thus, the direct response to stimulation of the affected eye and the consensual response in the normal eye are both reduced, compared to the responses when the normal eye is similarly stimulated. Such a reaction usually indicates damage to the optic nerve via the afferent pupillary fibers. This sign is positive early in optic nerve disease, when vision still is 20/30 or better. Abnormal pupillary reaction in any form generally indicates a serious eye disease. For the otolaryngologist, normal visual acuity and normal pupillary responses are comforting findings in evaluating eye problems.

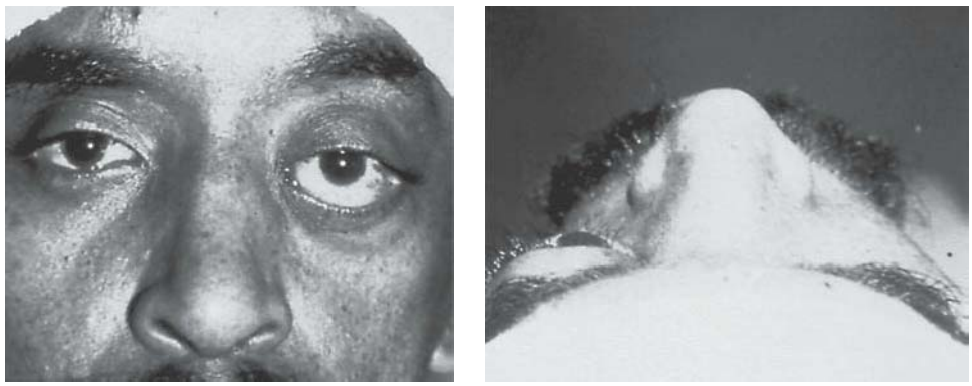


Figure 14.2 Proptosis of the left eye, viewed from anterior (**left**) and superior (**right**) positions.

Motility

Six muscles surrounding each eye are responsible for ocular motility. Several terms are used to describe various eye movements. The movement of one eye from one position to another is called *duction*. The simultaneous movement of both eyes from the primary, straight-ahead position to a secondary position (up, down, right, left) is called *version*. *Vergence* is the term applied to simultaneous rotation of both eyes inward (*convergence*) or outward (*divergence*). Evaluation of the extraocular muscle function is begun with general inspection to find any gross deviation of either eye (*heterotropia*). The patient is asked to look up, down, right, and left to reveal whether the deviation is the same in all fields of gaze (concomitant) or varies (nonconcomitant and usually neurologically significant) (Fig. 14.3). During these gaze movements, involuntary eye jerks, called *nystagmus*, may also be detected.

The flashlight used to evaluate pupillary reflexes also can be used to assess the corneal light reflex. The light should be symmetrically reflected in each pupil. If deviation is seen, the degree of abnormality can be estimated by the asymmetry of the light reflex in each pupil.

The cover test is used to evaluate motility. The patient is instructed to fix on an object. If both eyes appear straight (*orthotropia*), cover either one. If under cover the eye deviates, *phoria*, or latent deviation that becomes evident only when vision is interrupted, has been elicited. Usually, the eye resumes fixation when uncovered. If one eye is obviously deviated, the straight-ahead eye is covered. If the deviated eye rapidly moves to resume fixation, it most likely has good visual potential. The deviation can be eso (inward), exo (outward), hyper (upward), or hypo (downward). Motility disturbances may indicate congenital, neurologic, or metabolic abnormalities.



Figure 14.3 Heterotropia is characterized by gross asymmetry of eye movement.

Intraocular Pressure

Measurement of intraocular pressure (IOP) should be performed when assessing orbital trauma or before performing orbital, periorbital, or sinus surgery. The examiner can estimate IOP digitally by placing the tips of the index fingers on the patient's closed eyelids. All but gross abnormalities remain undetected when this technique is used. A tense globe might be appreciated on palpation as a firmness of the affected globe that is not present with the opposite globe. It is a "soft" sign but, if obvious, is a serious finding. Tonometry is the estimation of IOP with a specialized instrument. It can be performed with an indentation technique or an applanation technique. The former is used in the general screening process and is performed with a Schiotz tonometer. With the patient in a recumbent position, a drop of topical anesthetic is instilled into each eye. The patient is instructed to look straight ahead with both eyes open. Assistance in holding the eyelids open, with pressure on the orbital bones only, not the eye, may be needed. The plunger is gently placed on the center of the patient's cornea, and the corresponding scale reading is recorded. The test should require only 1 to 2 seconds of contact with the cornea. Normal IOP usually is 15 to 20 mm Hg, with an upper limit of 22 to 23 mm Hg. Both eyes should be tested, in order to obtain baseline levels in the "normal" eye and to compare the pressures between eyes, particularly after facial trauma.

Ophthalmoscopy

The final part of a pertinent eye examination is ophthalmoscopy. It is used to evaluate the internal structures of the eye, primarily the retina, retinal blood vessels, and optic nerve. A direct ophthalmoscope is used for this examination and provides an upright 3× magnified image. Great limitation of the field of view occurs, and the information is obtained as if the examiner is viewing through a small pupil. A 3-mm pupil gives only a 4-degree field of view, but a 7-mm pupil allows a 30-degree field of view. Therefore, routine dilation of the pupils with 0.5% or 1% tropicamide or 2.5% phenylephrine is recommended, with the following exceptions: known narrow-angle glaucoma, neurologic or neurosurgical observation, and some types of intraocular lens implants after cataract surgery. In rare instances, dilation of the pupil can precipitate an attack of acute angle-closure glaucoma that was previously unsuspected. This low risk should not be considered a contraindication to performing the examination. Because this form of glaucoma is rare and can be managed effectively, the benefits of improved ophthalmoscopy through dilated pupils outweigh the risks.

The examiner holds the ophthalmoscope in the right hand and uses the right eye to examine the patient's right eye. With the pupil dilated, reflected light from the ocular fundus produces a clear red reflex when viewed through

the ophthalmoscope with a 16 diopter lens at a distance of approximately 1 foot (0.3 m). Any alteration in the red reflex indicates abnormality in one of the optical structures of the eye and is always important. The patient's eye is then approached as closely as possible as the power of the lens in the ophthalmoscope is reduced until the optic disk comes into focus. The nerve head, at the back of the eye, should be evaluated for color, sharpness of margins, and appearance of the central depressed area, known as the *cup*. Systematic examination of the retinal vessels and background then is performed. The macular region deserves special attention for patients with vision loss. This examination is performed on both eyes.

Schirmer Testing

The Schirmer test is only a general qualitative screening test for tear production. It is often equivocal and only a glimpse of the tear production at the time of the test. Hydration status and environmental factors can change tear production even within a day's time. There are three components to the Schirmer testing, all three of which should be performed to gain as much information as possible.

The Schirmer I test can be performed with or without topical anesthesia (2). For all tests, the lower cul-de-sac is wiped clean of retained tears, gently, with a cotton-tipped applicator. For the unanesthetized test, the filter paper strip (Whatman filter paper no. 41) is notched and placed in the lower eyelid cul-de-sac and left in place for 5 minutes—the patient eyes can be open or closed. This test measures both basic tear production by the accessory tear glands as well as the reflex tearing from the lacrimal gland produced in response to the foreign body on the conjunctiva of the eyelid. A "wetting" of the paper of 10 mm or greater is considered "normal." The second part of the test is to apply two drops of 0.5% ophthalmic tetracaine solution to the inferior cul-de-sac, which eliminates the reflexive tear production by the lacrimal gland and measures the basic tear secretion by the accessory glands (i.e., meibomian glands). The test is then conducted similarly to the unanesthetized version. A paper "wetting" of less than 5 mm is considered abnormal. The third portion of the test is the Schirmer II test, which can be performed with the eyelid either anesthetized or unanesthetized. In this test, the ipsilateral nostril is stimulated with cotton from a cotton-tipped applicator to stimulate a neural reflex for tear production, similar to that which occurs naturally when a foreign body is inhaled into the nose. Any "wetting" under 15 mm is likely abnormal.

Quite a number of etiologies can explain inadequate tear production, including facial nerve dysfunction, advancing age, postmenopause, Sjogren disease and other autoimmune diseases, dehydration, and medications (antihypertensives, diuretics, birth control pills, psychotropics), just to name a few. The importance of Schirmer testing in otolaryngology–head and neck surgery is primarily in the preoperative assessment for eyelid surgery and in the diagnosis of autoimmune disorders affecting the head and neck region.

VISUAL ABNORMALITIES

Physiologically Decreased Vision

Refractive Error

A common cause of poor vision is refractive error or change in refractive error. Patients with *myopia* (nearsightedness) have an eye that is axially too long for its refractive system. Typically a young patient reports not being able to see the blackboard and having to sit at the front of the classroom. Simple prescription of concave lenses usually restores visual acuity to normal. Persons with *hyperopia*, or farsightedness, have an eye that is axially too short and need simple convex lenses to bring near objects into focus. *Aphakia* is a special form of hyperopia in which the refractive power of the eye is too weak following surgical removal of the lens. *Astigmatism* is the nonspheric curvature of the cornea and is extremely common with any refractive error.

Refractive visual surgery, in the form of LASIK (laser-assisted *in situ* keratomileusis) or PRK (photorefractive keratectomy), is becoming increasingly common among patients with myopia. Patients seeking elective reduction of physiologic myopia elect these procedures, which reshape the cornea to improve its curvature. New technology can produce a detailed topographic "map" of the corneal surface, which drives the reshaping process very precisely. These advances have reduced complications and produced more consistent results, including a decreased trend toward a hyperopic drift with time. Some patients need additional mild corrections after the primary surgery, called *enhancements*, to complete the visual improvement process. Side effects of corneal reshaping surgery include halo effect, double vision ("ghosting"), loss of contrast sensitivity, and glare.

Presbyopia

Presbyopia is the term used to describe the clinical need for reading glasses or bifocals as the patient enters the fourth and fifth decades of life. The crystalline lens hardens with age and becomes less elastic, decreasing ability to accommodate or focus for near vision. This is a normal physiologic mechanism and should not be considered a sign of disease. When a cataract forms and interferes with functional vision, it can be removed and replaced with a synthetic, polymer lens specific to the patient's vision system.

Pathologically Decreased Vision

Gradual Loss of Vision

In evaluating reduced vision in pathologic terms, best-corrected visual acuity must first be achieved to eliminate the physiologic abnormalities. The three most common causes of gradual loss of vision are cataract, senile macular degeneration, and glaucoma.

Cataract formation, the loss of transparency of the crystalline lens, is common. Increased density of the lens fibers

and changes in protein content occur, almost without exception, to some degree in every person with increasing age; however, the loss of transparency can be so marked that visual function is seriously hampered. The term *cataract* usually is reserved for the latter situation. Cataract formation usually is evolutional, but it occasionally has a specific cause, such as galactosemia, galactokinase deficiency, diabetic ketoacidosis, postradiation therapy, or trauma. If a metabolic abnormality can be corrected early in the course of cataract formation, some lens opacity can be reversed; however, there is no known reversal of lens changes due to senile cataract. Treatment is surgical removal of the cataract. The need for surgery usually depends on the patient's visual requirements and desires. In rare instances, the cataract damages the eye because of high pressure from rapid swelling and may have to be removed for other than optical reasons.

The operation usually is performed by means of opening the anterior capsule and extracting the lens material. The posterior capsule is left intact and the lens substance removed by *phacoemulsification*. After a person is *aphakic*, the optical power of the lens must be replaced to provide focusing ability. The patient can be fitted with spectacles or contact lenses after the eye has healed, but usually, a polymer intraocular lens is implanted during the surgical procedure, with the appropriate lens strength being determined preoperatively. It is comforting to inform patients that cataract surgery is one of the most successful operations performed.

A second important cause of gradual progressive decrease in vision among older persons is *senile macular degeneration*. The cause of this condition is unknown, but it may be related to a decrease in the blood supply to the macular area associated with hardening of the arteries in the posterior eye, which begins as a pigmentary disturbance in the macula and usually progresses slowly but steadily with increased scarring and often hemorrhage into the tissues. The disease is bilateral but usually asymmetrical. No effective treatment exists, and normal use of the eyes, as for sewing and reading, does not accelerate the process. Patients should be assured that macular degeneration is not a blinding disease because the peripheral vision is not disturbed. Patients with this condition always are able to move around unaided, even though their useful reading vision may be markedly decreased.

Unlike the two aforementioned visually disabling conditions, glaucoma characteristically produces a decrease in peripheral visual ability, but good reading vision is maintained until late in the disease. Mild glaucoma can normally be controlled with daily topical eye drops.

Sudden Loss of Vision

Sudden loss of vision is a dramatic event and usually is caused by an identifiable pathologic process. Some processes can be treated and controlled to allow restoration of vision, while others produce permanent loss of visual function. Vitreous hemorrhage unrelated to trauma can occur in advanced diabetes mellitus as a result of disease of the retinal blood vessels. The vitreous "haze" prevents complete examination of the retinal blood vessels, and the offending area often remains unidentified until the blood is reabsorbed. It can take months or years for the vitreous to clear in a relatively young person, producing marked disability, while it may never clear in an older person.

Central retinal arterial occlusion causes total and permanent loss of vision and abolishment of the direct pupillary reaction to light. On ophthalmoscopic examination, the fundus will appear pale with development of a cherry-red spot in the macula. The spot is caused by continued choroidal blood supply to the macula with the contrasting loss of circulation to the rest of the retina. The retinal arteries are narrow and may have fragmented blood columns ("boxcar sign"). The cause usually is an embolus from diseased carotid arteries, abnormal heart valves, or thrombosis from long-standing atherosclerosis. In rare instances, central retinal arterial occlusion is a vasospastic event associated with an inflammatory disease. Treatment aimed at relieving the obstruction through drug-induced vasodilation, ocular massage, and inhalation of 5% carbon dioxide and 95% oxygen usually is unsuccessful. Attacks of *amaurosis fugax* and central or branch retinal artery occlusion have been shown to be related to internal carotid artery stenosis (3). An increase in ulcerated free plaque surfaces appears, which might lead to arterial embolization. Duplex ultrasonography and continuous-wave Doppler ultrasonography can be used for obtaining a noninvasive diagnosis; however, magnetic resonance angiography (MRA) is rapidly gaining favor as a sensitive screening test for carotid stenosis.

Central retinal venous occlusion is more common and less dramatic than arterial occlusion, and it has a markedly better prognosis. On ophthalmoscopic examination, the fundus has a dramatic appearance, as if the entire view has been splattered with blood, and the observed vessels appear engorged and tortuous. Much of the hemorrhage clears with time, vision returns, and late complications of retinal anoxia are managed by the ophthalmologist.

Retinal detachment is not a rare occurrence. It is much more common among persons with high myopia (those with long eyeballs), after cataract surgery (~1 in 100), and following facial trauma. The mode of visual loss varies. The patient commonly reports a shadow or curtain in front of the eye, ascending or descending, depending on the direction of the spreading separation of the retina. Associated flashing lights and floaters may be seen as the retinal structure is disturbed. If the macula becomes detached, central vision is abruptly lost. At ophthalmoscopy, the detached retina is found to be pale and wrinkled and to project forward into the vitreous, often to the point at which objects viewed cannot be focused by the lens onto the retina. Surgical reattachment of the retina is successful in 60% to 80% of cases, but return of vision depends on early



Figure 14.4 Edema of the optic disk indicates optic neuritis.

diagnosis, length of time detached, and avoidance of late surgical complications.

Optic nerve compromise, whether in the form of ischemia or inflammation, is not as common as retinal detachment, but it is equally dramatic and important. A patient older than 55 years who has sudden loss of vision and perhaps has vague arthritic symptoms, low-grade fever, or temporal scalp tenderness should have the erythrocyte sedimentation rate (ESR) measured. If the ESR is elevated, the diagnosis is most likely *temporal arteritis*, with the opposite eye being at risk for parallel visual loss. Systemic steroid therapy should be initiated early to prevent the onset of inflammation in the other eye. For a younger person, if loss of vision is associated with edema of the optic disk, the diagnosis is likely *optic neuritis* (Fig. 14.4). The prognosis for return of vision is good, but the possibility that a demyelinating disorder, such as multiple sclerosis, is present must be strongly considered.

Sometimes, the report of sudden loss of vision is unfounded. This usually occurs when an older patient suddenly "discovers" a loss of sight that has existed for some time. Chance occlusion of the seeing eye reveals the visual loss, which is erroneously reported as being acute. The report of sudden loss of vision also can be associated with hysteria or malingering and the desire for secondary gain. This is especially true in young adolescents.

Transient Loss of Vision

Transient loss of vision can be part of the aura of migraine or a consequence of chronic papilledema. Visual blackouts are common in vertebral–basilar insufficiency after at least 80% narrowing of this vascular system from atherosclerosis. These blackouts are ominous because repeated attacks often are not transient and can be permanent. Abnormalities in the carotid system can cause temporary, usually unilateral, loss of vision (*amaurosis fugax*). Associated cerebral symptoms and hemiparesis may be noted. Because 15% to 20% of these patients later have a stroke, they need a complete vascular evaluation.

Diplopia

Diplopia is another symptom of visual abnormality. Physiologic diplopia is a normal phenomenon in which objects not within the area of fixation are seen as double. This is easily seen when one looks at a near object with attention directed at a distant object, which then appears double. Usually, this is not in one's conscious awareness. Diplopia can either be monocular or binocular, and this must be determined initially through eye cover testing (4). Pathologic diplopia is a cardinal sign of weakness of one or more of the extraocular muscles and usually is caused by neurologic disease, trauma, or diabetes mellitus. Diplopia also can occur with normal muscle function if the globe is displaced, as in slowly progressive e orbital disease or tumors that prevent proper alignment of visual stimuli. Monocular diplopia (that which does not go away when one eye is covered) is rare and usually due to splitting of light rays by an irregularity in the cornea, certain types of cataracts, or misaligned photoreceptors in the macula. More commonly, monocular diplopia is a neurotic or functional disorder.

RED EYE

The otolaryngologist–head and neck surgeon occasionally encounters a patient with a *red eye*, possibly in conjunction with another disease or after treatment. The condition causing the red eye often is a simple disorder, such as blepharitis or infectious conjunctivitis (viral), or a reaction to a surgical prep solution or postoperative topical antibiotic that is easily managed by the otolaryngologist if the proper diagnosis is made. In some instances, however, the condition causing a red eye is a more serious disorder, such as intraocular inflammation or acute glaucoma. A patient with one of these vision-threatening conditions requires the immediate attention of an ophthalmologist. The otolaryngologist must be able to differentiate minor irritation from a serious eye disease. Red eye can be caused by infection, inflammation, or allergic reaction of the eyelid, adnexal structures, or intraocular tissues. Other important causes are acute glaucoma, trauma, and various systemic diseases. If in doubt, refer the patient to an ophthalmologist.

Eyelid Abnormalities and Blepharitis

Many common disorders affect the eyelids. A sty (*hordeolum*) is an acute infection of one of the glands in the eyelid, similar to a boil or furuncle in other skin areas of the face. The patient typically has a red eyelid with moderate tenderness and swelling in the involved area. Associated redness

of the conjunctiva may be found. These lesions usually are self-limiting and drain spontaneously, or the patient can be treated with warm compresses and a short-term topical antibiotic such as azithromycin. A chronic lipogranulomatous structure known as a *chalazion* is caused by an abnormality in the meibomian glands of the eyelid. If the patient requests treatment (which is not usually urgent), this lesion can be improved by surgical curettage. Diffuse inflammation or infection of the eyelids is known as *blepharitis*. It characteristically has two forms. The first is a chronic staphylococcal infection of the glands surrounding the eyelashes. Abnormal oil secretions from these glands irritate the eye and cause redness and sometimes small, whitish infiltrates in the cornea near the limbus. The other form is *blepharitis* associated with typical seborrhea of the scalp, eyelashes, and eyebrows. These conditions tend to cause swelling of the eyelids, a moderate amount of erythema of the lid margins, and mild to moderate conjunctival injection. The patient describes having irritated eyes with scaling or crusting of the eyelashes. Treatment is long term and is directed at eradicating the contaminated flora, controlling the scalp seborrhea, and cleaning the lids with an ophthalmic lid scrub preparation. Anatomic abnormalities of the eyelids, such as entropion, with irritation due to misdirected eyelashes (*trichiasis*), or ectropion, which causes poor tear function and corneal exposure, can be eliminated as the cause of redness by simple observation.

Conjunctivitis, Episcleritis, and Scleritis

Conjunctivitis is inflammation of the mucous membrane covering the globe and lining the inner part of the eyelids. Conjunctivitis usually is infectious or allergic. Viral conjunctivitis caused by the adenovirus group is the common "pink eye" for which children are sent home from school as a public health preventive measure owing to a high transmission rate. Symptoms are mild, with only diffuse redness of the conjunctiva, minimal clear discharge, and perhaps a tender preauricular lymph node or associated pharyngitis. The condition is generally self-limited, but it is highly contagious in its early stages. Bacterial conjunctivitis is commonly caused by strains of *Staphylococcus*, *Diplococcus*, or *Haemophilus*. The patient has mild symptoms of "grittiness" and photophobia. The most characteristic finding is that the lids stick together overnight because of a mucopurulent discharge. If acute, copious purulence is present, the offending agent may be *Neisseria gonorrhoeae*, and further historical and systemic investigation should be performed. Routine culturing is recommended for documentation of infection, and a prompt response normally occurs to treatment with broad-spectrum topical antibiotics, such as a fluoroquinolone. If symptoms persist for more than 2 weeks, an alternative diagnosis should be entertained, or drug resistance suspected.

Allergic conjunctivitis can occur in response to topical medications, cosmetics, aerosols, or as part of an ocular–nasal hypersensitivity complex. The first exposure can be dramatic with severe itching and profuse watering associated with marked edema of the conjunctiva (*chemosis*). The eyelids may be swollen shut, similar to the allergic reaction to an insect sting. This condition can be unilateral or bilateral. It usually is managed with cold compresses and topical and systemic allergy therapy, with avoidance of the offending allergen, if possible.

Deep to the conjunctiva are the episcleral tissues and sclera. If the inflammation is not merely superficial, the patient will report a sensation of deep pain, and the erythema will appear dark red or purplish—*episcleritis* or *scleritis* should be considered. *Episcleritis* usually is an isolated patch of inflammation without significant sequelae. In contrast, more than 50% of cases of *scleritis* are associated with systemic disease, usually of a rheumatoid nature. A *pterygium* is a soft, fleshy growth of fibrovascular tissue from the conjunctiva that can later encroach upon the cornea. Usually, it is an innocuous disorder, which can be treated medically, unless the growth involves the visual axis over the pupil—at that point, surgical removal is needed. Recurrent inflammation of a *pterygium* can also produce a discrete area of conjunctivitis.

Keratitis

Keratitis is an inflammation of the cornea. Although often mild, this condition can be dangerous and threaten vision. Disruption of and infiltrates in the cornea always produce pain, photophobia, and decreased vision. The conjunctiva is injected, and iritis may be present. Keratitis caused by the herpes simplex virus is a concerning ocular condition. The infection typically forms a branching dendritic pattern on the cornea that can be readily seen on slit lamp examination. If recognized before corneal scarring occurs, the infection can be controlled with any of several antiviral medications. Long-term oral acyclovir use seems to remain effective in decreasing the number of ocular herpes simplex virus recurrences beyond 12 months (5). Iridocyclitis can be caused by the varicella-zoster virus, which affects the ciliary body and the skin of the tip of the nose along the nasociliary nerve.

Bacterial, viral, or fungal corneal ulcers are serious conditions that necessitate intensive therapy and cause prolonged morbidity. Ulcers caused by *Pseudomonas* organisms sometimes progress to perforation of the cornea within 24 to 48 hours despite intensive therapy. Because any disruption of the corneal epithelium can allow entrance of opportunistic organisms, infection must be considered, particularly after trauma and in the treatment of debilitated patients with a poor tear film. A topical ophthalmic antibiotic solution may be prescribed if bacterial superinfection is suspected or confirmed. A fluoroquinolone is usually prescribed. Topical steroids are not indicated in fungal and viral keratitis.

Iritis and Iridocyclitis

The iris and ciliary body anatomically constitute the anterior uveal tract. *Uveitis* is a general term that describes inflammation of the iris (*iritis*), ciliary body (*cyclitis*), or most commonly both (*iridocyclitis*). Acute iridocyclitis causes severe aching of the eye, intense photophobia, tearing, and in many instances, decreased vision. The redness usually is most evident around the limbus over the ciliary body ("ciliary flush"), unlike the diffuse redness of conjunctivitis. The pupil is constricted owing to direct irritation of the iris sphincter muscle, and the anterior chamber fluid is cloudy owing to the presence of inflammatory exudate and cells entering the aqueous fluid. Severe secondary glaucoma can occur if clumps of this debris block the filtration angle. In most acute cases of iritis not associated with severe corneal disease or trauma, the cause is unknown, but the condition may be associated with tuberculosis, sarcoidosis, ankylosing spondylitis, rheumatic diseases, gonorrhea, or Reiter syndrome.

The objective in managing iritis is suppressing inflammation and easing pain due to spasm in the ciliary body. This is achieved with topical steroids and a topical cycloplegic agent. Systemic analgesics often are needed. Varicella-zoster outbreaks can involve the iris and produce marked iridocyclitis. This appears to be more common with involvement of the external nasal nerve, a branch of the ethmoid nerve, which is related to the innervation of the iris. The herald sign of this disorder is a painful eye, usually red, which is associated with herpetic eruptions along the ipsilateral lower half of the nose. This is considered an urgent ophthalmologic condition and should be managed by an ophthalmologist. *Varicella-zoster ophthalmicus* is a frequent first manifestation of acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus infection (6). Acute retinal necrosis also may be present. Herpetic lesions of the face have the highest association with AIDS. An underlying immunodeficiency syndrome should be suspected and investigated when herpetic lesions involve the eye.



Figure 14.5 Proptosis, chemosis, and redness of left eye suggest serious orbital or cavernous sinus disease.

Miscellaneous Causes

Several other important pathologic processes must be considered in the differential diagnosis of red eye. If a history of trauma is known, a foreign body or abrasion must be considered. Patients with acute angle-closure glaucoma have severe pain, a cloudy cornea, a dilated and sluggish pupil, a marked decrease in vision, and an increase in IOP. *Dacryocystitis* (inflammation of the lacrimal sac) is characterized by painful swelling and erythema in the medial canthal area, which can cause systemic symptoms with fever and marked leukocytosis. Treatment consists of heat, antibiotics, and surgical drainage. Orbital cellulitis is a serious condition and can be life threatening among children and persons with suppressed immune function. If ocular motility is limited, attention must be given to monitoring pupillary reaction and observing optic nerve compression as an ominous sign of visual loss. A red eye associated with sudden proptosis is a sign of serious orbital or cavernous sinus disease (Fig. 14.5). Tables 14.2 and 14.3 summarize the signs and symptoms helpful in the differential diagnosis of red eye and the indications for referral.

TABLE 14.2 SYMPTOMS OF RED EYE

Symptoms	Referral	Acute Glaucoma	Acute Iridocyclitis	Keratitis	Bacterial Conjunctivitis	Viral Conjunctivitis	Allergic Conjunctivitis
Blurred vision	R	111	1–11	111	0	0	0
Pain	R	11–111	11	11	0	0	0
Photophobia	R	1	111	111	0	0	0
Halo	R	11	0	0	0	0	0
Exudation	0	0	0	0–111	111	11	1
Itching	0	0	0	0	0	0	11
Head cold, fever	0	0	0	0	0	0,11	0

R, referred to ophthalmologist; 0, absent; 1, mild; 11, moderate; 111, marked.

TABLE 14.3 SIGNS OF RED EYE

Signs	Referral	Acute Glaucoma	Acute Iridocyclitis	Keratitis	Bacterial Conjunctivitis	Viral Conjunctivitis	Allergic Conjunctivitis
Ciliary flush	R	1	11	111	0	0	0
Conjunctival injection		11	11	11	111	11	1
Corneal haze	R	111	0	1–111	0	0,1	0
Pupil	R	Middilated nonreactive	Small, with or without irregularity	Normal or small	Normal	Normal	Normal
Anterior chamber depth	R	Shallow	Normal	Normal	Normal	Normal	Normal
IOP	R	High	Usually low	Normal	Normal	Normal	Normal
Discharge		0	0	6	11 or 111	11	1
Preauricular node		0	0	0	0	1	0

R, referred to ophthalmologist; 0, absent; 6, present or absent; 1, mild; 11, moderate; 111, marked.

Guidelines for Treatment

Adult patients with bacterial conjunctivitis are treated with antibiotic drops rather than ointment, except at bedtime. Children are treated with ointment. A 10% to 15% solution of sodium sulfacetamide given four times daily for 4 days is recommended unless the patient has a sulfa allergy. Patients with sulfa allergies can be treated with tobramycin or gentamicin sulfate, or another topical solution may be substituted. Neomycin topicals are to be avoided because of the high incidence of allergic reaction and contact dermatitis. Cycloplegic eye drops, such as atropine, homatropine, or cyclopentolate hydrochloride, are used to reduce ciliary spasm to decrease pain. If these agents are prescribed, the patient must be warned of the side effects of decreased near vision and pupillary dilation. Topical anesthetic drops should be used for diagnosis only. Prolonged use can slow corneal healing and cause severe allergic reactions. Because these agents eliminate corneal sensation, the protective blink reflex is retarded, opening the pathway to corneal dehydration and injury.

Administration of topical steroids should be reserved for the ophthalmologist. If the condition is one best managed with steroids, the patient should be examined and treated by this specialist. Steroid eye drops make the patient feel better, but in conditions such as herpes simplex, keratitis, or fungal corneal ulcers, symptoms may decrease while the cornea is melting away and threatened by perforation. Several weeks of use of glucocorticoids can cause cataracts and elevation in IOP, which leads to typical glaucomatous optic nerve damage and visual loss.

Proptosis

Proptosis is a disconcerting presentation, both for the patient and the physician. The most common cause of proptosis is thyroid eye disease. Also to be considered are an expanding intraorbital mass, benign or malignant sinus disease, sphenoid ridge meningioma, and *idiopathic orbital inflammatory syndrome* (IOIS), also known as *orbital pseudotumor*. This condition of IOIS has no known cause and can affect any structure in the orbit. Its presentation may be insidious or abrupt (7). Typically, the diagnosis is one of exclusion and may be confirmed by a trial of oral steroids. If improved, then the steroid therapy may be continued until the condition has regressed. Occasionally, IOIS can be somewhat steroid-resistant, and low dose radiation therapy may need to be considered, weighing the risks and benefits. Both magnetic resonance imaging (MRI) and computed tomography (CT) scanning may be required to rule out other causes of proptosis.

OCULAR TRAUMA

When a patient sustains ocular trauma, the most important task is to differentiate a serious, potentially blinding problem from less serious problems. The care rendered by the first physician to examine a patient with ocular trauma frequently determines the visual outcome. A few minutes can make the difference between saving or losing sight. For these reasons, all patients with ocular symptoms should be treated according to an organized and evidence-based therapeutic plan. Posttraumatic (direct facial trauma) visual loss has a reported incidence ranging between 0.8% and 30% (8,9). Damage to the optic nerve, its tract, and projections in the brain are also causes of visual loss in the head trauma patient (10).

History and Examination

As in all specialties of medicine, a patient's symptoms and history provide clues about what the examination may reveal. A tearing or scratchy sensation usually is trivial,

but a chemical burn or penetrating injury can be visually devastating. The physician should always be cautious of a missed diagnosis. A trivial or seemingly minor injury can be accompanied by a small perforation of the globe or penetration of a minute foreign body into the eye. The likelihood of perforation should always be borne in mind during examinations, regardless of how minor the injury may appear. After the most careful examination, if the slightest doubt exists about the presence of perforation, prompt referral to an ophthalmologist is recommended and is usually the standard of care in a community.

A detailed history, as would be appropriate in outpatient care or in evaluating a chronic problem, is not indicated or necessary in an emergency. A focused, pertinent history is important, however. How did the trauma happen? For example, did something blow into the eye while the patient was walking outside, or was the patient grinding steel and struck in the eye by a piece of metal? When did the trauma happen? The chronology of events is extremely important. Also essential is a history of the eye. When a patient has a decrease in visual acuity, it is important to know whether that eye has had poor vision in the past or this is an acute change. Old trauma must be differentiated from the effects of a new injury.

After a history is obtained, a careful, focused examination of the structures involved should be undertaken, especially with documentation of visual acuity. This baseline is important from a medical legal point of view, and it is very helpful in ascertaining the extent of the injury and the progress of treatment. If a patient does not have his or her glasses for the examination because they were broken in the trauma, a pinhole test can be used to evaluate vision by obtaining the best possible acuity of the eyes.

Orbital Trauma

Trauma to the orbit can be superficial, resulting in only ecchymosis of the lid (black eye), or it can be extensive, involving the bony walls and intraocular structures. Knowledge of the orbital anatomy and its visualization on imaging studies, as well as indications for surgery, is very important for the otolaryngologist who cares for facial trauma patients (11). Plain radiographs of the orbits are of limited value after orbital trauma except for localizing embedded metallic foreign bodies. CT, both axial and coronal, provides the best information about osseous components of trauma. Soft tissue window algorithms can be used to assess hematoma formation, orbital fat prolapse, and other damage. Evidence of orbital emphysema on CT scan usually represents a loss of integrity of orbital walls. Although the air usually resorbs spontaneously, increased IOP and retinal artery compression can occur if extensive air is present due to volume expansion around the eye. Evaluation of extraocular muscle function can indicate intraorbital soft tissue entrapment in an orbital floor fracture. Subcutaneous emphysema in the eyelids can point to a medial wall fracture into the ethmoid air cells. Visual acuity should always be documented, as a decrease may indicate concomitant ocular damage. More than 30% of injuries to the bony orbit are associated with intraocular injury (12,13). If the injury is superficial or if the findings at radiography, motility studies, visual acuity testing, and globe inspection are normal, the patient can be reassured. Otherwise, a referral to an ophthalmologist should be made for further ocular examination and appropriate therapy.

Eyelid Laceration

Trauma to the eyelid can be routine or quite involved. A superficial laceration, parallel to the lid margin, is similar to a skin laceration in other parts of the body and can be repaired in the same manner. Foreign bodies, however, can be overlooked; therefore, the wound should be explored and irrigated gently before surgical closure. If deeper structures are involved, the anatomic relations of the levator palpebrae muscle, tarsal plates, and orbital septum must be identified, and the appropriate repairs performed if disrupted. Lacerations that involve the lid margin or are medial to the punctum and involve the canalicular structures require detailed surgical reconstruction. The primary repair is extremely important because secondary scar revision and attempts to reestablish the function of a scarred eyelid or tear-drainage apparatus are difficult. Faulty primary repair, through failure to suture the tarsus well and removal of marginal sutures too soon, can produce a notch in the eyelid that interferes with its ability to spread the tear film as well as causing epiphora. Irritation and constant tearing can be caused by loss of corneal epithelium as well as ulceration of the cornea. Complicated lacerations therefore should be managed by a surgeon knowledgeable in the anatomic and physiologic characteristics of the eyelids and associated structures.

Superficial Injuries of the Cornea and Conjunctiva

The eyelid and attached conjunctiva, although important, are considered superficial eye structures, and injuries to them often can be managed by a nonophthalmologist. Subconjunctival hemorrhage usually is without sequelae, behaving as a bruise elsewhere on the body. The patient should be reassured that the blood clears over a 10- to 20-day period. The hemorrhages can be caused by minor trauma or by coughing or sneezing; they also can occur spontaneously. Little or no value is seen in performing hematologic or blood coagulation studies for patients with spontaneous subconjunctival hemorrhages unless a history of frequent recurrence or other easy bleeding is given. In those cases, the possibility of blood dyscrasia should be considered, although most commonly the patient is noted to be on aspirin or other blood-thinning therapy. These

patients have a bright red eye, normal vision, and no pain. If subconjunctival hemorrhage is seen in conjunction with severe trauma, the otolaryngologist and ophthalmologist always must rule out more serious injuries to the deeper ocular structures.

Corneal or conjunctival foreign bodies first should be approached with irrigation. If this is not successful, they can be brushed out very gently with a cotton-tipped applicator or nudged out with a small pick or needle. One drop of topical anesthetic solution usually is all that is necessary to allow manipulation of the object. If a foreign body is not seen on ophthalmoscopic examination, but the symptoms or history indicate the presence of one, fluorescein stain can be used to outline a corneal abrasion. A small strip of fluorescein paper is moistened with sterile water, and this strip is applied to the inferior cul-de-sac while the patient looks up or to the superior cul-de-sac while the patient looks down. When a cobalt blue penlight or Wood lamp (ultraviolet light) is used, fluorescence may outline the abrasion. If the patient wears soft contact lenses, use of fluorescein should be avoided, because the dye can permanently stain the lenses. The pain of corneal abrasion is sharp and stabbing and is aggravated when the patient opens and closes his or her eyes. It is often associated with marked photophobia, unlike the deep ache of iritis and the superficial mild and intermittent discomfort of conjunctivitis.

If the abrasion is vertical over the cornea, the lid should be everted, and a foreign body may be found embedded in the conjunctiva of the upper lid. To perform lid eversion, the patient looks down while a cotton-tipped applicator handle, pencil eraser, or finger is placed just beneath the orbital rim. The eyelashes are grasped with the other hand and pulled straight out from the globe; the lashes are then pulled up and forward, and the eyelid flipped over the applicator stick or the base of the finger as a fulcrum. The everted lid is held against the orbital margin, and the underlying structures are examined. Approaching the patient with confidence makes this procedure simple.

Overwearing contact lenses or excess exposure to an ultraviolet sunlamp can cause severe punctate corneal damage with eyelid edema. Treatment usually is observational with symptomatic relief. Symptoms appear 6 to 12 hours after exposure or after the contact lenses are taken out. The patients experience marked light sensitivity and a feeling of sand or grit in the eyes. Superficial pain can be severe. Marked spasm of the lids is seen with associated tearing. It is not appropriate to use topical anesthetic eye drops to alleviate the mild and transient discomfort. Oral analgesics will provide adequate pain relief.

Misplacement of a contact lens is a common occurrence with patients. The lens usually can be found, with adequate evaluation, in the deep folds of the conjunctival fornices. The patient should be reminded that if it is not found, the lens did not migrate posteriorly into the intracranial structures but rather dropped out. This reassurance can only be rendered after a thorough examination.



Figure 14.6 Appearance of an injured eye with a corneal abrasion outlined with fluorescein dye.

Therapy for corneal abrasions, including treatment after removal of a foreign body, consists of antibiotic eye drops. This is recommended particularly if the injury was caused by contaminated material, such as a fingernail or a twig. If a large abrasion is present and the eye is quite inflamed, a cycloplegic agent can be used to reduce ciliary spasm and pain (Fig. 14.6). The eye often is patched for comfort for 24 hours to speed healing. Topical steroid or steroid–antibiotic eye drops should *not* be prescribed, and topical anesthetics should not be given for home use. Most small abrasions heal spontaneously within 24 to 48 hours and larger ones in less than a week.

Blunt Trauma

A severe blow to the eye or orbit can miraculously spare the ocular structures, or it can be devastating to them. The most common physical finding in cases of blunt trauma is *hyphema* (blood in the anterior chamber). If an eye has sustained a blow hard enough to cause ciliary body bleeding, which is believed to be the origin of the blood, the anterior chamber angle structures can be anatomically and physiologically disrupted and the filtration network compromised. The patient is at risk for development of increased IOP, either acutely or at a later time. Dislocated or subluxed cataractous lenses may also occur from blunt trauma to the orbit and eye. The vitreous can be detached and become hemorrhagic, and retinal holes or detachment may occur, leading to visual loss. Scleral rupture can occur anteriorly or posteriorly, and the optic nerve can be contused or avulsed. Blunt trauma to the eye necessitates a rapid and complete ophthalmologic examination with lifelong care and follow-up evaluations for significant injuries to the eye.

Penetrating Injuries

If the eye has been penetrated, urgent care must be administered by an ophthalmologist. If the otolaryngologist

suspects a penetrating eye injury, the eye should be protected and an immediate consultation requested. If foreign bodies are partially extruding from the eye, the diagnosis is evident. The foreign body should be left intact and removed in the controlled environment of an operating room. A key to the diagnosis of penetrating eye trauma is the appearance of a "peaked" or "teardrop" pupil. If the pupil is not round and is pulled to one side, the examiner should suspect a penetrating injury and treat the affected eye with extreme care, with no further manipulation of the orbit. The combination of lid laceration and hyphema also suggests penetration. To transport a patient with a penetration wound of the eye, an aluminum shield or a cone made from x-ray film, or a plastic drinking cup, can be placed over the involved eye to avoid pressure that can cause extrusion of intraocular contents. Tetanus prophylaxis is appropriate, especially if the etiology is unknown or was a potentially contaminated object.

Burns

An emergency that often comes to medical attention too late is a chemical injury, owing to the very short time that elapses before permanent damage is done to the eye. Serious alkali or acid burns are true emergencies. In the first few minutes after injury, the toxic solution must be diluted with any liquid available. It is not necessary to spend time attempting to neutralize the solution—immediate and profuse dilution is extremely important. Copious irrigation should be performed for at least 5 minutes; the eyelids should be held forcefully apart during irrigation. The patient can also be held over a drinking fountain or under a low pressure water faucet for irrigation. Topical anesthetic usually is needed to remove particulate chemical matter from the eye. If lid spasm is severe, a selective facial nerve block of the orbicular muscles lateral to the orbit (using a short-acting anesthetic agent such as lidocaine) may be considered to keep the eyelids open for irrigation. After the diagnosis is made and initial treatment completed, an additional 20 minutes of continuous irrigation with balanced salt solution or lactated (isotonic) Ringer solution as a continuous intravenous drip should be undertaken. Cycloplegic and antibiotic eye drops usually are administered, and a sterile eye patch is gently applied after all local therapy has been completed. Thermal or flash burns of the eye and eyelid are managed with the same general measures as other skin burns. The ocular sequelae of chemical burns can cause total blindness. Damage to the eyelids from chemical or thermal burns usually causes severe cosmetic disfigurement, permanent tearing, exposure keratitis, and corneal ulceration or perforation.

PEDIATRIC OPHTHALMOLOGY

As the study of childhood disease entails a distinct category of otolaryngology–head and neck surgery, problems of the pediatric eye should be considered separately.

Congenital Abnormalities

The ocular structures can be affected by developmental abnormalities and congenital anomaly syndromes. These range from minor cosmetic deformities to complete lack of any visual components. Congenital glaucoma is characterized by a large eye and marked photophobia. Childhood cataracts often are of known cause, such as a manifestation of congenital rubella or a consequence of an inborn error of metabolism. Any abnormality in the red reflex elicited through the ophthalmoscope during examination of a newborn should be cause for referral. The "cat's eye reflex," or white pupil, suggests many serious diseases, the most severe of which is the most common malignant intraocular tumor of children—retinoblastoma.

Strabismus

Most of the practice of pediatric ophthalmology centers on the care of patients with *strabismus* (failure of the two eyes to look at the same object) and *amblyopia*, an important preventable cause of vision loss. Strabismus is misalignment of the two eyes so that only one eye is directed at the specific object of regard. General ocular inspection may reveal gross deviation of one eye. The corneal light reflex provides an estimation of the amount of the deviation. The cover test can help detect almost every case of strabismus. A small amount of phoria is present among most patients with normal eyes and should not be cause for alarm.

All newborns should be examined for gross alignment of the eyes. Up to age 3 to 4 months, children often have uncoordinated eye movements and can temporarily manifest actual strabismus. An ophthalmologist should be consulted if occasional deviations persist beyond this age. Infants with constant deviations should be referred at any age, as soon as possible. The determination, by examination or history, that a deviation is intermittent is an important prognostic sign. Normal binocular vision can develop only with precise coordination of the two eyes. If the mental object of regard is seen by only one eye, and another object seen by the opposite eye, the brain suppresses the accessory image to avoid diplopia, thereby turning off the input from the deviating eye. If the eyes are straight at least part of the time (intermittent strabismus), or if the deviation alternates (first one eye assumes fixation and then the other), a chance exists for full development of visual potential with therapy.

Esotropia

Esodeviation is the most common type of strabismus, often manifesting itself soon after birth and occasionally necessitating surgery to straighten the eyes. Esodeviation also can appear in the 2nd or 3rd year of life and can be associated with an attempt to focus the eyes owing to marked refractive error, which often can be corrected with glasses alone.

Pseudostrabismus

Among children with large epicanthal folds, an appearance of esotropia can be quite marked, a condition called *pseudostrabismus*. When the folds flatten with age, the appearance changes, leading to the unfounded misconception that children outgrow strabismus.

Exotropia

Exodeviation is less common than *esotropia*. It usually occurs intermittently with fatigue, daydreaming, or when the child is in bright sunlight. Normally, after correct diagnosis, no treatment is required, save for reassurance. Long-term follow-up is recommended.

Amblyopia

Amblyopia is defined as unilateral defective vision, uncorrectable by glasses, in an otherwise normal eye. It occurs in about 5% of the young adult US population and is commonly known as a "lazy eye." Half of all patients with amblyopia will have or have had associated strabismus. Refractive amblyopia occurs when a marked difference exists in refractive errors of the two eyes. Like suppression to avoid diplopia in strabismus, the brain turns off the blurred image produced by the eye with the greater refractive error to obtain a clearer object of regard. Occlusion amblyopia occurs if opacities of the ocular media, such as ptosis, cataract, or macular lesions, prevent adequate sensory input. Retinoblastoma often manifests as esotropia due to macular involvement. All patients with strabismus need complete dilated ocular examinations.

Detection

Amblyopia, if detected early, often is curable. Treatment rarely is successful after age 9, and best results are obtained if the patient is treated before age 5. The key to this disease is early intervention. Prompt investigation is mandatory if a child has obvious strabismus. Even if the eyes appear straight during a routine pediatric examination, the examiner should observe how the child watches a light, follows a moving object, and reacts to having each eye covered alternately. If amblyopia exists, the patient probably will resent, vocally or through evasive movement, covering of the "good" eye. Even before a child can give a verbal response to visual acuity testing, he or she should be able to maintain central and steady fixation with each eye. By age 3, visual acuity can be measured with picture cards or single E charts. The examiner must be certain that only one eye at a time is participating in the test. Children always try to peek if the opposite eye is not properly occluded. Young children may not quite reach 20/20, but as long as both eyes are near that standard and equal, the parents can be reassured. Amblyopia may be present if a two-line difference is noted between the two eyes on a visual acuity chart or if best vision is only 20/30 to 20/40. Although amblyopia is a relatively minor visual impairment, many adults with a history of lazy eye have vision of only 20/200 or even less due to an unrecognized amblyopia in childhood.

Treatment

Therapy for amblyopia is based on the simple idea of forcing the child to use the affected eye. Proper spectacle correction is followed by patching the normally used eye. The duration of treatment is monitored by the ophthalmologist. After maximal amblyopic treatment, surgical correction of any residual strabismus is undertaken to prevent recurrence of the amblyopia and to improve cosmesis and minimize psychosocial problems. Early detection and prompt referral of patients with strabismus or amblyopia can be one of the most important contributions of a physician treating pediatric patients.

Suspected Child Abuse

Unfortunately, child abuse has become one of the leading causes of death in infancy. For those physicians who see pediatric patients in the emergency center, it is important to recognize the herald signs of child abuse ("shaken baby syndrome") and to notify child protective services when suspected. Retinal hemorrhage is a not uncommon feature of child abuse, seen in 32% of children being evaluated for abusive head trauma (14). It is a feature of this unfortunate condition that should be kept in mind.

THE EYE IN SYSTEMIC DISEASE

Neurologic Disease

The ocular manifestations of systemic disease always play an important role in general medicine. Neurologic and neurosurgical diagnoses often are made from eye examinations, and the disease course can be monitored with an ophthalmoscope because the eye is truly the "window to the brain." Finding a fixed, dilated pupil or Marcus Gunn pupil is important. Swelling of the optic disk or true papilledema is an important ophthalmoscopic finding, indicating increased intracranial pressure. A patient with papilledema usually has normal visual acuity, elevation of the disk with absence of the cup, blurred disk margins, venous engorgement, hyperemia of the disk, and hemorrhage and exudate around the disk. The presence or absence of venous pulsation is not a reliable sign. Inflammatory swelling of the optic disk (papillitis or optic neuritis), commonly a result of demyelinating disease, may appear ophthalmoscopically similar, but the patient reports markedly decreased vision due to direct nerve damage.

Optic atrophy, often described as an "aspirin disk," appears as a pale nerve head without normal capillaries on the surface. It is a nonspecific finding related to some form of optic nerve compromise. The presence of an atrophic nerve is sufficient to explain decreased visual acuity,

but it represents only a physical finding and is not sufficient to confirm a neurologic diagnosis. The cause of optic atrophy must be established from the history, further ophthalmoscopic or neurologic examination, and appropriate advanced imaging. Common causes of optic atrophy include optic sheath and sphenoid ridge meningiomas, temporal arteritis, multiple sclerosis (optic neuritis), stroke, and traumatic injury.

Thyroid-Associated Orbitopathy

Also known as Graves ophthalmopathy and thyroid orbitopathy, thyroid-associated orbitopathy (TAO) can raise both functional and cosmetic concerns. Although the cause of proptosis can be a primary or metastatic tumor, arteriovenous malformation, or carotid cavernous fistula, by far the most common cause of unilateral or bilateral proptosis is abnormal thyroid function. It has been reported that 90% of TAO are associated with hyperthyroidism, while the remaining 10% of patients are either euthyroid or hypothyroid (15). In classic Graves disease, the patient appears "bug-eyed" owing to exophthalmos and eyelid retraction (Fig. 14.7). Approximately 40% of patients with Graves thyroid disease will ultimately develop TAO (16). Ocular motility may be reduced because of infiltration of the muscles and periorbital tissues with an abnormal mucopolysaccharide substance. If the cornea becomes desiccated from exposure or if orbital pressure increases to the point at which papilledema or optic atrophy occurs, the thyroid condition is considered "malignant" and often necessitates immediate medical and surgical therapy. Surgical therapy may consist of orbital decompression, usually transnasal, endoscopic, with homografts implanted in the eyelids to extend the length of the tarsus and close the palpebral fissure for corneal protection. Results of thyroid tests may not correlate with the progress or severity of the eye findings, but combined evaluation and follow-up care with an endocrinologist are encouraged.

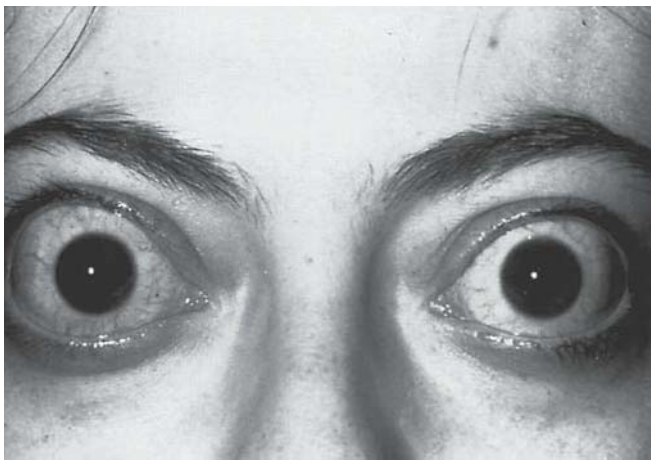


Figure 14.7 Exophthalmos and lid retraction due to Graves disease.

Collagen Vascular Disease

The external layers of the eye have a high collagen content. Inflammatory diseases that affect this tissue, such as rheumatoid arthritis or systemic lupus erythematosus, often cause external ocular inflammation. *Keratoconjunctivitis sicca* is the dry-eye component of Sjögren syndrome. Most of these diseases also have a vasculitis component, and retinal vascular sheathing and occlusions are common.

Systemic Infection and Metastatic Cancer

Systemic infection such as septicemia often establishes a metastatic focus in the eye, most commonly as choroiditis. Tuberculosis, syphilis, and histoplasmosis often are diagnosed in this manner. Orbital or elevated choroidal lesions often occur with metastatic carcinoma, especially metastasis from the lung and breast (Fig. 14.8).

Blood Dyscrasia

Blood dyscrasias, such as hyperviscosity syndromes, leukemia, or sickle cell disease, have characteristic retinal vascular patterns that may help confirm a diagnosis.

Ocular Side Effects of Medication

Ocular side effects, such as blurry vision and diplopia, are common side effects of many systemic medications. The increased IOP and cataractogenic effects of steroids have been mentioned. Ethambutol, chloroquine, and the phenothiazines are commonly used drugs with direct toxic effects on various ocular tissues. Patients taking these and other such medications need baseline examinations and periodic ophthalmic evaluation while on treatment.

Diabetes

Diabetes is associated with many eye changes, including transient changes in accommodation due to fluctuations



Figure 14.8 Orbital lesion due to metastatic carcinoma.

in blood glucose level, cataract formation, and the development of glaucoma. Retinopathy, however, makes diabetes the leading cause of blindness in the United States. Retinopathy is related to the duration and control of this metabolic disease. Within 15 to 20 years after the onset of diabetes, persons with juvenile- and adult-onset diabetes typically develop a visual disability. Good metabolic control can delay the onset of retinopathy, but it cannot totally retard the progression. Glycemia, hypertension, and abdominal obesity are determinants for retinopathy in a general population.

Diabetic retinopathy can be classified as nonproliferative or proliferative. *Nonproliferative* or "background" retinopathy consists of venous abnormalities, exudate, microaneurysms, dot-and-blot hemorrhage, and associated retinal edema. These are the earliest changes characteristic of diabetes, and they begin in the posterior pole of the eye, which is easily viewed with a direct ophthalmoscope. Patients with background retinopathy are generally not treated (unless macular edema is present) and can be observed with routine annual or biannual examinations. *Proliferative* retinopathy refers to the development of new, fragile blood vessels (neovascularization) in response to a hypoxia related to retinovascular disease. These vessels bleed into the retina, causing fibrosis and retraction of the retina to form a detachment, or bleed into the vitreous and cause sudden loss of vision through intravitreal fibrosis and traction on the retina. This end-stage diabetic disorder is called *retinitis proliferans*.

The current therapy for diabetic retinopathy includes vitrectomy and intraocular membrane stripping. After the onset of retinopathy, the 5-year survival rate for the retina is very low if left untreated. To prevent blindness, therapy is directed at the earliest sign of neovascularization. Laser photocoagulation, used to coagulate and destroy the hypoxic retina that is theoretically supplying the stimulus for neovascularization, produces the best long-term results for functional vision.

While retinopathy is the most well-known ocular disorder associated with diabetes, other ocular conditions can be associated with this metabolic disease (17). Cataract formation, *anterior ischemic optic neuropathy*, and *diabetic papillopathy* are conditions that not uncommonly occur with diabetes. Diabetes is also a risk factor for glaucoma, *ocular ischemic syndrome*, and possibly retinal vein and retinal artery occlusion. Patients with diabetes appear to also be more prone to corneal epithelial erosion or defects.

Hypertension and Arteriosclerosis

Hypertensive retinopathy and the retinal vascular changes of arteriosclerosis are quite characteristic. The term *arteriosclerosis*, not atherosclerosis, is better associated with changes in the retina. The central retinal artery usually divides into superior and inferior branches before it is visible on the optic disk; therefore, the vessels seen on ophthalmoscopy are arterioles. Diffuse narrowing of the retinal arterioles is the earliest sign of hypertension, which can be caused by the spasm of malignant hypertension of toxemia or renal disease and can be reversible if promptly treated. Hypertensive changes become permanent, however, if the pressure remains elevated for a prolonged period. Segmental arterial narrowing is the next progression, especially if the diastolic blood pressure remains at or greater than 120 mm Hg. Further damage to the vessel walls causes leakage of blood and plasma, forming superficial "flame-shaped" retinal hemorrhages, deeper dot-and-blot hemorrhages, hard and waxy exudates, and soft "cotton-wool" exudates (*retinal infarcts*). As a response to increased intracranial pressure or to anoxia of the optic nerve, papilledema develops. The 5-year mortality among patients with papilledema related to hypertension is greater than 90%. Large artery disease can also cause fluctuating visual loss, which may precede a cerebrovascular event (18).

Retinal arteriosclerotic damage revolves around changes in vessel wall transparency and abnormality in the arteriovenous crossings. Thickening of the arteriole wall increases in the light reflex stripe viewed through an ophthalmoscope. The thickening progresses until the light reflex appears to occupy the entire width of the blood column ("copper-wire" appearance) then progresses to the point at which no blood is visible at all, giving the characteristic white sclerotic "silver-wire" appearance. At points of arteriovenous crossing, the vessels are in a common adventitial sheath. As the arteriolar walls thicken, compression of the venules becomes apparent, first as tapering of the ends, progressing to "banking" with dilation of the venule distal to the crossing and finally to vascular occlusion with complete interruption of blood flow.

Separate categorization of these companion diseases can be important, even though in the advanced stages, almost without exception, the changes occur together. Specific hypertensive eye changes can alert the physician to the severity of the hypertension. More important, the arteriosclerotic changes mark the chronicity of the disease and mirror the condition of the vessels of the kidneys, heart, and brain. Elevated peripheral blood pressure should trigger a suspicion, leading to an ophthalmologic evaluation. Table 14.4 summarizes acute ophthalmic emergencies, including vascular disorders.

IMAGING IN OPHTHALMOLOGY

MRI is the most sensitive modality for evaluation of most disorders of the central nervous system, including stroke, white matter lesions, and hemorrhage; however, subarachnoid hemorrhage and acute stroke are better visualized with CT. CT imaging is the best imaging method for evaluation of orbital trauma. Within the orbit, MRI clearly is most effective for imaging the soft tissues, optic nerve, and retrobulbar space (19). MRA is an excellent screening tool for extracranial occlusive vascular disease, although it

TABLE 14.4 EMERGENCIES HYPERTENSION AND ARTERIOSCLEROSIS

Sudden loss of vision
Vitreous hemorrhage
Central retinal arterial occlusion
Retinal detachment
Optic nerve compromise
Red eye
Acute glaucoma
Intraocular inflammation
Keratitis
Corneal abrasion or ulceration
Anterior chamber bleeding
Penetrating injuries
Orbital burns
Extraocular muscle entrapment
Increased IOP after eye trauma
Proptosis after sinus surgery
Proptosis, chemosis, decreased motility, or decreased vision associated with sinusitis

slightly exaggerates stenotic lesions. If the carotid artery is found to be totally blocked at MRA, the patient probably cannot undergo surgical treatment. If intracranial aneurysm is suspected, however, conventional angiography remains the standard. MRI can be helpful in the diagnosis of craniopathy involving the orbit. For example, in third-nerve palsy, MRI can help identify brainstem infarcts, hemorrhage, and arteriovenous malformation; lymphoma and trauma involving the subarachnoid space; and cavernous sinus lesions such as cancer, aneurysm, and Tolosa-Hunt syndrome. The extent of periorbital sinus disease may be exaggerated with MR, so CT imaging may be considered as well.

High-resolution orbital A and B scans, 3-D ultrasound images, and ultrasonic color flow imaging can give important anatomic and histopathologic information about intraocular foreign bodies, masses, tumors, thyroid muscle disease, and vascular lesions.

OTHER OTOLARYNGOLOGIC-ASSOCIATED DISORDERS

Nonarteritic ischemic optic neuropathy (NAION) is a disease characterized by sudden visual loss that is painless and associated with nerve fiber bundle field defects, afferent pupillary defect, and optic disk edema. The onset most commonly occurs in the morning. NAION has recently been found to be associated with obstructive sleep apnea syndrome to a high degree (71%) (20). The damage is postulated to be due to impaired optic nerve head blood-flow autoregulation, secondary to repetitive prolonged apneas. Any acute visual disturbance in disturbed sleep patients warrants urgent ophthalmologic consultation.

Dry-eye syndrome is seen frequently in the older otolaryngology patient and is an important factor in surgery of the aging face or facial skin malignancy reconstruction. Incidence of dry eye is greater in older patients with a history of allergy or diabetes who use antihistamines or have generally poor health. Its incidence in the older population approaches 15% (21). Baseline evaluation using the Schirmer tear production test is a good starting point, but a formal ophthalmologic evaluation is recommended.

Significant precautions are to be taken by otolaryngologists in the use of lasers in the region of the face, head, and neck to prevent accidental eye injuries. Laser radiation can damage the eye by photomechanical, photothermal, or photochemical mechanisms. In otolaryngologic applications of the laser, thermal injuries are the most common, leading to protein coagulation. Retinal injuries can be most serious and are readily apparent ophthalmoscopically and angiographically. Retinal laser injuries do not cause chronic pain but can have disastrous visual consequences.

CONCLUSION

The clinical specialties of ophthalmology and otolaryngology–head and neck surgery have a great number of interfaces and overlaps, such that communication between the specialists in the care of patients with congenital, traumatic, neoplastic and inflammatory disorders. In particular, the perioperative evaluation of patients with disorders involving the orbit, globe, and adnexa benefits the otolaryngologist–head and neck surgeon in the diagnosis and management of potential complicating issues. The otolaryngologist–head and neck surgeon should freely consult the ophthalmologist and develop a collegial relationship, such that the patient will benefit from the collaboration. After all, it is always about the care of the patient.

HIGHLIGHTS

- If a person with normal sight is judged to see a certain-sized line at 20 feet (6 m) on an eye chart, a patient in comparison testing who can see that line at 20 feet is considered to have 20/20 vision. If the patient can see a line only at 20 feet that a person with normal sight sees at 200 feet (60 m), then the patient has 20/200 vision.
- A Marcus Gunn pupil is detected with the swinging flashlight test, in which light is shone in one pupil for 2 to 3 seconds and then rapidly switched to the other eye. A prompt constriction should appear in the normal eye, but with optic nerve damage or injury, the pupil gradually dilates.

- Sudden loss of vision can be caused by vitreous hemorrhage, central retinal arterial occlusion (which is irreversible), central retinal vein occlusion (which can be reversed in some cases), retinal detachment, optic nerve compression, or cerebrovascular accident.
- Physiologic diplopia occurs if an object in the near vision becomes double when gaze is focused on a far object.
- Pathologic diplopia occurs when objects appear in the direct fixation of gaze. It can be caused by neurologic disease, tumor, trauma, or a metabolic abnormality.
- Viral conjunctivitis as a cause of red eye is almost invariably associated with pharyngitis and an ipsilaterally enlarged preauricular node. It is highly contagious in its early stages.
- A patient with varicella-zoster skin eruptions on the tip of the nose also may have iridocyclitis because the ciliary body and the nasal skin are innervated by the same nerve.
- Topical anesthetic drops to the eye should be used only for diagnostic purposes. Prolonged use can retard corneal healing, cause severe allergic reactions, and, by eliminating corneal sensation, reduce the protective blink reflex.
- A horizontal laceration of the upper eyelid suggests injury to the levator muscle. Because a foreign body penetrating the eyelids also may have penetrated the globe, ophthalmologic consultation is mandatory.
- When vertical abrasion of the cornea is seen, it is likely that a foreign body is trapped in the upper eyelid. The eyelid should be completely everted and the conjunctiva closely examined.
- Chemical burns of the eyeball and eyelids should be continuously irrigated with Ringer lactate or balanced salt solution for at least 20 minutes, usually under local anesthesia.
- Retinopathy, in the form of retinal hemorrhages or tears, may be a sign of child abuse or "shaken baby" syndrome.

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Anesthesiology

15

Stewart J. Lustik *Shawn D. Newlands*

Anesthetizing a patient for head and neck surgery is one of the most challenging aspects of anesthesia practice, which includes inducing the anesthetic state (amnesia, hypnosis, and immobility), airway and fluid management, and monitoring of cardiac and respiratory function. Patients scheduled for such surgical procedures frequently have partial upper airway obstruction or impending decompensation. The urgency of the operation, comorbidities of the patient, and the stability of the airway guide the selection of the anesthetic technique, particularly the maneuvers needed to secure the airway. Successful surgical and anesthetic care are intertwined; therefore, continuous, thoughtful communication between the surgeon and anesthesiologist is paramount, and understanding the basic principles, physiology, and pharmacology of anesthetic care is crucial to the success of the otolaryngologist.

Anesthesia is administered in numerous ways. General anesthesia renders the patient unconscious using a combination of drugs, and regional anesthesia blocks conduction of painful stimuli at the neuronal level. The latter technique involves infiltration of a local anesthetic around the surgical site; peripheral nerves; major nerves, such as the brachial plexus; or spinal cord (spinal, epidural, or caudal block). Infiltration of major nerves or the spinal cord is rarely used in head and neck surgery.

LOCAL ANESTHESIA

Local Anesthetic Agents

Local anesthetic agents (Table 15.1) are weak bases that reversibly inhibit nerve conduction by crossing cell membranes and intracellularly blocking electrically excitable sodium channels. The cationic form of the local anesthetic does not readily cross the cell membrane; thus, tissue acidosis renders local anesthetic agents ineffective, and local anesthetics do not work well if injected into abscesses or areas of cellulitis. Local anesthetics are linear molecules constructed of a hydrocarbon chain separating a lipophilic end from a hydrophilic end. The lipophilic end contains a benzoic acid moiety, and the hydrophilic end contains a tertiary or quaternary amine group. Anesthetics are subdivided based on the type of linkage between the benzoic acid moiety and the hydrocarbon chain. Amide anesthetics (lidocaine, mepivacaine, bupivacaine, etidocaine, prilocaine, and ropivacaine) contain an aminoamide linkage, whereas an aminoester bond characterizes ester anesthetics (cocaine, tetracaine, procaine, chloroprocaine, and benzocaine). The potency of a local anesthetic is related to its lipid solubility. The onset of action is dependent on the relative concentration of un-ionized drug and may be hastened by adding bicarbonate. The duration of action is associated with the degree of protein binding and the local anesthetics peripheral vascular effects. Addition of epinephrine decreases systemic absorption, which increases the duration of the block and decreases the risk of local anesthetic toxicity.

For both classifications of local anesthetics, the type of bond dictates the site of metabolism and route of excretion. Hepatic microsomal enzyme systems degrade the amides into metabolites that possess varying degrees of anesthetic potency. This process can be inhibited in patients with hepatic disease or reduced hepatic blood flow due to congestive heart failure or drugs such as cimetidine or propranolol. Plasma pseudocholinesterase metabolizes the aminoester drugs. This process is more rapid than hepatic metabolism except in patients with a genetically abnormal plasma pseudocholinesterase. The liver produces pseudocholinesterase, so patients with liver dysfunction will also have decreased metabolism of ester local anesthetics.

Lidocaine is both a topical and injectable local anesthetic. A 4% solution is most effective for topical use, whereas 0.5% to 1% solution is effective for injection into soft tissues. To avoid lidocaine toxicity, the recommended safe dosage is 4.5 mg/kg without epinephrine and 7 mg/kg

TABLE 15.1 LOCAL ANESTHETIC AGENTS

Drug	Physicochemical Characteristics	Route of Metabolism[a]	Route of Administration	Maximum Dose with and without Epi	Side Effects or Complications
Cocaine	Aminoester	Plasma cholinesterase	Topical	2 mg/kg 150 mg	Possible induction of allergic reaction by benzoic acid metabolite Vasoconstriction, possible induction of ventricular ectopy if used with halothane
Benzocaine	Aminoester	Plasma cholinesterase	Topical	3 mg/kg 200 mg	Methemoglobinemia at high doses
Tetracaine	Aminoester	Plasma cholinesterase	Topical	1.5 mg/kg	Seizures and myocardial depression at large doses
Lidocaine	Aminoamide	Liver	Infiltration	4.5–7 mg/kg (300–500 mg)	Seizures after rapid intravascular injection
Bupivacaine	Aminoamide	Liver	Infiltration	2.5–3 mg/kg (175–225 mg)	Cardiac arrest possible without previous seizures after rapid intravascular injection
Ropivacaine	Aminoamide	Liver	Infiltration	2–3 mg/kg (200–250 mg)	Seizures after rapid intravascular injection
Mepivacaine	Aminoamide	Liver	Infiltration	4.5–7 mg/kg (300–500 mg)	Seizures with overdosage

[a]Local infiltration assumed.

with epinephrine. Dilutions of 1:100,000 or 1:200,000 of epinephrine are commonly used with injected lidocaine. The lower dose is preferable to minimize the likelihood of side effects and has efficacy equivalent to that of the higher dose. Intravascular absorption of epinephrine may cause hypertension, tachycardia, and arrhythmias. The arrhythmogenic effects of epinephrine can be exaggerated by concurrent use of pancuronium or inhaled anesthetics, particularly halothane. Mepivacaine has an efficacy and toxicity profile similar to that of lidocaine, but mepivacaine has a longer duration of action. The remaining aminoamide local anesthetic agents are less commonly used during otolaryngologic surgery. Bupivacaine, because of its long duration of action, can be used for nerve blocks or infiltrated into wound closures to provide postoperative pain relief. The total dose of bupivacaine injected into the soft tissue of the head and neck should be limited to 2.5 mg/kg when injected alone and 3 mg/kg when mixed with epinephrine.

Cocaine is unique among the topical anesthetics because, in addition to being an excellent topical anesthetic, it is a potent vasoconstrictor. For this reason, cocaine can be used alone in the upper aerodigestive tract for both anesthesia and control of hemorrhage. Cocaine also is unique among local anesthetics in that it is highly addictive and thus one of the most abused drugs. Therefore, cocaine is limited in clinical practice to the mucous membranes of the head and neck. Combinations of lidocaine and epinephrine, phenylephrine, or oxymetazoline have been shown to be as efficacious as cocaine for a number of purposes (1), so many otolaryngologists avoid cocaine. Four percent cocaine has a rapid onset of action (5 to 10 minutes) with duration of action up to 6 hours. Cocaine inhibits the uptake of epinephrine and norepinephrine by adrenergic nerve endings; therefore, it potentiates the effects of catecholamines. The use of cocaine in conjunction with epinephrine risks cardiovascular complications that can prove fatal. The total dose of cocaine applied to the mucosa should be limited to 2 mg/kg. Severe or even fatal toxicity from cocaine can be caused by either central nervous system (CNS) or cardiovascular effects, including coronary artery spasm. Cocaine is metabolized by plasma pseudocholinesterase, and patients with this deficiency are sensitive to the effects of cocaine. Alternatives to cocaine should be highly considered in patients with coronary artery disease, poorly controlled hypertension, a history of arrhythmia, or thyrotoxicosis. Tetracaine is another excellent topical anesthetic agent, especially for ophthalmologic procedures. Although it has 10 times the potency of cocaine, tetracaine lacks the vasoconstrictor effect. Benzocaine, used as a topical spray, produces profound topical anesthesia but can cause methemoglobinemia if used in large doses. This drug is often used as a topical application to the upper aerodigestive tract before endoscopic procedures.

Local anesthetic systemic toxicity (LAST) involves the CNS and cardiovascular system. The signs of CNS toxicity occur early, with tinnitus, circumoral numbness, and agitation serving as early markers and seizures and unconsciousness indicating severe toxicity. The cardiovascular response can range from hypotension to ventricular

dysrhythmias and cardiovascular collapse. Treatment includes immediate management of the airway to prevent hypoxia and acidosis followed by midazolam if a seizure occurs. Advanced cardiac life support (ACLS) protocols should be followed for cardiac arrest, except the only antiarrhythmic considered should be amiodarone. A 20% lipid emulsion bolus (1.5 mL/kg) has proven beneficial, especially to treat bupivacaine, which tightly binds to cardiac sodium channels, resulting in prolonged cardiac arrest. Ropivacaine and levobupivacaine are newer agents, which have efficacy similar to that of bupivacaine but are less cardiac and cerebral toxic (2). Several steps should be taken to reduce the likelihood of LAST, including using the lowest effective dose of local anesthetic and aspirating before each 5-mL injection (3). Unfortunately, an adult patient's weight or BMI does not correlate with the plasma level after a dose of local anesthetic; thus, the maximum total dose in Table 15.1 should be observed. Acute allergic reactions are uncommon with amide local anesthetics, but may occur with esters, as they are broken down into *p*-aminobenzoic acid derivatives, a known allergen.

Nerve Blocks

In otolaryngology, local anesthetic techniques are used in procedures such as cosmetic facial surgery, in which distortion of tissue is undesirable. Thus, the goal is to infiltrate small volumes of local anesthetic around the peripheral nerve that supplies the surgical field with sensation. Sensory innervation of the head and neck is primarily from the trigeminal system and the cervical plexus. Effective blockade of sensory branches from these systems necessitates a thorough understanding of the anatomic features of the head and neck (4). This technique involves the use of a 25-gauge needle to infiltrate lidocaine or bupivacaine around sensory nerve branches as they exit the facial skeleton. It is important to avoid direct intravascular injection, as the unintentional injection of a local anesthetic into the vertebral or carotid artery can precipitate a seizure. Therefore, the practitioner should always aspirate before injection of local anesthetic to prevent complications.

Procedures on the face performed with local anesthesia should begin only after the branches of the fifth cranial nerve are blocked. Blocking the supraorbital and supratrochlear nerves with 1 to 3 mL of local anesthetic produces anesthesia of the forehead. The supraorbital nerve is found exiting the orbit in line with the pupil through the supraorbital notch, which can often be palpated. The supratrochlear nerve is approximately 1 cm more medial. Anesthesia of the external nose necessitates blocking the bilateral anterior ethmoidal nerves and infratrochlear nerves. This block is accomplished with either transcutaneous or submucosal injection at the junction of the upper lateral cartilage and the nasal bones laterally that extend superiorly between the medial canthus and the nasal dorsum.

The maxillary branch (V2) of the trigeminal nerve can be blocked in the pterygopalatine fossa with either a transoral approach or a transcutaneous approach, beginning at the coronoid notch and traversing the infratemporal fossa. This block anesthetizes the maxilla, palate, maxillary dentition, and the skin and mucosa of the midface. Procedures that necessitate such extensive anesthesia of the midface are more frequently performed with general anesthesia; therefore, this block is not commonly used. However, blockade of the major terminal branches of the maxillary nerve are common.

Infraorbital nerve block anesthetizes the maxillary incisors, cuspids and bicuspids, associated gingiva, lower eyelid, anterior cheek, and upper lip. Less than 3 mL of solution is necessary. The nerve, which is in line with the pupil and approximately 1 cm below the infraorbital rim, is reached with either an external or sublabial approach. The palate can be anesthetized by blocking the anterior palatine and nasopalatine nerves as they emerge from the greater palatine foramen and incisive canal. Small volumes (0.5 to 1 mL) of anesthetic are needed. During anesthetization of the infraorbital nerve, care must be taken, as injection into bony foramina can cause pressure-induced or needle-induced nerve injury and permanent paresthesia.

The mandibular branch of the trigeminal nerve can be anesthetized at the skull base as it leaves the foramen ovale. The needle is placed through the coronoid notch and across the infratemporal fossa. The injection is made posterior to the lateral pterygoid plate. Blockade of this nerve is used for procedures on the mandible, gingiva, lower teeth, lower lip, anterior two-thirds of the tongue, and floor of the mouth. Most procedures that necessitate this extent of anesthesia are performed with general anesthesia. Peripheral nerve blockade is more commonly applied to branches of the mandibular nerve.

The inferior alveolar nerve can be blocked through a transoral approach as the nerve enters the mandibular foramen in the pterygomandibular space. This technique is commonly used in oral surgery for work on the lower teeth. The injection is immediately medial to the mandibular ramus approximately 1 cm above the occlusal surface of the posterior molars at the anterior–posterior level of the coronoid notch. With this technique, the needle is superior to the medial pterygoid muscle and immediately medial to the mandibular sulcus. Use of this approach commonly blocks the lingual nerve because it is slightly medial and anterior to the inferior alveolar nerve. Anesthesia of the buccal mucosa is accomplished by means of blocking the buccal nerve as it passes over the anterior ramus at the level of the occlusal surface of the molars. Another commonly blocked branch of the cranial nerve V3 is the mental nerve. This blockade is accomplished with an injection at the mental foramen between the two bicuspids at a level immediately below the tooth root apices. The approach can be intraoral or extraoral. In edentulous patients, the location of the foramen can be found in line with the pupil. This technique anesthetizes the lower lip, gingiva, and teeth from the bicuspids to the midline.

Blockade of the cervical plexus anesthetizes the neck, inferior and posterior auricle, and scalp. The cervical plexus arises from the C2, C3, and C4 spinal nerves. These spinal nerves can be blocked as they emerge from the foramina in the cervical vertebrae with an approach lateral to the sternocleidomastoid muscle. This blockade must be performed with care to avoid intrathecal or intravascular injection into the vertebral artery. With injections of large volumes, involvement of the phrenic nerve is likely and thus should be used with caution in patients with respiratory compromise. This technique can be useful in complex surgical procedures on cervical structures, but these procedures usually are performed with general anesthesia. An alternative is to block the cutaneous innervation from the cervical plexus more safely by means of injection of up to 10 mL of local anesthetic at the posterior border of the midpoint of the sternocleidomastoid muscle (Erb point).

Blockade of the superior laryngeal nerve can be attained by means of infiltration of local anesthetic where the nerve enters the thyrohyoid membrane immediately inferior to the lesser cornu of the hyoid bone. This technique blocks sensory innervation from the epiglottis to the vocal cords and facilitates endoscopic procedures and awake fiberoptic intubations.

GENERAL ANESTHESIA

The unifying characteristics of general anesthetic agents are rendering a patient unconscious and insensible to painful surgical stimuli while controlling unwanted autonomic reflexes. The precise mechanism of action of anesthetics is unknown, although they all act by either positively modulating $GABA_A$ receptors (e.g., etomidate and propofol), inhibiting glutamate receptors (e.g., nitrous oxide and ketamine), or affecting both receptors (e.g., barbiturates and potent inhalational agents). The variety of available anesthetic agents enables the anesthesiologist to tailor care according to the demands of different surgical procedures and patients.

Inhalational Anesthetic Agents

The characteristics of common inhalational anesthetic agents are given in Table 15.2. These agents exist as liquids at ambient temperature and pressure and are transformed by a vaporizer into gas for rapid absorption and elimination by the pulmonary circulation. After absorption through the alveoli, the agents are distributed to the brain and spinal cord, where the anesthetic effects occur, as well as other tissues throughout the body. The concentration in the brain is directly related to the alveolar concentration. Alveolar and thus brain anesthetic partial pressure are increased by factors that increase anesthetic delivery (higher inhaled anesthetic concentration and alveolar ventilation) and decrease uptake (low solubility and alveolar–venous partial pressure differences). The potency of inhaled anesthetics is defined as the minimum alveolar concentration (MAC). MAC is the concentration that will prevent movement in 50% of patients to surgical incision and is additive between inhalational agents.

TABLE 15.2 INHALATIONAL ANESTHETIC AGENTS

Drug	Physical or Chemical Characteristics	MAC (%)	Excretion	Cardiovascular Effects	Respiratory Effects	Side Effects
Nitrous oxide	Supplied as a liquid in a pressurized cylinder	104	Lungs	Slight depression	Slight depression	Megaloblastic anemia Increase in intracavitary pressure in obstructed body cavities
Halothane	*N*-Alkane	0.76	Lungs Kidneys	Primary myocardial depression	Not a bronchoirritant Mild respiratory depression	Extremely rare cause of allergic hepatitis Triggering of malignant hyperthermia
Isoflurane	Ether bond	1.15	Lungs	Slight myocardial depression	Bronchoirritation Moderate respiratory depression	No major side effects
Desflurane	Ether bond	6.0	Lungs	Slight myocardial depression Sympathetic stimulation	Bronchoirritation Moderate respiratory depression	Coughing Laryngospasm
Sevoflurane	Ether bond	1.85	Lungs	Slight myocardial depression	Not a bronchoirritant Mild respiratory depression	Degraded by carbon dioxide absorber into compound A Possible transient mild renal impairment

The most commonly used volatile inhalational agents are isoflurane, sevoflurane, and desflurane. These halogenated anesthetics are nonflammable and sufficiently potent to be administered as a single anesthetic agent. Halothane was a common agent for many decades, especially in children who needed a mask induction; however, it has been mostly replaced by sevoflurane, which has many advantages, including a smoother mask induction, quicker emergence, less myocardial depression, less arrhythmogenic potential, and a smaller incidence of postoperative liver dysfunction. These halogenated anesthetics have similar effects on cardiac and pulmonary function. In a dose-dependent manner over usual clinical doses, these agents increase heart rate and decrease systemic vascular resistance and blood pressure while minimally decreasing cardiac output. Pulmonary effects include a dose-dependent increase in respiratory rate and $PaCO_2$ while decreasing tidal volume and minute ventilation. Increased atelectasis under anesthesia leads to an increased shunt; this usually necessitates an inspired oxygen fraction of at least 25% to 30% to maintain reasonable hemoglobin saturation. Small concentrations of these agents severely depress the ventilatory response to acute hypoxia; therefore, patients must be closely monitored after extubation while being transferred to the post anesthesia care unit (PACU).

Sevoflurane and desflurane are nonflammable, volatile, halogenated agents that are completely fluorinated analogues of isoflurane. Because of low lipid solubility, both agents produce rapid awakening from general anesthesia compared with isoflurane; this difference in emergence time is pronounced in obese patients after prolonged surgery. Because of a high vapor pressure, desflurane requires a special vaporizer to deliver clinically useful concentrations of the gas. Sevoflurane is gentle on the airway and is the preferred agent by most anesthesiologists in pediatric patients that require a mask induction. Although preferred for their quick awakening properties, sevoflurane and desflurane are more costly than isoflurane.

The use of potent inhalational agents for maintenance of anesthesia offers several advantages in head and neck patients. First, the agents decrease bronchoconstriction by relaxing bronchial smooth muscle. Second, they produce reasonable muscle relaxation without the use of neuromuscular blocking drugs, allowing assessment of facial nerve function. Third, inhalational agents produce a moderate degree of hypotension and, in concert with a 15-degree head-up tilt, can reduce surgical blood loss. Hypotension should be used cautiously in elderly patients or patients with a history of hypertension or vascular disease.

Nitrous oxide is an odorless, nonhalogenated inhaled anesthetic often added in concentrations of 50% to 70% (0.5 to 0.7 MAC). Nitrous oxide is highly insoluble, which enables a rapid emergence. It is not a potent inhalational anesthetic, and the brain concentration sufficient to render a patient unconscious may not be achieved at atmospheric pressures. In combination with a halogenated anesthetic, nitrous oxide speeds induction and emergence from general anesthesia, in addition to attenuating some of the cardiovascular and respiratory effects. Although not flammable, nitrous oxide can support combustion, especially if delivered with a high concentration of oxygen, and thus nitrous oxide should not be used during laser endoscopy. Additionally, nitrous oxide quickly diffuses into closed, air-filled body cavities to rapidly expand volume; thus, it must be avoided in the presence of obstructive ileus, pulmonary bullae, or an unrelieved pneumothorax. The middle ear also represents an anatomic air cavity vented to the atmosphere only when the eustachian tube is open. If high concentrations of nitrous oxide are used, the nitrous oxide diffuses into the middle ear faster than nitrogen is able to diffuse out, resulting in an increase in intracavitary pressure that can be great enough to rupture the tympanic membrane or dislodge a graft during otologic surgery. Therefore, common practice is to avoid nitrous oxide or to limit the concentration to 50% and to discontinue administration 30 minutes before graft placement. Nitrous oxide undergoes minimal metabolism by the liver; however, prolonged exposure to high concentrations inhibits methionine synthase activity and can cause megaloblastic or aplastic anemia, although this is not seen with routine intraoperative dosing. Nitrous oxide increases pulmonary artery pressures and should be used cautiously in patients with pulmonary hypertension.

Emergence from a general anesthetic may be more challenging in patients after upper airway procedures. Upon extubation, these patients are more likely to have laryngospasm due to irritation from secretions and blood, which may lead to rapid arterial desaturation. If the anesthesiologist is unable to give positive-pressure ventilation by mask, jaw thrust should be exerted with pressure between the mandible and the mastoid process. If laryngospasm persists, an intravenous anesthetic should be administered and then a small dose of succinylcholine (20 mg) if necessary.

All of the inhaled halogenated anesthetics are triggers for malignant hyperthermia, a rare but well-known reaction. Malignant hyperthermia occurs more commonly if succinylcholine has been used for muscle relaxation. Characteristics of malignant hyperthermia include tachycardia, markedly increasing $PaCO_2$, metabolic acidosis, sustained muscle rigidity, myoglobinuria, and an increasing temperature (may be a late sign). These are manifestations of a generalized hypermetabolic state initiated by an inhibition of calcium reuptake into the sarcoplasmic reticulum of the skeletal muscle. If not controlled swiftly, malignant hyperthermia is fatal. The principles of management include discontinuing all volatile anesthetics and succinylcholine, hyperventilating with 100% oxygen, administering dantrolene 2.5 mg/kg up to 10 mg/kg, administering bicarbonate as needed to correct the metabolic acidosis, and total-body cooling. The surgery should be stopped as soon as possible. Any patient with a history

or family history of malignant hyperthermia should not receive halogenated anesthetic agents or succinylcholine for future procedures.

Intravenous Anesthetic Agents

For most surgical procedures, the first step in production of general anesthesia is intravenous administration of a hypnotic drug, followed by maintenance of anesthesia with an inhalational agent supplemented with narcotics. The intravenous induction is usually more acceptable to the patient than inhalation induction with a volatile agent. The drugs commonly used for this purpose share the ability to produce a state of unconsciousness rapidly, which coincides with a critical peak concentration in brain tissue. Awakening occurs when this concentration decreases, usually through redistribution of the drug from brain tissue to muscle and adipose tissue. Metabolism and excretion of the drug then take place in the liver and other organs (Table 15.3), but this is only of consequence for doses larger than for induction, such as in prolonged infusions.

Barbiturates are lipid-soluble, highly alkalotic compounds, the central ring structure of which consists of a fusion of urea and malonic acid. The two subgroups, thiobarbiturates, such as pentobarbital, and oxybarbiturates, such as methohexital, are differentiated by a sulfur or oxygen molecule attached to the urea moiety. The drugs of this family generally produce unconsciousness within 3 minutes of intravenous administration, and awakening usually occurs within 10 minutes of initial dosage. Hypotension after induction with barbiturates is usually caused by direct myocardial depression and vasodilatation of the peripheral capacitance vessels, causing a decrease in the venous return, which may be dramatic in patients with uncorrected hypovolemia. Barbiturates cause respiratory depression, including apnea at normal doses for induction of anesthesia. Like any other respiratory depressant, barbiturates should be administered with caution if a possibility exists that the airway may be difficult to maintain in the absence of spontaneous ventilatory effort. Etomidate is an imidazole intravenous anesthetic agent structurally related to the antifungal drug, ketoconazole. Etomidate produces minimal derangement of cardiovascular function, so it is preferred to barbiturates in operations on patients who are hemodynamically unstable, with decreased myocardial contractility, or coronary artery disease. Etomidate has less respiratory depressant effect compared with barbiturates; however, as with any anesthetic induction agent, administration may result in airway obstruction and apnea. Rapid administration can produce impressive myoclonus, which is of no clinical significance. Etomidate is formulated in a solvent containing propylene glycol, which produces pain and phlebitis during intravenous injection. The venoirritation can be lessened with the prior intravenous injection of 20 to 40 mg of lidocaine, and myoclonus can be ameliorated with administration of sedatives or narcotics before the injection. Etomidate inhibits 11-B hydroxylase and causes adrenal suppression and thus infusions or frequent repeated doses should not be used. It is also not an ideal ambulatory drug due to its high incidence of nausea and vomiting.

Propofol is a substituted phenol with a rapid onset and short duration of action. Awakening after a dose of propofol is effortless, with little residual sedation. Propofol causes profound respiratory depression when used in induction doses. It also causes a more pronounced attenuation of upper airway reflexes, which can be useful in the manipulation of the airway without muscle relaxants (i.e., the placement of a laryngeal mask airway). Propofol causes pronounced hypotension due to peripheral vasodilatation and blocking of the normal reflex tachycardia in patients with hypovolemia or decreased left ventricular function.

TABLE 15.3 INTRAVENOUS ANESTHETIC AGENTS

Drug	Physicochemical Characteristics	Route of Metabolism	Route of Excretion	Cardiovascular Effects	Respiratory Effects	Side Effects
Barbiturates	Barbituric acid ring contains either an S or an O molecule Highly alkalotic	Liver	Kidneys	Primary myocardial depression and venodilation	Induces apnea	Histamine release Possible induction of acute porphyria
Etomidate	Imidazole	Liver (rapid)	Kidneys	Minimal	Minimal	Myoclonus Venoirritation Adrenal suppression
Propofol	Substituted phenol	Liver, possibly lung	Kidneys	Vasodilation	Minimal	Histamine release Venoirritation
Ketamine	Cyclohexanone	Liver	Kidneys	Releases endogenous catecholamines	Stimulates production of oral secretions and predisposes to laryngospasm	Hallucinations Nystagmus

Propofol, which is formulated in a soybean emulsion, causes venoirritation after intravenous administration of the drug. The brief duration of propofol activity allows patients to return quickly to preoperative levels of mental alertness, even with prolonged infusions. This short context-sensitive half-time (i.e., half-time after termination of infusion) enables propofol to be used with an analgesic as a total intravenous anesthetic. A unique feature of propofol is that it is antiemetic, making it popular for the induction and maintenance of anesthesia for brief outpatient procedures.

Ketamine is a cyclohexanone derivative similar in structure and activity to the hallucinogen phencyclidine. Ketamine is unique in its mode of action in producing a state of anesthesia in that it appears to interrupt the perception of pain at the cortical level. A patient who has received an induction dose of ketamine appears to be conscious but neither responds to, nor has memory of, painful stimuli. This effect is described as the dissociative effect of ketamine. Ketamine induces amnesia and supports blood pressure through the release of endogenous catecholamines, and unlike the other intravenous anesthetic agents, ketamine produces intense analgesia. It does not produce respiratory depression among healthy persons who have not received premedication. It also is a profound bronchodilator and seems to protect upper airway reflexes and muscle tone, although airway obstruction is possible. Additionally, ketamine enhances the production of oral secretions and increases the likelihood of laryngospasm and thus should be used cautiously in patients with asthma or chronic obstructive pulmonary disease. Emergence from ketamine anesthesia can appear smooth, but patients may have hallucinations during the recovery period. These psychotomimetic effects can be attenuated with prior administration of benzodiazepines or propofol.

ANCILLARY AGENTS

Intravenous Sedative Agents

Benzodiazepines are one of the most useful drug families in anesthesiology, as they are commonly administered as premedicants to reduce anxiety and are also helpful for patients undergoing regional anesthesia. Midazolam is the most commonly used preoperative sedative as it is painless on injection, unlike diazepam, and a quicker onset and shorter duration of action compared with lorazepam. In preinduction doses of 1 to 3 mg iv, midazolam produces reliable anxiolysis, sedation, and amnesia without prolonging emergence. Benzodiazepines should be administered with care to patients with respiratory insufficiency or obstructive sleep apnea, as these patients appear to be more sensitive to the suppression of the ventilatory drive to CO_2. If oversedation occurs, benzodiazepines may be reversed with repeated doses of flumazenil 0.2 mg iv. Benzodiazepines reduce cerebral blood flow and metabolism and are effective in the control of grand mal seizures.

Narcotic Agonists and Antagonists

Narcotic agonists are a cornerstone of current anesthesia practice. Although the currently available narcotics differ widely in chemical structure, they share the ability to bind to specific opiate-receptor sites in the brain and spinal cord. The prototype mu-opioid receptor is responsible for producing analgesia and the narcotic side effects of meiosis, respiratory depression, bradycardia, constipation, and urinary retention. The other opioid receptors include kappa, delta, and sigma. The pharmacodynamics of opioids depend on the type of receptor activated and its affinity.

Morphine, a naturally occurring opium derivative, has been used for centuries as an analgesic and antidiarrheal agent. Morphine is fairly insoluble in lipids and effective when administered by the intramuscular, intravenous, epidural, or intrathecal route. It is inexpensive and possesses a long duration of action, although its high un-ionized fraction and low lipid solubility make its onset slow (15 to 30 minutes). Morphine can be used for premedication, postoperative pain control, or as an adjuvant to an intraoperative anesthetic. Pure nitrous narcotic techniques (nitrous oxide plus morphine) are rarely used now because of the high incidence of intraoperative awareness. The respiratory depressant effects of morphine are well known. Even a small dose can produce abrupt apnea among elderly or debilitated patients. Histamine release can cause a decrease in systemic vascular resistance and profound hypotension among patients with hypovolemia. Morphine has hepatic and renal pathways of metabolism and is excreted into the bile and the urine. However, the accumulation of active metabolites of morphine (morphine 3-glucuronide and morphine 6-glucuronide) can occur in patients with renal failure, causing narcosis and respiratory depression. Many practitioners have replaced morphine with hydromorphone because it has a similar duration of action with no histamine release or active metabolites.

Use of the potent, synthetic narcotics alfentanil, sufentanil, and fentanyl is usually restricted to the operating room, where equipment for ventilatory support is readily available. These drugs contain a piperidine ring and are noteworthy for their production of rapid, intense analgesia. Fentanyl and sufentanil are approximately 100 and 1,000 times as potent as morphine, respectively. With the onset of analgesia, abrupt, profound respiratory depression can occur. Fentanyl and sufentanil are lipid soluble and have a rapid onset of action (1 to 2 minutes) and peak effect (under 5 minutes). They can maintain cardiovascular stability even in large doses. Both drugs are metabolized by hepatic microsomal systems and excreted into the urine. Alfentanil, however, is fairly insoluble in fatty tissues. Its volume of distribution is much smaller than that of fentanyl or sufentanil, and a greater quantity of the drug is immediately available for hepatic degradation. These pharmacokinetic properties cause a shorter duration of activity

than is seen with fentanyl, especially after prolonged infusions. Profound bradycardia and hypotension can occur even among healthy persons after rapid intravenous administration of alfentanil; therefore, it should be given carefully to patients in hemodynamically unstable condition. Additionally, when given in large doses, opioids can cause chest wall rigidity, impairing ventilation. This condition is mediated through central mechanisms and can be treated with muscle relaxants.

Remifentanil is an ultrashort-acting opioid within the piperidine series of narcotics. It is metabolized rapidly by nonspecific plasma esterases, and thus, rapid awakening with little drug hangover and no residual analgesia are hallmarks of this drug, regardless of the duration of infusion. It is usually administered as an infusion, with doses ranging from 0.1 to 1 mg/kg/min, and it reliably suppresses autonomic and hemodynamic responses to surgical stimulation. Because of cost constraints and the fact that rapid shutoff of analgesia is undesirable in most surgical settings, the use of remifentanil is often limited to short endoscopic procedures or neurosurgical procedures requiring immediate postoperative neurologic assessment. Another drawback is the rapid tolerance that develops in patients on remifentanil, which has been demonstrated to necessitate increased postoperative opioid requirements (5). During emergence from anesthesia, it is important to implement a plan for postoperative analgesia in a timely fashion.

Naloxone antagonizes residual respiratory depression or other unwanted side effects that occur with opioids. Careful titration of naloxone (e.g., 1 mcg/kg iv q 2 minutes) may enable reversal of respiratory depression without a significant effect on analgesia or hemodynamic parameters. Additionally, one must be aware that the effects of naloxone can dissipate before metabolism of the narcotic is complete, and precipitate respiratory depression can occur.

Butorphanol, nalbuphine, and buprenorphine are drugs with mixed opiate agonist and antagonist properties. The advantage over pure narcotic agonists is production of analgesia with less risk of respiratory depression, although there is a ceiling effect on analgesia and these drugs are less commonly used than narcotic agonists perioperatively.

Neuromuscular Blocking Agents and Antagonists

Muscle relaxants claim a critical role in modern anesthesia practice (Table 15.4). They facilitate endotracheal intubation and enhance the intrinsic muscle-relaxant properties of inhalational halogenated agents. In otolaryngologic surgery, management of muscle relaxation can be particularly difficult. Periodic assessment of the integrity of the facial nerve is essential for the success of many types of surgery involving the ear or parotid gland. Eliciting a facial grimace by means of direct electrical stimulation of the nerve is the easiest method of facial nerve identification. A common approach is to avoid nondepolarizer muscle relaxants and use a high dose of an inhalational agent to produce a moderate degree of relaxation.

TABLE 15.4 NEUROMUSCULAR BLOCKING DRUGS

Drug	Physicochemical Characteristics	Route of Metabolism	Route of Elimination	Cardiovascular Effects	Approximate Onset of Maximum Block (min)	Approximate Duration of Activity (min)
Competitive inhibitors						
Atracurium	Benzylisoquinoline	pH-dependent Hoffman degradation	Kidneys	Hypotension from histamine release in large doses, CNS toxicity	3	40–60
Cisatracurium	Benzylisoquinoline	pH-dependent Hoffman degradation	Kidneys	None	2–3	40–60
Pancuronium	Steroid nucleus	Liver	Mainly kidneys	Tachycardia	3–4	60–90
Vecuronium	Steroid nucleus	Liver	Kidneys and liver	None	2–3	40–60
Rocuronium	Steroid nucleus	None	Kidneys and liver	None	1–2	40–60
Noncompetitive inhibitors						
Succinylcholine	Linear molecule that is a fusion of succinic acid and choline	Plasma cholinesterase	Kidneys	Bradycardia among children or when repeat bolus to adults	0.5–1 if no competitive inhibitor is given to block fasciculations	<10 but may be prolonged in presence of cholinesterase deficiency

The two major categories of relaxant drugs are competitive and noncompetitive inhibitors of neuromuscular transmission. The common site of activity for these drugs is the postsynaptic membrane of the nicotinic cholinergic receptor. Competitive blocking agents (nondepolarizing drugs) bind loosely to the receptor site and compete with acetylcholine in a concentration-dependent manner. Noncompetitive blocking agents (depolarizing drugs) bind strongly to the receptor site and mimic the electrophysiologic effect of acetylcholine at the end plate, depolarizing the membrane and rendering it incapable of further stimulation.

Succinylcholine is the only clinically used depolarizing neuromuscular blocking drug. It is similar in structure to acetylcholine and imitates its effects at the motor end plate. Muscle fasciculation heralds the onset of succinylcholine-induced paralysis unless specific measures are taken to block this effect. The drug has a rapid onset of action (less than 60 seconds) and a short duration of activity (less than 10 minutes) owing to its rapid metabolism by plasma cholinesterases, such that only a small fraction of the dose given actually reaches the neuromuscular junction. This pharmacokinetic profile makes the drug useful in the induction of anesthesia and in intubation for procedures in which muscle paralysis is not desired. Rarely, succinylcholine can be administered by means of intermittent bolus or continuous infusion; however, prolonged paralysis can occur if excessive doses are administered by either route. Succinylcholine can produce profound bradycardia mediated by stimulation of cardiac muscarinic receptors, especially in young children or if a repeat dose is given within several minutes. However, pretreatment with a small dose of atropine or glycopyrrolate blocks this phenomenon. Patients with abnormal or decreased cholinesterase will have a prolonged response to the action of succinylcholine. Potassium efflux from the intracellular fluid due to the activation of receptors is the unavoidable consequence of succinylcholine action. The average elevation of potassium concentration in the serum after a dose of succinylcholine is 0.5 to 1.0 mEq/L. For a healthy person with a normal preoperative potassium level, this elevation is of no physiologic significance; however, life-threatening hyperkalemia can develop among patients with massive crush injuries, burns, or paraparesis due to extrajunctional receptor release of potassium. Succinylcholine must also be avoided in patients with elevated baseline potassium levels, as in some patients with renal failure. Therefore, in these situations, succinylcholine must not be given. This drug also is a triggering agent for malignant hyperthermia, similar to the volatile anesthetics. In children, rhabdomyolysis, hyperkalemia, and cardiac arrest have been described, especially in those with previously undiagnosed myopathies. Because of these risks, succinylcholine should not be used in pediatric patients unless there is a clear indication, such as to prevent aspiration in a patient with gastric contents. Other side effects of the drug include increases in the intraocular and intracranial pressure soon after injection.

The nondepolarizing drug tubocurarine (curare) is the prototype of the benzylisoquinoline competitive neuromuscular blocking agents; however, it has been replaced by other drugs in its class, including atracurium and cisatracurium. Rapid boluses of atracurium result in histamine release and a consequent drop in blood pressure and increase in heart rate. Cisatracurium is a stereoisomer of atracurium and does not cause histamine release or hemodynamic changes. These drugs are not dependent on liver or kidney function for elimination and thus are popular for patients with liver or renal failure. Pancuronium, vecuronium, and rocuronium are competitive, nondepolarizing muscle relaxants that contain a steroid nucleus. Pancuronium has a 90-minute duration of activity, which is the longest of the clinically used muscle relaxants. It is degraded in the liver into potent active metabolites and is excreted primarily by the kidneys. Unlike vecuronium and rocuronium, which are hemodynamically stable, pancuronium produces a marked increase in heart rate after intravenous administration, in part because of its strong anticholinergic activity at the cardiac muscarinic receptors and in part because of its ability to block norepinephrine reuptake into presynaptic nerve terminals. These properties can cause atrial and ventricular tachydysrhythmia if the drug is given in combination with halothane, cocaine, or epinephrine-containing local anesthetic solutions. Most nondepolarizers have onset times ranging from 2 to 5 minutes, depending on the dose of administration and use of a priming dose. The only exception to this is high dose rocuronium (1.2 mg/kg), which can produce ideal intubating conditions in 60 seconds and is preferred in rapid-sequence inductions when succinylcholine is contraindicated. Examples of anticholinesterase agents used to terminate the effects of muscle relaxants include edrophonium and neostigmine. Each agent contains a quaternary ammonium group that renders the drug poorly soluble in body lipids. Edrophonium binds loosely and reversibly to acetylcholinesterase through a combination of electrostatic and hydrogen bonding to produce a rapid onset of action and a short duration of activity. Neostigmine, however, binds more tightly to acetylcholinesterase. The result is a longer onset of action and a longer duration of activity. Anticholinesterase agents block the activity of plasma cholinesterase and prolong the paralysis produced by succinylcholine. Administration of an inhibitor of acetylcholinesterase increases the amount of acetylcholine available for binding to the postsynaptic nicotinic receptors of the neuromuscular junction and to the muscarinic receptors in the parasympathetic ganglia. Stimulation of these muscarinic receptors produces bradycardia, salivation, bronchoconstriction, and an increase in gastrointestinal motility. These unwanted side effects can be blocked by the properly timed administration of an anticholinergic drug, such as atropine or glycopyrrolate. Drug pairs are selected with an effort to match respective time of onset and duration of activity, so atropine frequently accompanies edrophonium,

and glycopyrrolate commonly accompanies neostigmine. In Europe, sugammadex has been used as a specific antagonist to steroid-containing muscle relaxants, such as rocuronium. Sugammadex administration reverses neuromuscular blockade within 2 minutes without any hemodynamic effects (6). Safety concerns regarding sugammadex have delayed its approval in the United States.

Incomplete reversal of neuromuscular blockade is a frequent occurrence and accounts for critical respiratory events in the PACU, such as severe hypoxemia and upper airway obstruction (7). Reversal of paralysis is especially important in patients after undergoing upper airway surgery where edema and blood in the airway necessitate a strong cough and respiratory effort. Reversal of neuromuscular blockade may be assessed by a nerve stimulator and tests of strength, including a strong hand grip or 5-second head lift.

Antiemetics

Patients are at increased risk of postoperative nausea and vomiting (PONV) after undergoing ENT surgery, especially surgery on the inner ear. Vomiting after upper airway surgery may lead to complications and a high rate of patient dissatisfaction. The anesthesiologist has several classes of drugs to reduce the incidence of PONV, including steroids (dexamethasone 4 mg iv at the start of case), 5-HT3 antagonists, (ondansetron 4 mg iv at end of case), butyrophenones (haldol 0.5 to 2 mg iv), and promethazine (6.25 to 12.5 mg iv) (8). These drugs are most effective when used in combinations, and multiple intraoperative antiemetics should be given in patients with multiple risk factors for PONV (e.g., nonsmoker, female, h/o PONV, and postoperative opioids). These drugs are inexpensive and have only rare side effects, although promethazine causes sedation.

ANESTHESIA MONITORING

Technical improvements in anesthesia machines and respiratory and hemodynamic monitoring enable successful administration of anesthesia to patients who previously were considered too ill for surgery. Alarm systems that announce anesthesia circuit disconnection or warn of a hypoxic inspired gas mixture are standard features on modern anesthesia machines. Tissue oxygenation is assessed continuously with the noninvasive technique of pulse oximetry, and ventilation is monitored with real-time capnography. Despite modern technology, emergencies do occur, for which the anesthesiologist and surgeon must be aware (Table 15.5).

The Anesthesia Machine

The anesthesia machine consists of oxygen and anesthetic vapor delivery systems, a reservoir bag or ventilator used to assist patient ventilation, and a circuit that provides a conduit through which anesthetic gases or oxygen reach the patient. Oxygen flows to the patient from a wall source or an oxygen tank attached to the anesthesia machine. The rate of administration is controlled with calibrated flowmeters. Nitrous oxide, air, and helium also can be given in a similar manner. Inhalational anesthetic agents can be added to the inspired mixture by allowing the carrier gas to flow over and evaporate a pool of liquid anesthetic contained in an agent-specific vaporizer. The vaporizer accurately controls

TABLE 15.5 EMERGENCIES ANESTHESIA

Emergencies	Signs	Treatment
Malignant hyperthermia	Increased $ETCO_2$, rigidity, tachycardia, respiratory and metabolic acidosis, increased temperature (often a late sign), myoglobinuria	Discontinue the triggering agent, hyperventilate with 100% oxygen, stop procedure if possible, dantrolene 2.5 mg/kg, bicarbonate as needed, cool patient
Local anesthetic toxicity	Agitation, seizures, unconsciousness, ventricular dysrhythmias, cardiac arrest	100% O_2, midazolam if CNS effects, ACLS protocol for cardiac arrest, consider 20% lipid emulsion
Anaphylaxis	Hypotension, tachycardia, bronchospasm, hypoxia, urticaria, edema	Discontinue drug, 100% O_2, epinephrine, steroids, antihistaminics
Laryngospasm	Spasm of the laryngeal musculature due to secretions	Positive-pressure ventilation through a bag/mask with 100% O_2, succinylcholine if necessary
Latex allergy	Same as allergy/anaphylaxis	Treat same as anaphylaxis
Bronchospasm	Hypoxia, wheezing, increased airway pressures	Deepen anesthetic, β-adrenergic agonist, epinephrine

the amount of anesthetic vapor allowed to saturate the carrier gas and directly regulates the concentration of inhaled anesthetic. The anesthesiologist adjusts the depth of anesthesia by increasing or decreasing the amount of anesthetic vapor introduced into the delivery system. The anesthetist often monitors the end-tidal concentrations of inhalational agents that correlate to the patient's brain concentration. A reservoir bag or automatic ventilator is used to assist or control the patient's breathing. Newer anesthesia machines (e.g., the GE Aespire View) have multiple options for controlling ventilation, which rival ICU ventilators, including the ability to deliver up to 30 cm H_2O of PEEP, a peak inspiratory pressure of 60 cm H_2O, and a pressure-controlled volume-guaranteed mode. These machines with advanced ventilators are helpful in managing trauma patients or patients with severe lung disease.

An anesthesia breathing circuit makes the final connection between the machine and the patient. The inspiratory limb of a breathing circuit conducts each anesthetic-laden, oxygen-enriched breath from the machine to the patient. The expiratory limb of the circuit routes expired gas containing carbon dioxide through an adjustable relief valve into a scavenging system. One-way valves and an internal carbon dioxide absorber prevent rebreathing by the patient of any carbon dioxide–laden gas not vented into the scavenging system. An oxygen monitor with electronic alarm is located in the inspiratory limb of the breathing circuit to detect any deviation of the oxygen concentration from preset limits. This monitor is a necessary component, in a series of interconnected safety mechanisms, designed to prevent the catastrophic administration of a hypoxic gas mixture to the patient. Other links in this safety chain include an alarm and a cutoff valve that terminates nitrous oxide flow when oxygen line pressure is low.

Intraoperative Monitoring

Continuous, noninvasive measurement of arterial hemoglobin saturation is possible with pulse oximetry. A light-emitting diode is placed on a finger, toe, earlobe, or other appropriate area on the body, and shines two different wavelengths of light (660 and 940 nm) through the tissue. Oxyhemoglobin and reduced hemoglobin absorb light differently; thus, using the Beer law, the ratio of the absorbance spectra of these two wavelengths is calculated and expressed as percentage oxygen saturation. The oximetry unit does not directly measure Pao_2, and the pulse oximeter continuously displays a saturation of at least 98% through a range of Pao_2 values between 150 and 550 mm Hg. As the unit does not indicate a decrease in arterial saturation until Pao_2 decreases to less than approximately 100 mm Hg, a pulse oximeter is not useful for detecting a downward trend in arterial oxygen tension until Pao_2 decreases below this level. Depending on the shape of the oxygen–hemoglobin dissociation curve, an oxygen saturation of 90% usually correlates with a Pao_2 of 60 mm Hg.

Although pulse oximetry reliably detects arterial desaturation for most patients, limitations exist. A malpositioned sensor or nail polish may result in an inaccurate reading. Ambient light or the injection of biologic dyes such as methylene blue can artificially decrease the hemoglobin saturation displayed. Carboxyhemoglobin in patients who smoke tobacco or with carbon monoxide poisoning will read at the same level as oxyhemoglobin, causing an erroneous increase in saturation. Additionally, electrocautery or patient movement can cause mechanical interference with signal processing, and vasoconstriction initiated by hypovolemia, hypothermia, or hypotension can be so intense that the oximeter cannot detect pulsatile flow or determine a saturation value.

The adequacy of ventilation can be monitored continuously with capnography, a method of detecting the amount of carbon dioxide in expired gas. The actual measurement can be obtained with two different tools—an infrared analyzer or a mass spectrometer. Both methods provide nearly instantaneous feedback of the concentrations of oxygen, carbon dioxide, and inhalational agents in the inspired and expired gas. Infrared analysis is most commonly used and is based on the absorption of infrared light by carbon dioxide at specific optimal wavelengths (between 4,200 and 4,300 nm). Mass spectroscopy works on the principle of separating charged gases based on their molecular weights. Although mass spectroscopy is the gold standard monitor, these units are more expensive than infrared devices.

In anesthesia, capnography is necessary for monitoring and adjusting patient ventilation, but it also is helpful in other clinical situations. First, the absence of carbon dioxide in the expired gas of a patient after attempted intubation can indicate that the endotracheal tube is in the esophagus. Second, a rapid decrease in the baseline value of expired carbon dioxide can be caused by a decrease in the amount of blood entering the pulmonary circulation causing an increase in dead space, a circumstance that can occur after severe intraoperative hypovolemia, pulmonary thromboembolism, or an air embolism. An air embolism may occur during operations near the large veins in the neck, which are above the level of the heart in a sitting patient, thus encouraging air to be entrained back to the right atrium. If an air embolism is suspected by the anesthetist, the surgeon should be immediately notified so that attempts to prevent further air entrapment are initiated. Third, a failure of the carbon dioxide waveform to return to zero during inspiration indicates rebreathing due to either a faulty valve or an exhausted absorbent.

Hemodynamic Monitoring

The anesthesiologist may need to monitor intravascular volume status if there is anticipated large volume blood loss, for example, during extensive head and neck cancer surgery. Basic volume status assessments include blood pressure, heart rate, urine output, and calculations of

preexisting fluid deficit and ongoing maintenance and surgical losses. Other tools such as central venous pressure (CVP), systolic pressure variation, or esophageal Doppler monitoring enable a more accurate assessment. The internal jugular veins should be avoided for CVP monitoring during neck surgery; however, the subclavian vein carries a higher risk of pneumothorax. An arterial line has minimal risk and can be used to calculate the systolic pressure variation or pulse pressure variation with positive-pressure breathing, both of which are excellent predictors of hypovolemia that will respond to fluid administration (9). Guiding intraoperative fluid administration with an esophageal Doppler to continuously monitor preload and cardiac output has proven to reduce hospital time and decrease complications (10).

Temperature Control

Airway procedures may make it necessary to measure a patient's temperature in areas other than the esophagus, such as bladder (urinary catheter probe) or axilla. Forced air warming has been successful in maintaining patients' temperatures greater than 36 degrees centigrade, which reduces perioperative morbidity and mortality.

Depth of Anesthesia

There are several available depth of anesthesia monitors, the most common of which uses bispectral technology. A probe is placed on the patient's forehead to record the electroencephalogram, which is displayed as a number between 0 (isoelectric) and 100 (awake). The likelihood of intraoperative awareness (~0.2% in all cases) is reduced if the bispectral index (BIS) is kept below 60, and recovery time is reduced if the BIS is kept above 40 (11). However, the BIS has not proven better in preventing intraoperative awareness than monitoring the expired gas concentration.

AIRWAY MANAGEMENT

Assessing the Airway

Careful preoperative airway assessment is essential for the safe induction of anesthesia. Difficulty in managing the airway is the single most important cause of anesthesia-related morbidity and mortality. Successful management of a difficult airway begins with recognition. Acute airway compromise needs immediate attention and may be exhibited by tachypnea, accessory muscle use, stridor, or hypoxia. In stable patients, one should acquire a thorough history with special reference to symptoms that suggest airway abnormalities, such as hoarseness, dyspnea, orthopnea, dysphagia, or a history of previous head or neck disease. Additionally, a history of previous airway difficulties with intubation should be explored, and any available anesthesia records from previous intubations must be reviewed. The ease of direct laryngoscopy and intubation must be evaluated in all patients. During the preoperative physical examination, the following characteristics may indicate the presence of a difficult airway: long upper incisors, overbite, interincisor distance less than 3 cm, highly arched or narrow palate, a bull neck, and decreased neck extension (12). The inability of the patient to protrude mandibular incisors anterior to the maxillary incisors is also predictive of a difficult intubation. In addition, a distance of less than three fingerbreadths between the mentum and the thyroid cartilage (the thyromental distance) is a nonreassuring finding and may be affected by previous surgery or radiation. To assess temporomandibular joint mobility and the adequacy of the oral cavity, the patient should be asked to open his or her mouth as widely as possible and fully extend the tongue. At this time, the mouth should be examined for loose teeth, prostheses, or an unsuspected mass. The size of the tongue relative to the actual size of the oral cavity can be visually graded by using the Mallampati scoring system. This test is performed with the patient in a seated position with his or her head in a neutral position and mouth opened as wide and tongue protruded as far as possible. Classification is then determined, depending on the visible structures. When the tip of the uvula, tonsillar pillars, and soft palate are visible, the grading is class I and usually corresponds to a complete visualization of the cords or a grade 1 view. When the tonsillar pillars and the base of the uvula are visible, with the tip of the uvula obscured by the posterior tongue, the grading is class II. Progressive difficulty in intubation usually corresponds to a limited view of the pharyngeal structures, including a view of only the soft palate (class III) and the hard palate (class IV). Predictive values of single tests have not been found to be high; however, by using several different tests, most patients with potentially difficult airways can be identified and managed appropriately.

The airway of some patients may be difficult to manage during induction because of an underlying pathologic condition, such as head and neck cancer, obstructive sleep apnea, facial trauma, or congenital abnormalities. Predictors of difficult mask ventilation include a body mass index greater than 30, history of snoring, age greater than 57, severely limited jaw protrusion, and the presence of a beard (13). Long-standing rheumatoid arthritis can cause atlanto-occipital subluxation and extreme laryngeal deviation. Patients who have intrathoracic tracheal compression from extensive mediastinal adenopathy, retrosternal goiter, or massive neoplasia in the anterior mediastinum can prove easy to intubate but impossible to ventilate if the mass obstructs the trachea after loss of spontaneous respiration. In many cases, the surgeon has evaluated the pathologic condition that makes the airway abnormal and a preprocedure discussion between the anesthetist and otolaryngologist is imperative. Patients scheduled for laryngectomy may have undergone radiation therapy to the head and neck that caused epiglottis fibrosis, laryngeal edema, or trismus.

Partial airway obstruction from laryngeal or oropharyngeal masses may already exist and necessitates careful planning of intubation techniques. One study demonstrated a four-fold increased risk of failed Glidescope (video laryngoscope, Verathon Inc., Bothell, WA) intubation in patients with a neck scar, radiation, or mass (14). Ventilation or intubation of patients with some congenital anomalies can be impossible if apnea occurs. These syndromes include Beckwith-Wiedemann, Crouzon, Down, Goldenhar, Pierre Robin, Treacher Collins, and Turner syndromes; congenital rubella; and mucopolysaccharidosis.

Thorough study of an airway found to be abnormal before surgery can prevent catastrophe during induction of anesthesia. In addition to history and physical exam, the size, site, and degree of obstruction of an airway lesion may be elucidated through direct visualization or radiologic scans. Flow-volume loops are helpful in assessing the degree of tracheal obstruction caused by large cervical or intrathoracic masses. Presence of a tracheal mass may necessitate maintaining spontaneous breathing until the endotracheal tube is placed distal to the mass to prevent tracheal obstruction that may result from positive-pressure mask ventilation. Fiberoptic laryngoscopy or tracheobronchoscopy performed with topical anesthesia with the patient awake and breathing spontaneously can be invaluable in the evaluation of a patient who has grossly distorted anatomic landmarks.

Securing the Airway

After completion of the airway assessment, a plan can be constructed for securing the airway. There are multiple management decisions, including awake versus asleep intubation, noninvasive versus invasive techniques (e.g., tracheostomy or cricothyrotomy), and whether or not to preserve spontaneous ventilation. If no suspicion of a difficult airway exists, routine intubation can be performed, although the anesthesiologist must always have backup plans for an unanticipated difficult airway. If the airway seems as if it may be difficult to manage, securing the airway with the patient awake and spontaneously breathing may be the safest route. Anesthetizing the airway is accomplished with nerve blocks (e.g., bilateral glossopharyngeal and superior laryngeal nerves) and transtracheal injection of 4% lidocaine or with inhaled nebulized and sprayed local anesthetics (e.g., 6 mL total of 4% lidocaine). Administering glycopyrrolate (0.2 to 0.4 mg iv) 30 to 60 minutes prior to arrival in the operating room will reduce secretions and thus improve the topicalizaton and the laryngoscopic view. The patient may then be judiciously sedated with a patient appropriate combination of midazolam (anxiolysis and amnesia), fentanyl (attenuates cough reflex), and dexmedetomidine (up to 1 mcg/kg iv over 15 minutes) while the airway is anesthetized. The airway is then usually secured with fiberoptic intubation, although other awake options include direct laryngoscopy (including video-assisted techniques such as the Glidescope or CMAC [Karl Storz, El Segundo CA]), or retrograde intubation. In the case of severe anatomical abnormalities or a glottic lesion, a transtracheal catheter with subsequent jet ventilation or tracheotomy with local anesthesia may be the initial plan. In pediatric or uncooperative patients, an awake intubation may not be an option, and a gentle mask induction while keeping the patient spontaneously breathing, followed by a fiberoptic intubation may be the best alternative. However, as the patient deepens with anesthesia, airway collapse with subsequent difficulty in ventilation is possible.

If the decision is to perform an asleep intubation, preoxygenation with 100% oxygen prior to induction allows the anesthetist several minutes to intubate in case of difficulty with mask ventilation or intubation (15). If the trachea is unable to be intubated with direct laryngoscopy, successful positive-pressure ventilation with mask and reservoir bag allows for consideration of many airway techniques in the armamentarium of a well-trained anesthesiologist. Most anesthesiologists are skilled in several, but not all, techniques of management for a difficult airway and should use the techniques that work best for them. The anesthetist also must be prepared to use several techniques should one or more fail. Fiberoptic intubation is the most widely used of the second-line intubation techniques, although disrupted or severely abnormal anatomic features or bleeding in the airway can preclude successful navigation of the airway by all but the most expert endoscopists. Video-assisted laryngoscopes, light wand, gum elastic bougie, and retrograde intubation are all options, depending on the skill set of the anesthesia team. A combination of video-assisted laryngoscope with a fiberoptic scope has also proven successful. Care should be taken to avoid multiple intubation attempts, as this may lead to airway edema and difficulty with mask ventilation. Oral and nasopharyngeal airways are useful in the ventilation of patients with obstruction at the level of the oral cavity and oropharynx, respectively. If intubation fails and mask ventilation is difficult despite two provider ventilation (one provider gives two-handed jaw thrust and the other provider compresses the bag), then an laryngeal mask airway (LMA) should be inserted. Failure of the LMA necessitates emergency airway ventilation, such as a rigid bronchoscope by the otolaryngologist or transtracheal jet ventilation. If this is unsuccessful, emergent invasive airway access must be obtained by either cricothyrotomy or tracheotomy. Chapters 63 and 64 contain a further discussion of airway management, tracheotomy, and cricothyroidotomy.

Extubation of a patient who was a difficult intubation also requires careful planning. It may be beneficial to remove the endotracheal tube over an intubating stylet, which may remain in the trachea to facilitate reintubation until adequate spontaneous ventilation is assured.

There may be some cases for a general anesthetic where the anesthesiologist decides that the airway does not need to be secured with an endotracheal tube and a laryngeal

mask airway is preferred. Compared with endotracheal intubation, an LMA is placed without muscle relaxant, it is inserted blindly, and there are fewer hemodynamic changes with placement and less coughing with emergence. Although an endotracheal tube is considered a more secure airway for most ENT surgery, an LMA offers improved emergence and better airway protection during nasal surgery (16).

ANESTHETIC CONSIDERATIONS FOR ENDOSCOPIC PROCEDURES

For a conscious, cooperative patient, careful orotracheal topical anesthesia and intravenous sedation may be adequate for the performance of brief, atraumatic laryngoscopic procedures, such as vocal cord injection. For more complicated procedures, general anesthesia is induced and an endotracheal tube may or may not be inserted. In most procedures, a small-diameter, cuffed endotracheal tube (e.g., microlaryngeal tube with internal diameters of 5 mm and a high volume, low pressure cuff) does not obstruct the view of the larynx and allows efficient gas exchange and protection of the airway from blood; however, some surgical techniques necessitate complete absence of an endotracheal tube. In these situations, intravenous agents and neuromuscular relaxants meet the requirements of general anesthesia, whereas oxygenation and ventilation occur through a ventilating laryngoscope or an Albert Sanders injector. High-frequency positive-pressure ventilation is an alternative approach. Topical anesthesia combined with general inhalational or intravenous anesthetics also can be used for bronchoscopy. A ventilating bronchoscope provides an avenue for gas exchange, although apneic oxygenation with insufflation of oxygenation through a small-bore catheter placed above the carina is sometimes necessary. High rates of fresh gas flow from the anesthesia machine are needed to compensate for the leak that occurs around the bronchoscope. As in laryngoscopy, pulse oximetry is essential for monitoring patient safety, and a small dose of glycopyrrolate facilitates visualization by reducing secretions.

A controversy exists over the best type of endotracheal tube to minimize the risk of airway fire during carbon dioxide laser laryngoscopy or bronchoscopy. All tubes, except metal or ceramic, can ignite in the airway under appropriate conditions. Many anesthesiologists use laser-resistant endotracheal tubes or an ordinary polyvinyl chloride or red rubber endotracheal tube that has been closely wrapped its entire length with metallic tape designed to reflect the energy of the laser away from the tube. The cuff should be filled with normal saline tinted with methylene blue to make it apparent if the cuff is punctured. Because the cuff remains uncovered, an explosion or fire can occur if the laser beam penetrates it. A less serious problem is misdirection of the laser should the beam come into contact with the reflective tape. Even a properly wrapped laser tube can ignite if the endoscopist directs a high-wattage beam of collimated light at a single spot on the tube for too long. Management of a laser fire in the airway demands immediate disconnection of the circuit from the endotracheal tube, removal of the burning tube, extinction of the flame with normal saline, reestablishment of ventilation, and then bronchoscopy to remove debris and assess residual damage to surrounding tissues (17).

Other measures used to reduce the risk of airway fire include the avoidance of nitrous oxide, use of less than 30% inspired oxygen, a helium–oxygen rather than an oxygen–air inspired gas mixture, and packing the trachea around the cuff of the endotracheal tube with wet sponges. Additionally, all operating room personnel should wear protective goggles, and the eyes of the patient should be covered to prevent corneal or retinal thermal injury.

PREOPERATIVE PREPARATION

Evidence-based fasting guidelines by the American Society of Anesthesiologists have been established to reduce the incidence of perioperative aspiration, which carries a high risk of morbidity (18). Liquids (e.g., soda, apple juice, water, black coffee or tea) are rapidly cleared from the stomach (half-life 11 minutes), and thus, they may be ingested in unlimited quantities up to 2 hours prior to surgery. Breast milk may be given within 4 hours. A light meal, such as toast and milk should not be taken within 6 hours of surgery. Full meals with fat or alcohol delay stomach emptying and an 8-hour fast is usually recommended. If the patient has delayed stomach emptying (e.g., diabetic gastroparesis), a decision may be made to prolong the fasting guidelines further.

Most medications should be continued on the day of surgery, with a few exceptions. In patients without heart failure, angiotensin converting enzyme inhibitors and angiotensin receptor blockers should be withheld because they may cause profound and resistant hypotension when combined with general anesthetics. Insulin needs to be adjusted as is outlined in Chapter 3. A patient's cardiologist should be consulted regarding perioperative anticoagulation in patients with coronary artery stents. Patients with stents should always continue their aspirin unless there is a major concern regarding the effects from significant blood loss. Current recommendations are for patients with drug-eluting stents to have clopidogrel continued for at least 1 year and 4 to 6 weeks after bare metal stents. The concern is that the patient will be at high risk of stent reocclusion because stopping aspirin and clopidogrel each make the patient hypercoagulable, along with the hypercoagulable state of surgery.

HIGHLIGHTS

- Common local anesthetics belong to two structural classes, the amines and the esters, which differ in route of excretion.
- Local anesthetics block sodium channels intracellularly and are more effective in the base (nonionized) form because of the ease with which they enter the cell.
- With knowledge of head and neck anatomy, small amounts of local anesthesia can be used to create regional blocks of the major sensory nerves of the head and neck and permit extensive procedures under local anesthesia.
- Careful preoperative airway assessment, an understanding of basic anesthesia monitoring and airway equipment, and judicious use of anesthetic agents known to produce respiratory depression aid in the prevention of catastrophic airway loss.
- Knowledge of local anesthetics and drugs used in general anesthesia will aid in the recognition of common side effects and complications to ensure rapid treatment.
- Isoflurane, sevoflurane, and desflurane have replaced halothane as the most commonly used general anesthetics.
- Nitrous oxide is not potent enough to be used for general anesthesia by itself, but is often added to improve hemodynamic stability and speed emergence.
- Benzodiazepines produce reliable anxiolysis, sedation, and amnesia and are commonly used prior to anesthetic induction and during procedures under local anesthesia.
- Knowledge of different opioid drugs will help in the management of postoperative pain, especially in patients with advanced cancer.
- Muscle-relaxant drugs are either competitive (nondepolarizing) or noncompetitive (depolarizing) inhibitors of neuromuscular transmission that work at the postsynaptic membrane of the nicotinic cholinergic receptor.
- Knowledge of anesthetic techniques and pharmacologic principles allows safe and effective anesthetic management of nearly all otolaryngologic patients.
- Recognition of potentially difficult airways preoperatively allows not only an effective plan but also possible alternatives when necessary.
- Close cooperation between anesthesiologists and surgeons, based on a mutual understanding of needs, is essential for a successful patient outcome.

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16 Endocrinology

Paul G. van der Sloot *Runhua Hou*

The endocrine system is a complex, highly integrated system of controls that plays a very important role in homeostasis. Hormone effects can be local, regional, or systemic, reflecting autocrine, paracrine, and endocrine functions. Beyond the high degree of integration within the system itself, there are complex interactions between the endocrine system and other important body systems, in particular, the nervous system. As a result, disruption of normal endocrine function often leads to systemic pathology. At the same time, manipulation of the endocrine system with drugs that block hormone receptors or drugs that mimic hormone actions can provide therapeutic benefits in a wide range of diseases.

PITUITARY

Anatomy and Embryology

The pituitary gland is one of the control centers of the endocrine system. It is composed of an anterior and posterior lobe. In some animals, but not humans, there is a distinct intermediate lobe. The anterior lobe develops by week 4 to 5 gestational age. It begins as an evagination of the ectoderm of the oropharynx known as Rathke's pouch. Eventually, the pouch is pinched off and is separated from the pharynx by the sphenoid bone. It is often referred to as the adenohypophysis. The residue of Rathke's pouch demarcates the separation between the anterior and posterior lobes. The most superior part of the pouch surrounds the neural stalk and is called the pars tuberalis. Occasionally, cells of Rathke's pouch are left behind and may form a craniopharyngioma.

The posterior lobe begins as an evagination of the floor of the third ventricle. The lumen walls eventually fuse to form the neural stalk. A small invagination in the floor of the third ventricle is also formed and is known as the median eminence. The median eminence, neural stalk, and posterior lobe form what is referred to as the neurohypophysis. Approximately 100,000 neurons of the hypothalamus project down through the neural stalk forming the hypophyseal tract. Their nerve terminals form the posterior lobe of the pituitary. In response to appropriate stimuli, these cells secrete antidiuretic hormone (ADH), also known as vasopressin, or oxytocin.

The anterior lobe cells are 50% somatotrophs secreting growth hormone (GH), 10% to 25% lactotrophs secreting prolactin, 15% to 20% corticotrophs secreting adrenocorticotropic hormone (ACTH), 10% to 15% gonadotrophs secreting luteinizing hormone (LH) or follicle-stimulating hormone (FSH), and 3% to 5% thyrotrophs secreting thyroid-stimulating hormone (TSH).

Blood supply to the pituitary is via the inferior and superior hypophyseal arteries. The capillaries of the inferior artery supplying the posterior lobe form a plexus that drains into the dural sinus. A small portion of them form the short hypophyseal portal veins that drain into the anterior lobe of the pituitary. The anterior lobe is supplied by the superior hypophyseal artery via the long hypophyseal portal veins formed by its capillaries. These veins surround the cells of the median eminence from whence neurohormones are secreted. A second plexus of fenestrated capillaries forms around the anterior lobe of the pituitary to enhance delivery of hormones to this part of the pituitary. Veins draining the anterior lobe drain into the cavernous sinus and eventually to the jugular veins.

The developed pituitary sits in a bony pouch called the sella turcica. The anterior wall is called the tuberculum sella, the posterior wall the dorsum sella. They are flanked by the anterior and posterior clinoid processes, respectively. These clinoid processes are connected by a reflection of the dura mater called the diaphragma sella. Thus, the entire sella is surrounded by dura. It is outside the arachnoid and cerebrospinal fluid and so is outside the blood–brain barrier. An important anatomical relationship is the optic chiasm, which is approximately 5 mm above the diaphragma sella and anterior to the stalk of the pituitary. Laterally, it is flanked by the cavernous sinus.

ANTERIOR PITUITARY

Growth Hormone

GH is a 19–amino acid polypeptide with two disulfide bridges and a four helical structure. It has several forms but in general has a half-life of about 20 minutes. It is considered an anabolic hormone. Its effects are mediated via insulin-like growth factors 1 and 2 (IGF1 and 2) produced by the liver and other target tissues. Cartilage growth at epiphyseal growth plates is stimulated resulting in an increase in bone mass. IGF 1 and 2 also have lipolytic effects resulting in increased lean body mass. An increase in organ size and function is also seen. GH also antagonizes insulin action resulting in insulin resistance. Its synthesis and secretion are stimulated by the release of growth hormone–releasing hormone (GHRH) from the arcuate nucleus of the hypothalamus into the hypophyseal portal system. Its secretion but not its synthesis is inhibited by somatostatin released by the periventricular nuclei of the hypothalamus. It is also inhibited via an IGF feedback loop at the level of the hypothalamus and pituitary. Ghrelin produced in the hypothalamus and by neuroendocrine cells of the gastric mucosa binds to the growth hormone secretagogue receptor stimulating GH release (1).

GH is secreted in pulsatile fashion with typically five pulses over 24 hours. The largest pulse occurs at the onset of sleep (2). Peak levels of GH occur during puberty with a general decline with age from that point. GH resistance in childhood results in Laron dwarfism, manifested by central facial dysmorphism and obesity. GH excess results in gigantism if present during development and in acromegaly if occurring in adulthood. Greater than 99% of these cases result from pituitary adenomas, usually macroadenomas. Gigantism results from hormone excess prior to epiphyseal plate closure. Acromegaly, which occurs in about 50/million population, results in increased IGF1 and subsequent proliferation of bone, cartilage, and soft tissue. Presenting symptoms include carpal tunnel syndrome, hyperinsulinemia and glucose intolerance, and hypogonadism due to decreased gonadotropin secretion. Excess GH levels may be seen in McCune-Albright syndrome (polyostotic fibrous dysplasia, precocious puberty, hyperthyroidism, hypercortisolism, and hyperprolactinemia) even though an adenoma is not present. It can also be associated with pituitary adenomas in multiple endocrine neoplasia type 1 (MEN-1). GH deficiency can be treated with hormone replacement therapy. GH excess associated with pituitary adenoma is typically treated with surgery plus or minus radiation therapy. Medical therapy can include somatostatin analogues.

Prolactin

Prolactin is a single-chain protein made of 199 amino acids with 3 disulfide bridges. It is very similar in structure to GH. Its main actions are the stimulation of breast development and milk production. It has many lesser understood functions and inhibits GHRH release. Its release is stimulated by thyrotropin-releasing hormone produced by the hypothalamus. Galanin, produced by the hypothalamus and pituitary, can also stimulate prolactin release. Inhibition occurs mainly through dopamine release by the tuberoinfundibular cells of the hypothalamus into the hypophyseal portal system. There is a negative feedback loop with prolactin stimulating tyrosine kinase activity in the tuberoinfundibular cells and subsequent release of dopamine.

Secretion of prolactin follows diurnal patterns with sleep-related increases in prolactin levels. Lactotroph hyperplasia is seen during pregnancy and lactation but usually normalizes within months of delivery. Excess prolactin occurs most commonly with dopamine antagonist drugs and primary hypothyroidism but can also be the result of other pituitary adenomas compressing the pituitary stalk. Up to 30% to 40% of pituitary adenomas are prolactinomas. Symptoms include infertility, menstrual irregularities or amenorrhea, and galactorrhea in females. Males experience a decrease in testosterone levels, decreased sperm production, and gynecomastia. Treatment of prolactin excess caused by pituitary adenomas is medical using dopamine agonists including bromocriptine and cabergoline (3). Surgery and radiation therapy are reserved for patients unresponsive to medical therapy.

Adrenocorticotropic Hormone

ACTH is derived from a large precursor, pro-opiomelanocortin, which is cleaved by enzymatic action. Cleavage of the precursor also gives rise to melanocyte-stimulating hormone and opioid peptides. The main action of ACTH is on the renal cortex, stimulating release of glucocorticoids and androgens. Release of ACTH is stimulated by corticotropin-releasing hormone (CRH) release by hypothalamic CRH-producing cells in the median eminence. The action of CRH is potentiated by ADH. Inhibition of ACTH release is via a negative feedback loop where glucocorticoids detected at the level of the hypothalamus inhibit CRH release. Changes in osmolality and blood volume induced by ADH also have an inhibitory effect on CRH release. Secretory patterns follow a circadian rhythm with a nadir in the evening and a peak in the early morning. Secretion is pulsatile with up to 40 pulses per day. Amplitude rather than frequency of pulses determines the circadian rhythm. There is, however, a significant reserve in the system that can be mobilized in response to stress including infection, inflammation, and trauma.

Excess glucocorticoid production results in Cushingoid symptoms. Most commonly, Cushing's is a result of exogenous glucocorticoids but rarely can be caused by a pituitary adenoma. Up to 15% of pituitary adenomas are corticotroph adenomas. Some release excess ACTH resulting in Cushing's disease. However, a number of these are silent corticotroph adenomas, usually macroadenomas

with hemorrhage and mass effects including bone erosion (4). Treatment for these tumors is surgical with or without radiation therapy.

Gonadotrophs, Luteinizing Hormone, and Follicle-Stimulating Hormone

LH and FSH are homologous peptides that are released by the same cells of the anterior pituitary. They also share significant homology with TSH and bHCG. Each has a common alpha and distinct beta subunit. Posttranslational processing of carbohydrate side chains is also critical to hormonal signaling. The action of LH and FSH differs in males and females.

In females, LH stimulates cholesterol production for steroidogenesis in luteal cells of the ovary. It also enhances cytochrome P450–linked enzyme activity to synthesize pregnenolone and induces 3b-hydroxysteroid dehydrogenase, 17a hydroxylase, and 17,20 lyase activity. FSH regulates ovarian estrogen synthesis by inducing 17b hydroxysteroid dehydrogenase and aromatase. It also induces follicular growth, oocyte maturation, and androgen production. In males, Leydig cell LH receptors induce testicular testosterone production in response to LH. FSH may have a role in spermatozoa development.

Gonadotropin-releasing hormone release from the hypothalamus is pulsatile. The frequency and amplitude of the pulse determines the effect on LH and FSH secretion. The amplitude of the response is greater for LH than FSH. Generally, a decrease in pulse frequency induces LH secretion; an increase in pulse frequency induces a decrease in LH secretion. Inhibition is via a feedback mechanism. Testosterone inhibits LH and FSH release at both the hypothalamus and pituitary level. In fact, castration leads to an increase in gonadotropin levels. Gonadotropin release is also regulated by gonadal peptides inhibin A and B.

A deficiency in gonadotropins causes hypogonadism with decreased sex steroid production. If during childhood it is complete, there is a failure of male sexual development. In females it leads to amenorrhea. If partial, in males it leads to decreased libido, impotence, decreased fertility, and obesity. In females, partial deficiency leads to oligomenorrhea, vaginal dryness, hot flushes, decreased bone density, decreased breast tissue, and infertility.

Pituitary tumors of gonadotropin origin comprise about 15% of pituitary adenomas. Treatment is usually surgical but may be reserved for complications or impending complications since growth is variable. Stereotactic radiation may have a role for tumor control.

Thyroid-Stimulating Hormone

Thyrotrophs comprise approximately 5% of anterior pituitary cells. THS is a glycoprotein heterodimer composed of an alpha and beta subunit noncovalently linked. The beta subunit confers the specific action of TSH. The half-life of TSH is approximately 50 minutes. Its action is to stimulate thyroid follicle cells to synthesize and release thyroid hormone.

Stimulatory control occurs via thyroid-releasing hormone (TRH) released from the hypothalamus. Peak TSH levels occur approximately 30 minutes after TRH release. TRH stimulates both alpha and beta subunit transcription. Inhibition occurs through T3 feedback. T3 inhibits both alpha and beta subunit transcription. TSH release is also inhibited by dopamine, glucocorticoids, somatostatin, and some anti-inflammatory medications.

Thyrotroph cells of the anterior pituitary are developed by 12 weeks gestational age. TSH levels rise immediately after birth and remain elevated for about 5 days before reaching adult levels. TSH secretion also follows a circadian rhythm with a peak levels at 11 PM and 5 AM.

Deficiency of TSH in childhood leads to mental and growth retardation. In adults, it leads to hypothermia and fluid retention, along with voice, hair, and skin changes. Excess leads to palpitations, arrhythmias, weight loss, tremor, and nervousness.

Tumors of thyrotroph origin are rare and compose less than 1% of all pituitary adenomas. When they do occur, they are usually macroadenomas and often show bony erosion on presentation. Surgery is the primary treatment for these tumors. Radiation may be used as adjuvant therapy. Medical therapy is occasionally used and often involves octreotide, a somatostatin analogue. This is usually combined with symptomatic management that may include propylthiouracil (PTU), propranolol, and occasionally total thyroidectomy.

POSTERIOR PITUITARY

Antidiuretic Hormone

ADH, also known as vasopressin, is a nonapeptide with a six–amino acid chain connected by a cysteine–cysteine bridge to a three–amino acid tail. It is well conserved across mammalian species. Stimulation of the cell body in the hypothalamus leads to an action potential propagated along the axon to the nerve terminal in the posterior pituitary. This causes an influx of calcium and subsequent extravasation of neurosecretory granules. At any time, there is a 30- to 50-day basal supply stored in the neurosecretory granules. Its half-life is approximately 15 minutes.

ADH plays a critical role in water homeostasis and osmolality of body fluids. It plays a lesser role in blood pressure/volume control, which is controlled to a greater degree by the renin–angiotensin system. V1 receptors for ADH are found in blood vessel walls, V2 in renal collecting duct epithelium, and V3 receptors play a role in factor VIII production. High pressure/volume receptors in the carotid sinus and aortic arch along with low pressure/volume receptors in the atria and pulmonary venous system send afferent signals via cranial nerves IX and X to the

brain stem. Vagotomy results in increased ADH activity. ADH interaction with the V1 receptor leads to arterial and venous constriction. Interaction with the V2 receptor leads to water reabsorption resulting in decreased urine volume and increased urine concentration. Together, these effects lead to an increase in blood volume/pressure. Generally, decreased blood pressure/volume leads to ADH release, and increased blood pressure/volume inhibits ADH release.

Osmotic receptors in the hypothalamus respond to changes in blood osmolality. Osmolality is mainly a function of sodium concentration and is tightly controlled maintaining a range from 280 to 295 mOsm/kg H_2O. Basal ADH levels are 0.5 pg/mL. A 1% change in plasma osmolality will lead to a rapid release of ADH from secretory granules. There is a linear relationship between serum ADH levels and osmolality up to ADH levels of 6 pg/mL when maximum urine concentration is occurring.

Diabetes insipidus (DI) is defined by large volume, hypotonic dilute urine. The term insipidus means tasteless, as opposed to mellitus, which means sweet. There are three mechanisms that result in DI, so defined: (a) an inability to synthesize or secrete ADH, (b) nephrogenic—an inappropriate renal response to ADH—and (c) transient DI of pregnancy due to accelerated metabolism of ADH. A similar presentation can occur with excess water ingestion. This can be differentiated from an inability to synthesize or secrete ADH using serum sodium levels, which will be increased with hypothalamic DI and decreased in primary polydipsia. Hypothalamic DI may occur immediately after surgery in the region of the pituitary or hypothalamus (5). Patients ask for cold liquids and have large volume urine. More rarely, DI can be associated with craniopharyngiomas, pinealomas, and suprasellar germinomas. About 50% of DI is idiopathic.

Oxytocin

Oxytocin is the other hormone released from nerve terminals of the posterior pituitary. Release of oxytocin stimulates myometrial contraction at parturition. It also stimulates smooth muscle activity in the breast, promoting milk letdown with nursing. Release is mediated via mechanical and tactile receptors stimulated by suckling, leading to an afferent stimulus of the supraventricular and supraoptic nuclei. This causes a pulsatile release of oxytocin. At the end of pregnancy, parturition leads to a 200-fold increase in the responsiveness of myometrial cells to oxytocin.

PARATHYROID AND CALCIUM METABOLISM

The Parathyroid Glands

The parathyroid glands are derivatives of the third and fourth branchial pouches. The third pouch contains the primordia of the thymus and inferior parathyroid glands. The inferior parathyroids descend in the neck with the thymus typically reaching their destination in the anterior mediastinum at about the level of the inferior poles of their respective thyroid lobes. The fourth pouch gives rise to the superior parathyroid glands, which descend to their orthotopic position near the upper pole of the respective thyroid lobe. The fascia enveloping the thyroid gland can envelope the superior parathyroid glands as well. Even when the parathyroid glands are in their usual positions, the superior glands tend to be more posteromedial in position than the inferior glands. Supernumerary glands are not uncommon with up to 2.5% of the population having six glands. The normal adult weight for a parathyroid gland is 30 to 50 mg.

Ectopic locations for the parathyroid glands are not uncommon and reflect the direction and extent of descent during development. Superior glands can be found in the retro- or paraesophageal space and can be found in the posterior superior mediastinum. They can also be intrathyroidal (6). Inferior gland position is slightly more variable. Descent with the thymus leads to ectopic glands in the anterior superior mediastinum and even within the thymus. Up to one of three missed parathyroid adenomas will be found in the anterior mediastinum.

Blood supply to the parathyroid glands is usually via the inferior thyroid artery, but there are often multiple collaterals in the area. More rarely, the superior glands are supplied by the superior thyroid artery and the inferior gland by the inferior thyroid artery. Even more rarely, both glands are supplied by the superior thyroid artery. Venous drainage parallels arterial supply.

Parathyroid hormone (PTH) is an 84aa peptide cleaved from a larger precursor called pre-PTH. Its amino-terminal is the active portion of the hormone. It binds to receptors in bone and the kidney affecting an increase in serum calcium levels. In the kidney, receptor activation leads to an increase in $1,25(OH)_2D3$, the active form of vitamin D. In turn, vitamin D augments calcium absorption in the intestine as well as increasing the influx of calcium from bone and kidney. There is a small direct effect of PTH that causes an increase in calcium absorption in the cortical ascending loop of Henle but a more pronounced effect promoting calcium reabsorption from the distal convoluted tubule and the connecting tubule. Phosphate reabsorption in the proximal and distal tubules is strongly inhibited by PTH. In the bone, PTH has direct effects on osteoblasts and preosteoblasts. Osteoblast production of collagen is inhibited and maturation of preosteoblasts is inhibited. Effects on osteoclasts, or bone resorbing cells, are indirect via preosteoblasts and osteoblasts, which send cell signals to osteoclasts to mature, resorb bone, and inhibit apoptosis. Interestingly, constitutive PTH leads to bone resorption, but intermittent PTH favors an increase in bone mass. This has been used clinically. Teriparatide, an amino-terminal segment of PTH administered subcutaneously, is an FDA-approved treatment for severe osteoporosis.

Secretion of PTH is stimulated by a decrease in serum ionized calcium levels. Not only does PTH secretion vary inversely with ionized calcium levels but the PTH response for a given level of hypocalcemia is more dramatic if the rate of fall of ionized calcium is greater. Inactivation of the receptor for calcium through mutation is seen in familial hypocalciuric hypercalcemia. Chronic calcium receptor activation is also seen with genetic mutations and causes hypoparathyroidism with hypocalciuria. $1,25(OH)_2D3$ does not affect secretion of PTH. However, it does suppress PTH gene transcription. Increased phosphate levels stimulate PTH secretion indirectly by decreasing blood calcium and $1,25(OH)_2D3$ levels. Beyond the increased transcription and secretion of PTH, parathyroid cell number increases in the setting of hypocalcemia, low levels of $1,25(OH)_2D3$, hyperphosphatemia, and uremia. This is a slower response, and even if the underlying cause for the increased cell replication is no longer present, the resulting hyperparathyroidism can persist. This represents tertiary hyperparathyroidism.

Primary hyperparathyroidism is defined by the inappropriate hypersecretion of PTH. Seventy-five to eighty percent is caused by one or more adenoma, 20% by diffuse hyperplasia and <1% to 2% by parathyroid carcinoma. Carcinomas are usually associated with very high PTH levels and can be part of hyperparathyroidism–jaw tumor syndrome (parathyroid carcinoma and fibrous jaw tumors). Primary hyperparathyroidism is characterized by increased renal calcium absorption, phosphaturia, increased $1,25(OH)_2D3$, and increased bone resorption. The prevalence is thought to be approximately 0.04/1,000 population, but because many of those with primary hyperparathyroidism are asymptomatic, the numbers may be higher. DNA mutations including those of protooncogenes PRAD-1 and cyclin D1 have been implicated (7). There is some evidence that a remote history of neck irradiation may increase the risk. These mutations cause not only an increase in cell numbers but a decreased response of those cells to serum calcium levels. Parathyroid hyperplasia is seen in the MEN syndromes type 1 and 2a. In type 1 MEN, hypercalcemia is seen in 95% of patients and usually present in the second or third decade of life. In type 2a MEN, only 5% to 20% of patients manifest symptoms of hyperparathyroidism.

The natural history of asymptomatic primary hyperparathyroidism is uncertain, although there is evidence of increased fracture risk (8). Current indications for surgery are controversial but include those (a) <50 years of age, (b) who cannot participate in appropriate follow-up, (c) with a serum calcium level >1.0 mg/dL above the normal range, (d) with urinary calcium >400 mg/24 h, (e) with a 30% decrease in renal function, or (f) with complications of primary hyperparathyroidism, including nephrocalcinosis, osteoporosis (*T*-score <2.5 SD at the lumbar spine, hip, or wrist), or a severe psychoneurologic disorder (9). Medical management for the remaining asymptomatic hyperparathyroid patients includes semiannual clinical evaluations, avoidance of diuretics and immobility, maintenance of adequate hydration, and limiting oral calcium to 800 mg/day. Symptomatic patients have combinations of decreased cortical bone, hypercalciuria associated with nephrolithiasis, and even renal failure, flank pain, polyuria/polydipsia, conjunctival calcifications, GI symptoms, and pathology that may include pancreatitis, neuropsychiatric problems, and neuromuscular complaints. Although symptoms can sometimes be difficult to directly attribute to hyperparathyroidism, the recommendation for symptomatic patients is for surgery unless it is otherwise contraindicated. In those patients that cannot undergo surgery, bisphosphonates like alendronate can improve bone density but have minimal effects on serum calcium and PTH. Calcimimetics like cinacalcet can lower serum calcium and PTH but do not affect bone density.

Secondary hyperparathyroidism is defined by the appropriate hypersecretion of PTH. It can be seen with decreased serum calcium levels secondary to excess urinary loss, or inadequate intake, hypophosphaturia due to aluminum poisoning, kidney disease and decrease calcium levels, and decreased $1,25(OH)_2D3$ levels secondary to decreased sunlight exposure or malnutrition. Treatment is directed by the underlying cause.

Calcitonin

Calcitonin is a 32aa polypeptide with a disulfide bridge. Although it is an important component of calcium metabolism in many species, its importance in humans remains uncertain. It is secreted by intrathyroidal C-cells of neural crest origin. It is incorporated into the thyroid gland as the ultimobranchial bodies (the primordia of the C-cells) merge with the developing thyroid. In other species, calcitonin causes a decrease in tubular resorption of calcium in the kidneys and decreases osteoclast-mediated bone resorption. However, in humans, thyroidectomy has no significant effect on bone density and even high-dose exogenous calcitonin has minimal long-term effects (10).

Secretion of calcitonin is closely related to serum calcium levels. C-cells have the same calcium receptor as parathyroid chief cells, and increased calcium levels cause an increase in calcitonin secretion. There are a number of gastrointestinal hormones that stimulate calcitonin secretion as well. Their role in calcium regulation is uncertain. Inhibition is through somatostatin via an autocrine secretion. Transcription for calcitonin in C-cells is inhibited by $1,25(OH)_2D3$.

Vitamin D

With sun exposure (UV radiation), the cutaneous precursor of vitamin D, 1,7dehydrocholesterol, undergoes cleavage to form a thermally labile product that subsequently undergoes a rearrangement to form vitamin D. Excess sun

exposure leads to alternative rearrangement leading to biologically inert products. Subsequently, the precursor product undergoes a 25 hydroxylation, which occurs in the liver. This is followed by 1-alpha hydroxylation in the proximal convoluted tubule of the kidney. 1-Alpha hydroxylase activity is stimulated by PTH and hypophosphatemia. The product of this hydroxylation has an inhibitory effect on 1-alpha hydroxylase. The final product $1,25(OH)_2D3$ has a half-life of 6 to 8 hours. Vitamin D is also obtained through the diet. Fortified dairy products and cereal, egg yolks, and fish oil are major sources.

Vitamin D binds to nuclear receptors found in most tissues. Vitamin D precursors have an affinity but a much lesser affinity for the same receptors. Although present in most tissues, receptor binding has its greatest effect in the intestine. Receptors in the jejunum and duodenum, when bound, induce calcium channels important for intestinal absorption of calcium. A normal diet contains 700 to 900 mg of calcium. Typically, 30% to 35% is absorbed. Vitamin D effects on bone include increased differentiation of osteoclasts and osteoclast-mediated bone resorption.

Hypercalcemic Crisis

There are many conditions that can cause hypercalcemia. The two most common etiologies are primary hyperparathyroidism and malignancy. Together, they account for about 90% of all cases. In the hospital setting, malignancy is often the underlying culprit in hypercalcemia. In the outpatient clinic, primary hyperparathyroidism is the dominant etiology for chronic asymptomatic hypercalcemia. Hypercalcemic crises are the result of severely elevated calcium levels due to any cause, malignancy being the most common, and are associated with a significant mortality rate. Calcium levels between 13 and 15 mg/dL require aggressive treatment, while levels above 15 mg/dL can be life threatening and demand emergent therapy. The severity of symptoms is related to not only the absolute calcium level but also the rate of calcium level elevation. Hypercalcemia due to malignancy carries a poor prognosis as life expectancy is generally less than 6 months when hypercalcemia develops. Patients often present with acute mental status changes, confusion, bone or muscle pain, constipation, and fatigue. On examination, they appear to be dehydrated, with varying degree of mental status change. Laboratory evaluation invariably demonstrates elevated calcium levels with low, normal, or elevated PTH levels depending on the etiology. Hypercalcemia may be accompanied by acute renal insufficiency.

The pathogenesis of hypercalcemia is mediated through 3 different mechanisms. It can be due to elevated PTH, which activates osteoclasts and bone resorption, increases calcium absorption from the gastrointestinal tract, as well as reducing calcium excretion in the urine. This is the underlying mechanism of hypercalcemia occurring in primary hyperparathyroidism. Hypercalcemia can also be due to elevated parathyroid hormone–like protein (PTHrP) in patients with squamous cell carcinoma of the lung, head and neck, cervix, esophagus, vulva, and skin, as well as breast cancer, renal cell, and bladder cancer. PTHrP has similar functions to PTH and occupies the same receptors, but its secretion is not regulated by calcium level. The third mechanism is through lymphokines or cytokines such as TNF-beta, IL-1, lymphotoxin, or $1,25\ (OH)_2D$ released locally by tumor cells. These factors act on osteoblasts to stimulate bone resorption and cause hypercalcemia. This occurs often in patients with breast cancer or any cancer with metastasis to the bone or hematogenous tumors such as multiple myeloma, leukemia, and lymphoma.

The treatment of hypercalcemia includes aggressive IV hydration, judicious use of diuretics, bisphosphonates, calcitonin, and steroids. This combination approach can decrease serum calcium by 3 to 9 mg/dL within 24 to 48 hours in most patients, enough to relieve acute symptoms, prevent death from hypercalcemic crisis, and permit diagnostic evaluation. In a patient with hypercalcemic crisis, the critical first step in treatment is hydration. Patients are invariably dehydrated due to vomiting, poor intake, and a decreased ability to concentrate the urine induced by hypercalcemia. Rehydration with IV normal saline should be given as a bolus of 1 to 2 L initially, then at 200 mL/h for the first 24 hours in patients without a history of congestive heart failure. Subsequently, IV normal saline can be given at 100 mL/h until fluid status is replete. Care should be taken to prevent magnesium and potassium depletion. Loop diuretics such as furosemide can be given to patients to hasten calcium excretion only in the setting of adequate rehydration. Diuretics given too early in a dehydrated hypercalcemic patient may worsen hypercalcemia and renal insufficiency.

Calcitonin inhibits osteoclast action through receptors on the osteoclast. It also increases renal calcium excretion by inhibiting renal tubular calcium reabsorption. Therefore, it is a very effective agent within the first 24 hours of treatment of hypercalcemia as it can reduce calcium level within hours. However, its effect is short lasting secondary to tachyphylaxis, and it should not be used beyond the first 48 hours of treatment. The other benefit of calcitonin is that it has anesthetic effects, which can relieve the severe bone pain associated with hypercalcemia.

Bisphosphonates are the mainstay of treatment to lower calcium levels. Bisphosphonates are analogues of pyrophosphate, with a high affinity for bone, and reduce calcium levels by inhibiting osteoclast action, therefore suppressing bone resorption. This effect, however, takes 3 to 6 days to become effective and therefore cannot acutely lower calcium levels. Either pamidronate 30 to 90 mg or zoledronic acid 1 to 4 mg can be given intravenously to patient with hypercalcemia. Dose reduction is generally recommended in the setting of renal insufficiency. Repeat therapy as frequently as every month is necessary in patients with recurrent hypercalcemia due to malignancy.

Glucocorticoids can be helpful in hypercalcemia due to some malignancies. They increase urinary calcium excretion and decrease intestinal calcium absorption when given in pharmacologic doses. They are especially useful in those osteolytic malignancies such as multiple myeloma, leukemia, Hodgkin disease, other lymphomas, and carcinoma of the breast. They are also effective in treating hypercalcemia due to vitamin D intoxication and granulomatous disease such as sarcoidosis.

Other agents such as gallium nitrate and plicamycin are not used often nowadays, given their toxicity and better alternative therapies. Occasionally, dialysis may be needed in patients who have renal failure and hypercalcemia.

Hypocalcemia

Acute hypocalcemia generally occurs as a result of hypoparathyroidism due to thyroid or parathyroid surgery. Sometimes, it is caused by "hungry bone" syndrome experienced by patients postoperatively following surgery for a large parathyroid adenoma. Occasionally, other anions such as citrate, bicarbonate, or phosphate may complex with ionized calcium to decrease its concentration precipitously. The symptoms of hypocalcemia correlate closely with the rate of decrease in calcium levels but not necessarily with the absolute calcium level. Patients with chronic hypocalcemia generally tolerate the low levels of calcium quite well without significant symptoms. However, for those patients with hypocalcemia after thyroid or parathyroid surgery, the symptoms can be quite pronounced. Patients often have numbness and paresthesias, especially around their mouth and nose tip. Muscle spasm, carpopedal spasm, and facial grimacing can occur as well. Laryngeal spasm, convulsions, respiratory arrest, and cardiac arrhythmias can result in mortality if not treated immediately. Patients sometimes have increased irritability, depression, or psychosis. On examination, muscular hyperactivity can be demonstrated with Chvostek sign or Trousseau test. Treatment of hypocalcemia includes oral or IV calcium. To acutely increase calcium level in a symptomatic patient, 20 mL of calcium gluconate (180 mg elementary calcium) can be given over a 10-minute period. This is followed by infusion of 60 mL of calcium gluconate in 500 mL of D5W over 4 to 6 hours (12). Concurrent magnesium deficiency must be treated as well. Calcium given intravenously has a very short half-life, and therefore, calcium levels go down quickly once IV calcium is discontinued. Once oral intake resumes, patients can take either oral calcium carbonate or calcium citrate at doses of 1 to 2 g of elementary calcium three times per day. The dose is adjusted based on calcium levels. Calcium citrate is preferred in those with a history gastric reflux disease and on antiacid treatment as calcium is better absorbed in an acidic environment. Calcium carbonate is better taken with meals based on the same principle. Calcium should be given in divided doses as there is a limit to intestinal absorption at any given time. Calcium is mostly absorbed in the duodenum and proximal jejunum. The active transportation of calcium relies on the calcium transporter, and vitamin D increases the active transportation of calcium. To increase calcium absorption in patients with permanent hypoparathyroidism, calcitriol in a dose of 0.25 to 1 mcg/day is often necessary. The goal of treatment is to maintain calcium level between 8 and 8.8 mg/dL to avoid hyperphosphatemia given calcitriol increases both calcium and phosphate absorption. Long-term treatment of hypocalcemia aims to relieve symptoms and to avoid hyperphosphatemia or hypercalciuria. Hydrochlorothiazide can be used in difficult cases to reduce calcium excretion in the urine and stabilize the calcium level.

THYROID

The thyroid gland develops by the third week of gestational life, and thyroid hormone synthesis begins at about 11 weeks gestation. The thyroid gland secretes two related hormones, triiodothyronine (T3) and thyroxine (T4). These hormones bind to nuclear receptors in multiple organ systems and alter the transcriptions of numerous genes. They regulate cell differentiation during development and maintain thermogenic and metabolic homeostasis in the adult.

Thyroid hormone is synthesized in the thyroid follicular cells. Normally, thyroid follicular cells surround secreted colloid to form follicles. The basolateral side of follicular cells apposes the blood stream, and the apical side of the follicular cells faces the follicular lumen. The colloid is made of thyroglobulin (Tg), the protein precursor of thyroid hormones. The first step in thyroid hormone synthesis is iodide uptake. Iodide uptake into the follicular cell is regulated by sodium iodide symporter at the basolateral side, and efflux into the lumen is controlled by a protein called pendrin located on the apical side. Once iodide enters the follicular cells, it translocates to the apical membrane of thyroid follicular cells where it is oxidized. This organification reaction requires thyroid peroxidase (TPO) and hydrogen peroxide. The reactive iodine atom is then added to selected tyrosyl residues within Tg. Coupling of the iodotyrosines in Tg occurs through an ether linkage mediated by TPO. Either T3 or T4 can be produced depending on available iodine atoms in the iodotyrosines. After coupling, Tg is taken back into the thyroid cells and processed in lysosomes subsequently releasing T4 and T3 into blood stream. Uncoupled mono- and diiodotyrosines are deiodinated to recycle any iodide that is not converted into thyroid hormones.

Thyroid hormone synthesis is regulated by TSH secreted by anterior pituitary thyrotrophs and TRH produced by the hypothalamus. TRH and TSH positively stimulate thyroid hormone synthesis and production. On the other hand, thyroid hormones negatively regulate TRH and TSH production. In thyrotoxicosis, the excessive thyroid hormone directly downregulates TSH secretion and inhibits TRH-mediated

stimulation of TSH. On the contrary, in hypothyroidism, inadequate thyroid hormones stimulate TSH secretion as well as enhance TRH-mediated stimulation of TSH to increase thyroid hormone and maintain homeostasis. Iodine can also affect thyroid hormone synthesis. In iodine deficient areas, compensatory enlargement of the thyroid gland is commonly seen. Iodine excess can temporarily lead to decrease in thyroid hormone synthesis; this is called the Wolff-Chaikoff phenomenon. However, in 2 to 3 weeks, a normal functioning gland will escape this phenomenon and resume thyroid hormone synthesis. Patients with underlying autoimmune thyroid disease often cannot escape this phenomenon, and chronic iodine overload leads to hypothyroidism. Besides TSH and iodide, IGF-1, epidermal growth factor, transforming growth factor beta, endothelin, and various cytokine can influence thyroid hormone synthesis and release.

The thyroid gland releases 20-fold more T4 into the circulation than T3. Both T3 and T4 are bound to thyroxine-binding globulin, transthyretin, and albumin. Overall, about 99.98% of T4 and 99.7% of T3 is protein bound. Only free hormone is active. Because of the lower binding affinity for T3 compared to T4, there is more free T3. T4 is converted into T3 peripherally by type 1 or type 2 deiodinase. T4 is converted to reverse T3, an inactive thyroid hormone by type 3 deiodinase. Illness, fasting, acute trauma, and a variety of medications (PTU, propranolol, amiodarone, and glucocorticoids) inhibit T4 conversion to T3 but increases T4 conversion to rT3 (11).

Thyroid hormones exert biologic effects by binding to their nuclear thyroid hormone receptors alpha and beta. Both T3 and T4 bind thyroid hormone receptors but the affinity is 10 to 15 times higher for T3 compared to T4, and therefore, T3 is much more biologically active. The nuclear receptors are made of a central DNA-binding domain and a C-terminal ligand-binding domain. These receptors bind to specific DNA sequences called thyroid response elements in the promoter regions of target genes. Binding to some of the thyroid response elements leads to inhibition of gene transcription while in others leads to stimulation of gene transcription. This explains the diverse effects of thyroid hormones on multiple gene transcription.

Thyroid Storm

Thyroid storm is an extreme of hyperthyroidism. The mortality rate due to cardiac failure, arrhythmia, or hyperthermia is as high as 30% even with treatment (12). Thyroid storm most often occurs in patients with Graves disease, although it can occur in patients with toxic multinodular goiter. Patients often have untreated or inadequately treated hyperthyroidism. It is frequently brought on by another medical condition, such as acute illness (stroke, infections, DKA, preeclampsia, parturition), trauma, surgery (especially on the thyroid), or radioactive iodine treatment, which leads to an acceleration or decompensation of the hyperthyroid state.

Patients present with an exacerbation of hyperthyroidism manifested by fever, delirium, high-output heart failure, diarrhea, vomiting, irritation, confusion, coma, or jaundice. On examination, there is a widened pulse pressure, sinus tachycardia or arrhythmia, an enlarged thyroid gland, tachypnea, and hyperthermia. It is a hyperadrenergic condition. Laboratory evaluation often shows suppressed TSH and elevated fT3 and fT4. The level of elevation of thyroid hormone does not necessarily correlate with the occurrence of thyroid storm. Liver function tests and alkaline phosphatase may be slightly abnormal as well. The diagnosis of thyroid storm is based on history and physical examination, and a scoring system has been developed that may be useful in management (12).

The management of thyroid storm includes maintaining adequate circulatory volumes, reducing thyroid hormone synthesis, reducing T4 conversion to T3, and supportive therapy. To reduce thyroid hormone synthesis, either methimazole or PTU can be used. PTU has the additional advantage of inhibiting T4 conversion to T3, the most active form of thyroid hormone and therefore is the preferred agent for patients in thyroid storm. Patient in thyroid storm generally requires a high dose of PTU; the dose often needs to be at 200 to 300 mg every 4 to 6 hours to be effective. A 600-mg loading dose should be given first. Once the clinical condition improves, the PTU dose can be reduced or switched to methimazole. Methimazole has the advantage of a longer half-life and therefore can be given once per day to improve compliance. When oral intake is not possible, PTU or methimazole can be given rectally. To reduce thyroid iodide organification via the Wolff-Chaikoff phenomenon, potassium iodide (at five drops every 6 hours) or iopanoic acid (0.5 mg every 12 hours) may be given orally 1 hour after the first dose of PTU (12). The delay after PTU permits inhibition of iodine incorporation into newly synthesized thyroid hormone. Excessive iodide transiently inhibits thyroid iodide organification and therefore reduces thyroid hormone synthesis. This effect, however, does not last more than 2 to 3 weeks, and beyond that time, escape develops and thyroid iodide organification resumes. Therefore, this is only a temporizing measure before a more permanent treatment solution such as surgery or radioactive iodine can be instituted. The benefit of using iodide in thyroid storm is that it allows time for either methimazole or PTU to become effective. To reduce the hyperadrenergic state, beta-adrenergic blocking agents, including propranolol, atenolol, or metoprolol can be used. Propranolol is the preferred agent because it is a nonselective beta receptor blocker and at higher doses inhibits T4 to T3 conversion. It can be given 1 to 2 mg IV every 4 to 6 hours when oral intake is in question or orally at 40 to 60 mg every 4 to 6 hours. For patients with a history of asthma or obstructive lung disease or heart failure, a selective beta1 blocker like atenolol is a better agent to use. Glucocorticoids suppress conversion of T4 to T3 and therefore can also be used in patients in storm to reduce

active thyroid hormone levels. It should also be used if there is hypotension present to treat possible coexisting relative adrenal insufficiency. Glucocorticoids can be given as prednisone 60 mg/day or dexamethasone 1 to 2 mg/day. Besides these measures, supportive therapy is important. For hyperthermia, a cooling blanket can be used. Care should be taken to prevent a precipitous temperature decline. If blood pressure is low, volume expansion with normal saline and pressors may be needed to support the circulation. Cardiac arrhythmias may require pharmacotherapy and anticoagulation. The underlying cause needs to be aggressively sought and treated to avoid additional morbidity.

Myxedema Coma

Myxedema coma is another extreme of thyroid dysfunction. It has a high mortality rate despite treatment. Any cause of hypothyroidism can lead to myxedema coma. A typical patient with myxedema coma is an elderly female with a history of long-standing hypothyroidism not being treated or treated inadequately. There is almost always a precipitating factor such as underlying infection (pneumonia, urinary tract infection), medications (e.g., sedatives, anesthetics, antidepressants)), congestive heart failure, myocardial infarction, gastrointestinal bleeding, cerebrovascular accidents, poor oral intake, cold exposure, or an exacerbation of another chronic illness. Symptoms develop insidiously often delaying diagnosis. Patients present with hypothermia, hypoventilation, confusion, and/or coma. Physical examination reveals a confused patient with hypothermia, bradycardia, yellow-tinged skin, periorbital edema, dry skin, and nonpitting peripheral edema. Laboratory testing reveals elevated TSH and decreased fT4. Early diagnosis is essential in reducing mortality and morbidity.

The treatment of myxedema coma is to supplement thyroid hormone, maintain circulation, support respiratory system, and treat the underlying etiology. The precipitating factor needs to be aggressively sought. If found, it should be treated appropriately. Unfortunately, the underlying cause cannot always be found. To replace thyroid hormone, intravenous levothyroxine at a dosage of 300 to 500 mcg should be given as a loading dose as it can saturate the thyroid hormone receptors in different tissues. Subsequently, 50 to 100 mcg IV can be given once per day. Once the clinical condition improves, levothyroxine can be given orally. The advantage of using the intravenous form of levothyroxine is that it bypasses the GI tract to eliminate the effects of malabsorption resulting from bowel edema in a severely hypothyroid patient. For those with a history of heart disease, thyroid hormone dose reduction is often necessary to prevent acute MI or decompensation of myocardial function. Before treatment with levothyroxine, adrenal insufficiency often needs to be ruled out. In a patient with concurrent adrenal insufficiency, use of levothyroxine can precipitate an adrenal crisis. Patients with myxedema coma have impaired adrenal reserve and hydrocortisone 50 mg IV q6h is often necessary. It can be quickly tapered once the clinical condition improves. Supportive therapy in a myxedema coma patient is essential. Warming blankets can be used to slowly increase temperature, but care should be taken to avoid increasing the temperature to normal too quickly and should be used only if the temperature is below 30 degrees. Patients in myxedema coma often develop constricted peripheral vasculature to maintain their blood pressure. Increases in body temperature can lead to peripheral artery dilatation and result in rapid collapse of the circulation. For patients who are hypotensive, volume expansion with isotonic crystalloids or whole blood and judicious pressor use is often necessary to maintain adequate blood pressure. Glucose is necessary if there is hypoglycemia. Hypotonic fluids should be avoided because they may exacerbate water retention secondary to reduced renal perfusion and inappropriate vasopressin secretion. Sedatives should be avoided or used at reduced doses because the metabolism of most medications is impeded. Respiratory support with mechanical ventilation is often necessary and may be prolonged. If there is underlying infection, broad-spectrum antibiotics should be empirically used while waiting for blood culture and drug sensitivity results to come back. Myxedema coma has a very high mortality rate. It requires aggressive treatment if positive outcomes are to be achieved.

ADRENAL GLANDS

The adrenal gland is composed of the cortex and the medulla. The medulla is made of chromaffin cells that secrete catecholamines and their metabolites that alter heart rate, blood pressure, vascular tone, and carbohydrate metabolism. The cortex consists of three different layers. The outermost layer, the zona glomerulosa, secretes mineralocorticoid aldosterone, which regulates blood pressure, vascular volume, and Na and K metabolism. The middle layer zona fasciculata secretes glucocorticoids, which regulate immune response and stress response as well as modulating intermediary metabolism. The glucocorticoids are bound to cortisol-binding globulin and albumin. Only the free form is the biologically active form, which is less than 5% of all cortisol. The innermost layer zona reticularis produces adrenal androgen dehydroepiandrosterone, which is important for secondary sexual characteristics in females. A variety of adrenal disorders occur as a result of over or under functioning of each of the individual layers. The most common diseases are discussed in the following sections.

Primary Aldosteronism

Primary aldosteronism is due to an adenoma or hyperplasia of the outer layer of the adrenal cortex. Overproduction of aldosterone leads to hypertension and hypokalemia,

hallmark features of the disease. About 1% of patients with hypertension have primary aldosteronism. The mortality rates of patients with primary aldosteronism are slightly higher than those without it. This is thought to be due to aldosterone's effect on the cardiovascular system independent of its effect on blood pressure. Symptoms of primary aldosteronism include headaches, muscle weakness, fatigue, nocturnal polyuria, or cramping. Patients characteristically do not have edema and have diastolic hypertension. Laboratory evaluation shows normal or high normal sodium level, hypokalemia, metabolic alkalosis, suppressed renin, and elevated aldosterone level. A normal potassium level does not exclude primary aldosteronism. The screening test for this disease involves measurement of the aldosterone/renin ratio. If the ratio is above 25, further confirmatory tests are necessary. A salt loading test with measurement of the 24-hour urine aldosterone level during the last 24 hours of a 72 hours test can either confirm or exclude the diagnosis. During this test, adequate salt intake is necessary and can be achieved by giving patients NaCl tablets 2 g three times per day. A 24-hour urinary sodium level should be measured to verify adequate salt intake during the test. Once hyperaldosteronism is confirmed, imaging such as CT of the adrenal gland can to be pursued. Aldosterone-secreting adenomas can be tiny, and therefore, a dedicated fine-cut CT is often necessary to visualize the adenoma. For patients younger than age of 40, identification of a unilateral adenoma combined with biochemical evidence of hyperaldosteronism is adequate to recommend unilateral adrenalectomy. For those who are older than 40, even with the identification of a unilateral adenoma (given increased incidence of benign nonfunctioning adrenal adenoma), and for those without a distinct adenoma on either side, further lateralization studies such as adrenal vein sampling is necessary. Treatment for primary aldosteronism includes surgery or medical therapy. Surgery is preferred for younger patients with unilateral adenoma. For older patients or patients with bilateral adrenal hyperplasia, treatment with spironolactone, triamterene, or amiloride can achieve good control of blood pressure and potassium levels. With adequate control, patients with primary aldosteronism achieve excellent outcomes (13).

Secondary Aldosteronism

Secondary aldosteronism is due to normal activation of the renin–angiotensin system in response to hypertension or any edema disorders such as cirrhosis or congestive heart failure. There is secondary overproduction of renin due to decreased renal perfusion pressure or renal blood flow rather than primary overproduction of renin due to a renin-producing tumor. The laboratory evaluation for secondary aldosteronism demonstrates both elevated renin and aldosterone, which distinguishes it from primary aldosteronism. Treatment for secondary aldosteronism is to correct the underlying etiology.

Adrenal Insufficiency

Adrenal insufficiency can be due to primary or secondary causes. All primary causes result in the destruction of the adrenal glands bilaterally and subsequent adrenal insufficiency. Common etiologies are autoimmune adrenalitis, chronic granulomatous disease (predominantly tuberculosis), bilateral adrenalectomy, bilateral adrenal gland metastases, thrombosis, hemorrhage, and viral or fungal infections. Secondary adrenal insufficiency is due to suppression by chronic exogenous steroids or occurs as a result of pituitary insufficiency leading to inadequate ACTH production. Patients generally present with insidious onset of malaise, weakness, nausea, vomiting, abdominal pain, dizziness, poor appetite, weight loss, hypotension, and occasionally hypoglycemia. Hyperpigmentation occurs in those with primary adrenal insufficiency. If not recognized, adrenal crisis can happen in patients undergoing surgery, experiencing trauma, or having concurrent infections. Laboratory testing demonstrates no abnormality at the mild stage but with persistent progression of disease, shows hyponatremia, hyperkalemia, and decreased chloride and bicarbonate levels. The diagnosis is made with a cosyntropin stimulation test, which is performed by administrating 250 mcg of cosyntropin and measuring cortisol level 30 and 60 minutes afterward (14). Treatment is directed at adrenal hormone replacement. It can be achieved with either hydrocortisone 20 to 30 mg in 2 divided doses given 2/3 in the morning and 1/3 around 4 PM or prednisone 5 to 7.5 mg once per day in the morning. Patients with primary adrenal insufficiency require replacement of mineralocorticoids in the form of fludrocortisones 0.1 to 0.2 mg/day. All patients with adrenal insufficiency should carry medical identification and should be instructed to self-administer parental glucocorticoids when oral intake is not possible. Patients will need to double or triple steroid dose during periods of other intercurrent illness. During trauma or surgery, the stress dose of hydrocortisone at 50 to 100 mg three times daily should be given initially then tapered quickly to home steroid dose guided by clinical response.

Acute adrenal insufficiency can be due to acute hemorrhagic destruction of adrenal glands secondary to pseudomonas or meningococcemia, anticoagulant therapy or a coagulation disorder, or rapid withdrawal of steroid in patients with chronic steroid use. During adrenal crisis, the stress dose of steroid is administered. Pressor support along with other supportive therapy such as sodium and water replacement is essential as adrenal crisis has a high mortality rate.

Cushing's Syndrome

Cushing's syndrome is a result of excessive glucocorticoid. It could be due to adrenal adenoma, adrenal carcinoma, adrenal hyperplasia, pituitary adenoma, exogenous glucocorticoid treatment, or ectopic ACTH/CRH sources such

as lung, thymus, or pancreatic tumors (15). Patients often present with weight gain, emotional liability, fatigability, easy bruises, paroxysmal muscle weakness, amenorrhea, hirsutism, frequent infection, and osteoporosis. On physical examination, key features are truncal obesity; hypertension; moon facies; supraclavicular fat pad; buffalo hump; violaceous striae of the abdomen, hips, and breast; and thin skin. To diagnose Cushing's disease, hypercortisolism needs to be demonstrated by an increased 24-hour urine cortisol, increased midnight salivary cortisol, or an abnormal 1-mg-dexamethasone suppression test. To further confirm hypercortisolism, a 2-day low-dose dexamethasone suppression test can be pursued. If results are abnormal, the etiology of hypercortisolism can be determined by measuring ACTH levels or performing a high-dose dexamethasone suppression test. Patients with adrenal Cushing's disease often have low or suppressed ACTH, while those with pituitary Cushing's disease frequently have normal or high ACTH levels. Patients with ectopic Cushing's syndrome resulting from lung cancer or lung carcinoids invariably have a very elevated ACTH level. The high-dose dexamethasone test is helpful to distinguish between pituitary versus nonpituitary Cushing's disease. Only patients with pituitary disease will have a suppressed result on the high-dose dexamethasone test. Tumor localization can be achieved with CT of the adrenals for adrenal causes, MRI of the pituitary gland for pituitary pathology, or CT of the chest and abdominal for ectopic sources. The primary treatment for Cushing's disease is surgery. Medical therapy is limited and includes ketoconazole, mitotane, metyrapone, and other agents. These treatments are useful when surgery is not possible. After surgery, replacement therapy with glucocorticoids is often necessary given patients often have transient adrenal insufficiency. The dose of steroid should be tapered off slowly in 6 months to 1 year. Some patients may require a taper taking more than 1 year. During the taper process, stress dose steroid should be used in times of surgery, sickness, or trauma. Adrenocortical cancer is rare but has a poor prognosis. Surgery is the mainstay of treatment. Radiation or adjuvant chemotherapy with mitotane or other agents can be used.

Pheochromocytoma

Pheochromocytoma is a tumor of adrenal or extra-adrenal chromaffin cells. It is unilateral in sporadic cases but may be multilateral, especially in familial cases. The majority of pheochromocytomas are benign. Ten percent of them are malignant. Pheochromocytomas are present in about 0.1% of hypertensive patients and are often fatal if undiagnosed or mistreated. The clinical features are mostly related to the release of catecholamines. Classic presentation includes episodic hypertension, palpitation, and cold sweats. Over half of the patients can have hypertensive paroxysms or crises, which can be alarming and resistant to treatment. However, some patients present with chronic hypertension and never have an episodic symptom. Laboratory evaluation demonstrates elevated 24-hour urine metanephrines or plasma metanephrines. CT or MRI of the adrenals often identifies the tumor. Functional studies with an MIBG scan may be necessary when biochemical evaluation is indeterminate or metastasis is suspected or the adrenal lesion is more than 5 cm. Treatment for pheochromocytoma is surgery. Pheochromocytomas can have devastating consequences intraoperatively, and treatment with α-adrenergic blocker should be instituted before addition of beta-adrenergic blockers. Phenoxybenzamine can be started at 10 mg bid and titrated up to 30 mg tid depending on blood pressure response. Volume expansion is essential to reduce positional hypotension. This can be easily achieved with adequate fluid intake along with a high salt diet. Other medications such as prazosin, calcium channel blockers, and angiotensin-converting enzyme inhibitors are alternative blood pressure management agents if patients could not tolerate phenoxybenzamine. Beta blockers such as propranolol at 10 mg three to four times per day are useful for tachycardia. After complete resection, catecholamine levels return to normal 2 weeks after surgery, and 75% of patients have a cure of their hypertension. Lifelong follow-up of pheochromocytoma is necessary given the low albeit still present chance of recurrence.

THE PANCREAS AND GLUCOSE METABOLISM

Glucose, a monosaccharide, is an absolute requirement for neuronal survival. For that reason, glucose homeostasis and its control via pancreatic hormones is critical. Insulin and glucagon are the primary regulators of glucose metabolism in the body. Carbohydrates in their various forms are first ingested. In the gut they are, for the most part, broken down into monosaccharides, mainly glucose. There, glucose is absorbed via the GLUT family of transporters into cells of the gut. What is not immediately used is stored. In the liver and muscle, it is stored as glycogen. It is also converted into fatty acids, which are eventually incorporated into triglycerides in adipose tissue. Through a variety of mechanisms, the liver is also an important organ in the control of blood glucose levels.

The liver, muscle, and adipose tissue all possess insulin receptors. In the liver, insulin promotes glycogen synthesis and inhibits glycogen phosphorylation. It does not affect glucose uptake in the liver. In muscle and adipose tissue, insulin induces rapid uptake of glucose by recruiting GLUT transporters. Subsequently, muscle converts glucose to glycogen, and in adipose tissue, glucose is converted to fatty acids. Insulin also increases uptake of amino acids into muscle. It suppresses breakdown of glycogen in both muscle and liver and inhibits release of amino acids from muscle and fatty acids from adipose tissue.

Glucagon has opposing actions to insulin. It binds to a G-protein-linked glucagon receptor that stimulates cAMP.

Its eventual action includes the breakdown of glycogen into glucose, production of glucose from amino acids, and the release of fatty acids from adipose tissue, which are eventually converted into ketoacids in the liver.

The absorptive state of an individual relative to carbohydrate ingestion determines insulin/glucagon ratios.

Insulin

Insulin is a 51–amino acid protein with significant homology to insulin-like growth factor 1 and 2. Synthesis occurs in the beta islet cells of the pancreas. Initial synthesis forms preproinsulin and includes a signal peptide, along with A and B chains connected by a polypeptide. The signal peptide is quickly cleaved as is the connecting peptide, and eventually, the A and B chains form the active product.

Secretion of insulin is pulsatile, typically at 10-minute intervals. The half-life of insulin is approximately 3 minutes. Fifty percent of synthesized insulin is taken up by the liver in what is termed the "first-pass" effect. The remainder has effects on the peripheral tissues. Secretion is stimulated by a number of factors. Both plasma glucose and amino acids stimulate insulin secretion, and their effects are synergistic. Triglycerides and free fatty acids have a lesser stimulatory effect. A number of gastrointestinal hormones and GH also stimulate secretion. Cholinergic and alpha-adrenergic neurons of the autonomic nervous system stimulate insulin secretion as well. Secretion occurs in two phases: there is an initial release of insulin stored in secretory granules followed by a more gradual and stable release in response to *de novo* synthesis. Suppression of insulin secretion occurs via adrenaline and cortisol as well as beta-adrenergic neurons of the autonomic nervous system.

Glucagon

Glucagon is a 29-aa protein initially synthesized as proglucagon in the alpha cells of the pancreas. A signal peptide is cleaved to form glucagon and other by-products. The half-life of glucagon is approximately 3 minutes. Like insulin, approximately 50% of secreted glucagon is taken up by the liver in what is termed the "first-pass" effect.

Glucagon secretion is stimulated by low glucose levels and protein meals if they are high in alanine and arginine. GH and adrenaline are other hormones that stimulate glucagon secretion. Secretion is also stimulated by exercise, stress, and starvation. Secretion is suppressed by insulin and glucose and to a lesser degree by somatostatin.

Diabetes Mellitus

Diabetes mellitus (DM) is defined by elevated blood glucose concentrations. There are three criteria for diagnosing DM: (a) symptoms of diabetes and plasma glucose concentrations greater than 200 mg/dL (11.1 mmol/L) at any time, (b) fasting plasma glucose concentrations greater than 126 mg/dL (7 mmol/L), or (c) plasma glucose levels two hours postglucose load greater than 200 mg/dL.

Type I Diabetes Mellitus

Type I DM is a T-lymphocyte–mediated autoimmune disease that eventually results in the destruction of the islets of Langerhans of the pancreas. Although there appears to be a genetic element to the etiology of type I DM, the mechanism is uncertain. It predominantly affects Caucasians and tends to occur in patients <20 years of age. Male and female distribution is approximately equal.

Type II Diabetes Mellitus

Type II DM is associated with insulin resistance as well as decreased insulin levels. Thirty to ninety percent of cases have a genetic element. This is supported by the fact that it is very prevalent in certain ethnic groups. Prolonged high glucose levels result in a decrease in hepatic glucose production and increased levels of insulin. Eventually, the increased insulin levels cause a depletion of beta cells. There is also a downregulation of GLUT transporters in peripheral tissue. All of this results in increased plasma glucose levels.

Complications

Most complications relate to blood vessel damage. Some are due to accelerated atherosclerosis and are often termed macrovascular effects. They include effects on the coronary, carotid, and femoral arteries. Accelerated atherosclerosis due to diabetes is manifested by endothelial injury, increased platelet adhesion, and aggregation as well as direct effects of hyperglycemia on plaque formation. Microvascular effects of diabetes result from the thickening of the capillary basement membranes with resulting changes in permeability and a loss of structural integrity. They are manifested in particular by retinopathy, nephropathy, and neuropathy.

Diabetic Ketoacidosis

Diabetic ketoacidosis can be fatal if it is not treated in a timely fashion. This is due to absolute insulin deficiency and glucagon excess leading to increased gluconeogenesis, glycogenolysis, and ketosis. This most often occurs in those with type 1 diabetes. Occasionally, patients with type 2 diabetes may also develop ketoacidosis but it is rare. Patients classically present with polyuria, polydipsia, abdominal pain, nausea, vomiting, and shortness of breath. In severe cases, lethargy and coma develop. On exam, patients often have signs of volume depletion (in severe cases, hypotension), tachycardia, Kussmaul respiration, and a fruity breath. Laboratory testing shows elevated blood glucose more than 250 mg/dL, positive ketones, and metabolic acidosis along with electrolytes disturbance. Arterial pH is often less than 7.3 and in severe cases can be less than 7.

There is often a precipitating cause, which can be infection such as pneumonia, UTI, and URI or missing an insulin dose in those with a diagnosis of type 1 diabetes, myocardial infarction, stroke, or any other concurrent illness. The treatment should focus on volume replacement, insulin treatment, potassium replacement, and supportive therapy. Fluid replacement with NS is used first; 1 to 2 L of normal saline should be given as a bolus during the first 1 to 2 hours of treatment in those without cardiac history and making urine. IV fluids should then be changed to 0.45% saline given at 150 to 300 mL/h. When BG decreases to less than 250 mg/dL, D5 should be added to the 0.45% saline to keep BG between 200 and 250 mg/dL until the anion gap closes. For insulin therapy, 5 to 10 units of insulin can be given as a bolus initially. Afterward, it can be given at 0.1 unit/kg/h. BG should be monitored on an hourly basis. The target BG decrease should be 50 to 75 mg/dL/h. The drip rate can be titrated up or down depending on BG level and rapidity of BG changes. A well-validated protocol often works well. These patients often have an absolute potassium deficiency. It should be replaced as long as the potassium level is below 5 mg/dL and the patient is making urine. Electrolytes should be monitored every 4 hours initially and then daily. Patients generally improve within the first 24 hours with appropriate treatment. Once the patient begins to eat, insulin should be switched to SQ, and there should be a 2- to 3-hour overlap between IV insulin and long-acting insulin before discontinuing IV insulin to avoid recurrence of DKA. Meal time short-acting insulin needs to be started as well. The underlying causative factor should be actively sought and treated accordingly. Patients should be educated regarding self-management of diabetes and appropriate "sick" day insulin dosing to avoid future episodes of DKA.

Hyperglycemic Hyperosmolar State

Hyperglycemic hyperosmolar state (HHS) is a severe condition with a very high mortality rate. This occurs often in those with type 2 diabetes as a result of relative insulin deficiency leading to increased gluconeogenesis and glycogenolysis. Different from DKA, ketosis is often absent. Marked dehydration is a key feature in HHS due to osmotic diuresis and inadequate oral intake. A concurrent illness such as MI, stroke, and infection is often the precipitating cause. Patients usually present with a history of decreased oral intake, confusion, and coma. On exam, tachycardia, hypotension, and altered mentation are commonly seen. Laboratory test shows severe hyperglycemia, generally between 600 and 1,200 mg/dL; hyperosmolarity; and renal insufficiency. In contrast to DKA, acidosis and ketones are classically absent. Treatment is similar to DKA but with emphasis on more aggressive fluid replacement given the fluid deficit is often 9 to 10 L compared to 3 to 5 L in DKA. Initially, 1 to 3 L of fluid should be given over 2 to 3 hours. Care should be taken to avoid too rapid correction of hyperosmolar state leading to worsening of neurologic function. Sodium levels can be corrected with hypotonic fluid. To correct a free water deficit, 0.45% saline should be used when the patient is hemodynamically stable. Insulin therapy is important as well, and the dose is generally higher than that given in DKA. Patients often have a larger deficit in potassium, and careful replacement is essential to avoid arrhythmia. One important issue in HHS is the timely correction of the underlying etiology precipitating this condition as it is often an important factor in the mortality related to this condition.

Hypoglycemia

Hypoglycemia can be fatal or may lead to seizure and other severe neurologic sequelae. It is most often due to excessive exogenous insulin in the hospital setting. Patients present with palpitations, shakiness, sweating, hunger, anxiety, fatigue, cognitive impairment, confusion, or coma. On exam, pallor, diaphoresis, and tachycardia are seen. The treatment for mild hypoglycemia is to provide glucose containing fluid, food, or glucose tablets. About 15 g of carbohydrate will generally raise BG about 30 to 50 mg/dL. In those unable to eat, 25 g of glucose in the form of D50 can be given by a bolus infusion followed by IV infusion of D5 or D10. Glucagon injection can be given when there is no IV access or patient is not alert enough to eat. Once BG improves and patient becomes alert, a proper meal should be consumed.

Multiple Endocrine Neoplasia Syndromes

MEN syndromes can be classified into type 1, type 2a, and type 2b (Table 16.1). It is a group of autosomal dominant diseases affecting susceptible families with variable penetrance. MEN1 typically presents with early onset primary hyperparathyroidism, pancreatic neuroendocrine tumors, and pituitary adenoma. The cardinal feature of primary hyperparathyroidism is multigland neoplasia. The diagnosis of MEN1 is suggested by early onset of disease, multigland disease, and frequent recurrence of primary hyperparathyroidism. Pancreatic neuroendocrine tumors are the second most common manifestation of MEN1 and tend to occur concurrently with primary hyperparathyroidism. They are a major cause of morbidity as more than one-third display malignant features including hepatic metastasis (16,17). Gastrinomas account for more than half of all pancreatic neuroendocrine tumors and are often multiple, making surgical cure impossible. The currently suggested treatment is medical therapy with proton pump inhibitors (18). Among the pituitary tumors, prolactinoma is the most common type of adenoma. The MEN1 gene encodes a tumor suppressor protein menin. Mutation in MEN1 gene leads to uncontrolled cell growth in selective tissues in patients with MEN1 syndrome (19). The MEN1 gene has been mapped to chromosome 11.

TABLE 16.1 MEN SYNDROMES

Syndrome	Neoplasias
MEN1	Hyperparathyroidism (90%–95%)
	Pancreatic neuroendocrine tumors (75%–80%)
	Pituitary adenoma (65%)
MEN2a	Medullary thyroid carcinoma (97%–100%)
	Hyperparathyroidism (50%–60%)
	Pheochromocytoma (10%–35%)
MEN2b	Medullary thyroid carcinoma (90%)
	Pheochromocytoma (40%–50%)
	Mucosal neuroma (100%)
	Marfanoid habitus

The classic MEN2a patients have medullary thyroid cancer, pheochromocytoma, and primary hyperparathyroidism. The genetic abnormality responsible for MEN2a is a mutation of RET proto-oncogene located on chromosome 10. Medullary thyroid cancer occurs as a result of c cell hyperplasia and develops universally in MEN2a. The treatment of medullary thyroid cancer is total thyroidectomy. There is a direct correlation between MEN2a mutation and development of medullary thyroid cancer. Prophylactic thyroidectomy should be performed as early as possible on those carriers of the mutation to optimize outcomes. Pheochromocytoma occurs in more than 50% of the patients and is often bilateral and multicentric and almost always found in the adrenal gland. It typically occurs later than medullary thyroid cancer. Primary hyperparathyroidism occurs less often than in patients with MEN1, occurring in about 15% to 20% of patients.

MEN2b patients are affected by medullary thyroid cancer, pheochromocytoma, mucosal neuromas, and marfanoid habitus. The mucosal neuromas and marfanoid habitus are the most distinct features and are recognizable in childhood. Neuromas are present on the tip of the tongue, under the eyelids, and throughout the gastrointestinal tract (17). The MEN2b mutation involves RET proto-oncogene too, but the specific point mutation is distinct from MEN2a resulting more aggressive types of MTC with metastasis developing in children sometimes prior to 1 year of age. The incidence and clinical course of pheochromocytoma are similar to that in MEN2a.

Other malignant and nonmalignant tumors are also found at higher frequency in patients with MENs such as subcutaneous or visceral lipomas and cutaneous leiomyomas, angiofibromas, and collagenomas (16). For patients with MENs, a strong family history is often present. Genetic testing is helpful in diagnosis of MENs. It is especially important for those with MEN2a or MEN2b as identification of the mutation will alter management and mandate long-term follow-up. It should be routinely performed on family members to identify carriers of the mutated RET proto-oncogene. The genetic testing in MEN1 patients serves the purpose of guiding long-term follow-up (16). It should be routinely performed on family members to identify carriers of the mutated RET proto-oncogene.

HORMONE-SECRETING TUMORS

Catecholamine-Secreting Tumors

Catecholamine-secreting tumors are seen in 2 to 8/million population. They may secrete epinephrine, norepinephrine, or dopamine. They are often divided into what are termed pheochromocytoma, a tumor of the adrenal medulla, and paraganglioma, which can be associated with other sites of chromaffin cell origin, including the para-aortic parasympathetic nerves, cervical and mediastinal parasympathetics, the organ of Zuckerkandl (at the origin of the inferior mesenteric artery), and the wall of the bladder. These tumors are equally distributed between the sexes, and 10% to 20% have a familial component. They usually occur in the third to fifth decade of life. When they occur in children, they are almost always familial. Pheochromocytomas are discussed elsewhere in this chapter. The focus here is on paragangliomas, particularly, of the head and neck.

Head and neck paragangliomas are less likely to be secreting tumors than paragangliomas elsewhere (about 5%). About 15% to 20% are genetic and tend to occur at an earlier age. Mutations in succinate dehydrogenase, a tumor suppressor gene, are most commonly associated with familial paraganglioma. (20) Mutations involving the C and D subunit are more commonly associated with head and neck paraganglioma. Inheritance is autosomal dominant. Up to 50% of familial paraganglioma may be multifocal. Mutations associated with the B subunit are more likely to be malignant but are typically associated more with paraganglioma of the abdomen and pelvis. Paraganglioma of the head and neck rarely is associated with von Hippel-Lindau disease.

Symptoms are often determined by the site of origin, many of them being found incidentally. Paraganglioma of the jugular or tympanic plexus may present with hearing loss or a mass in the middle ear. Vagal paraganglioma may present with vocal cord paralysis. Carotid body paraganglioma may present with a mass in the neck. Even though only a small percentage of these are secreting tumors, because of the risk of multifocality including the possible presence of a pheochromocytoma, screening for fractionated plasma free metanephrines or 24-hour urine for metanephrines and other catecholamine products may be indicated.

Diagnosis of head and neck paraganglioma is made by MRI with gadolinium enhancement. Flow voids are prominent because of the vascular nature of the tumor. Angiogram may be a useful adjunct, both to visualize the tumor and to embolize large vascular tumors.

TABLE 16.2 ENDOCRINE DISORDER DIAGNOSIS

Endocrine Diagnosis	Symptoms	Tests
Pituitary adenoma	Related to hormone excess or deficiency, mass effects	MRI of pituitary glands, stimulation or suppression tests for hormone abnormality
DI	Polyuria, polydipsia	Urine specific gravity, plasma osmolarity, water deprivation test
Syndrome of inappropriate secretion of ADH	Delirium, fatigue	Serum electrolytes, urine osmolarity, urine sodium level
Hypercalcemia	Fatigue, anorexia, bone and joint pain, renal colic, hematuria, constipation, delusion	Serum calcium, phosphorus, albumin, PTH, alkaline phosphatase, sestamibi scan, 24-h urine calcium/creatinine
Hypocalcemia	Muscle irritability, tetany	Calcium, magnesium
Diabetes	Polyuria, polydipsia	HbA1c, fasting, or 2-h oral glucose tolerance test
Diabetic ketoacidosis	Confusion or coma, acetone breath	Electrolytes, ketone, blood gas
Hyperthyroidism	Increased metabolic rate	TSH, fT4
Hypothyroidism	Cold intolerance, fatigue, constipation, impaired mental functions, dry brittle hair	TSH, fT4
Carcinoid tumors	Diarrhea, flushing, wheezing, valvular disease	24-h urine 5-HIAA
Pheochromocytoma	Hypertension, "spells"	Plasma or 24-h urine metanephrines, CT or MRI or ^{131}MIBG

Definitive treatment is surgical, but in cases of multifocality, the decision for surgery and the timing of that surgery may be difficult because of the associated morbidity. Radiation therapy may control growth of the tumor for a period of time but is not a cure (21). Malignancy can only be determined by the presence of paraganglioma in lymph nodes by pathology.

Carcinoid Tumors

These tumors are often associated with the GI tract, although they can be associated with the lung and rarely other parts of the body. They are neuroendocrine tumors of enterochromaffin cell origin. They can produce a wide array of hormones including gastrin, gastrin-releasing peptide, ghrelin, calcitonin, pancreatic polypeptide, ACTH, CRH, and GHRH, as well as somatostatin, glucagon, and calcitonin gene–related peptide. The most commonly secreted is the glycoprotein chromogranin A. Incidence is 2.8 to 4.5 per 100,000 population. They are most often classified using the World Health Organization system as well-differentiated endocrine tumors, well-differentiated endocrine carcinoma, and poorly

TABLE 16.3 ENDOCRINE EMERGENCIES

Endocrine Diagnosis	Emergency	Complication
Pituitary adenoma	Pituitary apoplexy	Loss of vision
DI	Hypernatremia	Seizure or coma
Syndrome of inappropriate secretion of ADH	Hyponatremia with sodium <125 mEq/L	Seizure or coma
Hyperparathyroidism	Hypercalcemia > 13 mg/dL	Arrhythmias, renal failure, death
Hypoparathyroidism	Hypocalcemia <7 mg/dL	Laryngospasm, seizures
Diabetes	Diabetic ketoacidosis	Coma, death
Hyperthyroidism	Thyroid storm	Heart failure, delirium, death
Hypothyroidism	Myxedema coma	Coma, death

TABLE 16.4 PERIOPERATIVE CONSIDERATIONS

Catecholamine-producing tumors

Alpha-adrenergic blockade for 7–10 d prior to surgery
- Phenoxybenzamine 10 mg BID, increasing 10–20 mg every 2 to 3 d
  - Titrate to BP < 120/80 mm Hg with systolic >90 mm Hg

Beta-adrenergic blockade after meeting targets with alpha-adrenergic blockade
- Propranolol 10 mg every 6 h, titrating up for goal heart rate of 60–80 beats/min

Calcium channel blockers can be used as alternative or in conjunction with prior regimen
- Nicardipine

Intraoperative acute hypertension
- Nitroprusside 0.5–5 mg/kg/min then titrated or
- Phentolamine 1 mg test followed by 5 mg bolus 10–15 mg infusion
- Nicardipine 5 mg/h then titrate up for desired effect

Intraoperatively—avoid fentanyl, ketamine, morphine, atropine, halothane, and desflurane

Thyrotoxicosis

Preoperative goal—restore normal metabolism
- Antithyroid agents
- Propylthiouracil 150–200 mg every 8 h, then titrate to effect
- Methimazole 10–15 mg BID initially, then titrate

After normalization
- Saturated solution of potassium iodide 2–3 drops/d for 7–10 d
- Lugol solution 5–10 drops/d for 7–10 d

Propranolol used as an adjunct for residual adrenergic symptoms
- 20–60 mg every 6–8 h

DI

Post–pituitary surgery
- Desmopressin IV 0.5–2 mcg
- 6–24-h effect

Posttrauma
- Desmopressin 0.25–2.7 mU/kg/h
- Fluid replacement as appropriate

Prior to routine procedure
- Parenteral or nasal dose prior to surgery if NPO

differentiated endocrine carcinoma. Well-differentiated endocrine tumors are typically serotonin-secreting midgut tumors that are small, noninvasive, and have a low proliferative index. Well-differentiated endocrine carcinomas are characterized by serotonin-producing tumors with or without carcinoid syndrome, possibly bronchial carcinoid. They are larger and often present with metastases and have a higher proliferative index. Both well-differentiated tumors and carcinomas may be functioning or nonfunctioning. Poorly differentiated carcinomas (small cell tumors) are larger more invasive tumors with the highest proliferative index.

Carcinoid tumors of the foregut and midgut secrete serotonin and have elevated urine 5-hyrdroxyindoleacetic acid. Foregut tumors more often primarily secrete 5-hydroxytryptophan, a precursor to serotonin.

Carcinoid syndrome is characterized by flushing, diarrhea, right-sided heart failure, and sometimes bronchial constriction and increased urinary levels of 5-HIAA. It is associated with tumors of the small intestine and proximal colon and is a function of tumor mass and location of metastases. It is less often associated with bronchial carcinoid tumors.

HIGHLIGHTS

- The residue of Rathke's pouch separates the anterior and posterior lobes of the pituitary gland.
- Fifty percent of anterior pituitary cells are somatotrophs secreting GH.
- The pituitary lies outside the arachnoid space and the CSF containing compartment of the dura.
- GH effects are mediated by IGF1 and 2.
- Medical therapy for prolactinomas involves dopamine agonists bromocriptine and cabergoline.
- ACTH secretion is pulsatile with up to 40 pulses per day.
- LH, FSH, TSH, and bHCG all share a common a common alpha subunit but distinct beta subunits.
- TSH release follows a circadian rhythm with peak levels around 11 PM and 5 AM.
- ADH plays a critical role in water homeostasis and the osmolality of body fluids. It is characterized by high volume, hypotonic, dilute urine.

- PTH levels vary inversely with ionized calcium levels, and PTH response is greater for a given level of hypocalcemia if the rate of decrease in calcium is higher.
- Primary hyperparathyroidism is defined by the inappropriate hypersecretion of PTH.
- Vitamin D receptors in the duodenum and jejunum induce calcium channels in the gut with subsequent intestinal absorption of calcium.
- Insulin induces glycogen synthesis in the liver but does not increase glucose uptake by the liver. It does recruit GLUT transporters in muscle and adipose tissue, thus inducing glucose uptake in those tissues.
- Complications of diabetes are usually related to macrovascular disease associated with accelerated atherosclerosis or microvascular disease associated with thickening of capillary basement membranes.
- Mutations in the succinate dehydrogenase are commonly associated with familial paraganglioma.
- Hypothalamic DI can occur after surgery in the vicinity of the pituitary and hypothalamus.
- Thyroid function is positively regulated by TRH released by hypothalamus and TSH produced by pituitary gland. It is negatively regulated by thyroid hormones produced by thyroid gland.
- TSH and fT4 are most useful tests to evaluate thyroid dysfunction.
- Thyroid hormones bind to nuclear receptors to exert its function. Both T3 and T4 are produced by the thyroid gland, but T3 is the more biologically active thyroid hormone.
- Genetic testing in MEN2b patients is essential as it can identify carriers of the RET proto-oncogene mutation so that prophylactic treatment can be performed.
- Pheochromocytoma is rare but has high mortality if not recognized or treated appropriately. Adequate alpha-adrenergic receptor blockade along with fluid expansion is essential in reducing perioperative mortality.

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17 Rheumatologic, Granulomatous, and Other Systemic Diseases Affecting the Head and Neck

Valentin D. Marian *Anurag Gandhi* *Shawn D. Newlands*

The otolaryngologist can play two important roles in the care of patients with systemic medical disorders first seen with head and neck symptoms. The first role is to diagnose these disorders based on clinical findings in the head and neck, through a high index of suspicion for these diseases. The second role is, in collaboration with a rheumatologist or infectious disease specialist, to manage head and neck manifestations of these diseases. This chapter covers an array of rheumatologic, granulomatous, and other systemic diseases that might, commonly or rarely, be seen for diagnosis or treatment by an otolaryngologist. The theme of this chapter is systemic diseases that can affect multiple head and neck sites. Amyloidosis and bony lesions are included in this chapter because they do not neatly fit into other anatomical or discipline-specific chapters in this text. Diseases that are limited to one head and neck site are discussed in the site-specific chapters of the text.

RHEUMATOLOGIC DISEASES

Rheumatologic diseases have patterns of organ involvement that not only overlap each other but overlap other diseases as well, which frequently makes specific diagnosis difficult. When first recognized as a distinct histopathologic characteristic for a collection of diseases, perivascular collagen deposition prompted the name *collagen vascular diseases*. However, the term "collagen vascular disease" is a misnomer, these diseases affect many different proteins in addition to the collagen, and they affect many structures in addition to vascular structures. Subsequently, the association of the collagen vascular diseases with immunologic reactions to body proteins prompted many to call these disorders *systemic autoimmune diseases*. This collection of diseases includes not only classical connective tissue diseases, such as systemic lupus erythematosus (SLE), Sjögren syndrome, and scleroderma, but also vasculitides and musculoskeletal autoimmune syndromes. In contrast with systemic autoimmune disease are the organ- or tissue-specific autoimmune diseases, such as type I diabetes mellitus, Hashimoto thyroiditis, myasthenia gravis, and multiple sclerosis. In addition, many pure connective tissue diseases (such as scurvy, Ehlers-Danlos, and Marfan syndrome) are not autoimmune in nature.

The exact cause of systemic autoimmune diseases remains obscure. The prevailing histopathologic feature of these diseases is a varying amount of connective tissue and blood vessel inflammation with abundant fibrinoid deposits (Fig. 17.1). The tissue distribution of the inflammatory response and the pattern of organ involvement differentiate one systemic autoimmune disease from another. Specific autoantibodies are associated with some of these entities (Table 17.1), although many of these autoantibodies are present in several autoimmune diseases and other conditions. Thus, clinical diagnosis is based on the constellation of symptoms, signs, laboratory tests, and histopathology. Diagnostic criteria have been developed for the majority of these conditions.

Systemic Lupus Erythematosus

SLE is a common systemic autoimmune disease. According to a recent report from the National Arthritis Data Working Group, approximately 250,000 Americans have systemic lupus (1), making the incidence of the disease approximately 1 in 1,400, with nine women affected for every man. The course of SLE is highly variable, affecting primarily women of childbearing age. The disease also is three times more common in African-Americans than in white Americans. Protean systemic manifestations include arthritis, constitutional symptoms, photosensitive skin eruptions, serositis (pleurisy, pericarditis), nephritis, leukopenia, anemia, hypercoagulability, and central nervous system (CNS) involvement (most commonly cognitive dysfunction and intractable headaches). The classification

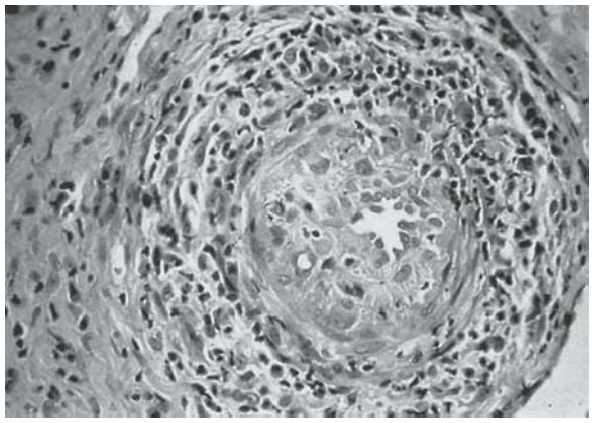


Figure 17.1 Necrotizing and fibrinoid necrosis is seen in many connective tissue diseases. This biopsy from a patient with PAN shows an infiltration of eosinophils and polymorphonuclear leukocytes with medial necrosis and intimal proliferation.

criteria for SLE are outlined in Table 17.2 (2). Infectious complications related to active SLE and immunosuppressive treatment are now the most common cause of death in early active SLE, and accelerated arteriosclerosis is the main cause of late mortality (3), although the survival rate with this disease is now about 90% at 10 years and 70% at 20 years; this rate has been improved over time (4).

Head and Neck Manifestations

The head and neck manifestations of SLE are dominated by skin and mucosal lesions. In 35% to 40% of patients, a malar or "butterfly" rash is the first sign of the disease and is commonly precipitated by sunlight exposure (**Fig. 17.2**). Thirty-seven percent of patients with SLE have photosensitive skin, and sunlight exposure can trigger not only the skin rash but also systemic disease exacerbations. Additional manifestations of SLE are seen in many forms. Associated oral lesions are in general of three types: erythematous, discoid, and ulcerative. Discoid lesions are superficial; have a well-defined elevated border; may be painful; and show pronounced hyperemia, edema, and white dots with a tendency toward bleeding. Localized telangiectasia may produce a red halo effect around the affected mucosa, and secondary moniliasis and xerostomia also are common. Ulcerative lesions are usually shallow, often occur in crops, most commonly are found on the hard palate, but the buccal mucosa or nasopharynx is affected in one-third of patients. Involvement of larynx and nasal mucosa has been described. Mucosal ulceration is painful, may persist or be cyclical, and tends to occur with disease flare. Erythematous lesions are the most common; they are usually painless, red, flat, and have ill-defined borders. Histologically, mucosal lesions in SLE demonstrate orthokeratosis and parakeratosis alternating with areas of epithelial atrophy. Keratotic plugging, acanthosis, and pseudoepitheliomatous hyperplasia are common findings. Superficial, perivascular, and deep lymphocytic infiltration can be seen throughout the mucosa, and skin lesions may show only inflammation or, by immunofluorescence (IF), immune deposits at the dermal–epidermal junction.

Numerous other head and neck problems may be associated with SLE. In 3% to 5% of well-established cases,

TABLE 17.1 AUTOANTIBODY RELATIONS IN RHEUMATOLOGIC DISEASES

Disease	Autoantibody
SLE	ANA (95%–100%), Anti-ds DNA (50%), Anti-Sm (25%), Anti-ss DNA (80%), Anti-La/SSB (20%), Anti-Ro/SSA (50%)
RA	ANA (50%), RF (90% in severe disease)
Primary Sjögren syndrome	ANA (65%), RF (85%), Anti-Ro/SSA (75%), Anti-La/SSB (% of those with Anti-Ro/SSA)
SSc	ANA (80%), Anti-Scl-70 (30%), Anti-centromere (30%)
Polymyositis/ dermatomyositis	ANA (80%), Anti-Jo-1 (20%)
MCTD	ANA (100%), Anti-U1-RNP (100%), RF (55%)
Granulomatosis with polyangiitis	c-ANCA (90%)

TABLE 17.2 CLASSIFICATION CRITERIA FOR SYSTEMIC LUPUS ERYTHEMATOSUS (2)

Clinical Criteria

1. Acute or subacute cutaneous lupus lesions
2. Chronic cutaneous lupus lesions
3. Oral or nasal ulcers
4. Non-scarring alopecia
5. Synovitis involving 2 or more joints, characterized OR tenderness in 2 or more joints and at least 30 minutes of morning stiffness
6. Serositis
7. Renal disease (proteinuria >500 mg protein/24 hours OR red blood cell casts)
8. Neurologic (seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, acute confusional state)
9. Hemolytic anemia
10. Leukopenia (<4,000/mm^3 at least once) or lymphopenia (<1,000/mm^3 at least once)
11. Thrombocytopenia (<100,000/mm^3) at least once

Immunologic Criteria

1. Elevated ANA level
2. Elevated Anti-dsDNA antibody level
3. Anti-Sm antibody positivity
4. Antiphospholipid antibody positivity
5. Low complement
6. Direct Coombs' test (in the absence of hemolytic anemia)

The diagnosis of SLE requires satisfaction of four of the clinical and immunologic criteria, including at least one clinical criterion and one immunologic criterion, or if biopsy-proven nephritis is compatible with SLE in the presence of ANAs or anti-dsDNA antibodies. All clinical criteria count only if not other cause is apparent.



Figure 17.2 Facial rash in the butterfly distribution typical of SLE.

recurrent nasal mucosa ulcerations occasionally lead to nasal septal perforation. Inflammatory changes of the larynx and trachea have been described, including true vocal fold thickening or paralysis, cricoarytenoid arthritis, hoarseness due to recurrent laryngeal nerve paralysis, edema with airway obstruction due to necrotizing vasculitis, and subglottic stenosis. Up to 25% of SLE patients report dysphagia. In 10% of SLE patients, acute enlargement of the parotid gland occurs and may be unilateral, tender, and confused with acute parotitis. Additionally, xerostomia may become a chronic problem. Sicca complex alone or in association with secondary Sjögren syndrome is a common finding in SLE patients.

Neuropathy also is a major characteristic of SLE, and in 15% of patients, the cranial nerves are affected. The neuropathy may involve the motor supply to the extraocular muscles, the sensory divisions of the trigeminal nerve, the motor divisions of the facial nerve, the vestibular portion of the vestibulocochlear nerve, or the optic nerve. Sudden hearing loss also has been described with SLE, although a definitive link has not been established. Such hearing loss may be due to thrombosis or vasculitis, although temporal bone studies have been inconclusive. A nonspecific lymphadenopathy associated with SLE in some cases appears to be related to skin or mucosal lesions.

Discoid lupus erythematosus is a subtype of SLE in which cutaneous lesions result in significant scarring but with no visceral involvement. These lesions are well-demarcated, erythematous, edematous papules that depigment and scar on resolution. The face is involved in 85% of cases, the scalp in 60%, and the ear in 44%. Associated leukoplakia of the tongue and oral mucosa may occur.

Treatment

Management of this severe and complex disease is complicated and specialized, and as such, requires a rheumatologist (5). Because many SLE patients are highly photosensitive, avoidance of sun exposure and liberal use of sunscreens are recommended. The general treatment of SLE includes nonsteroidal anti-inflammatory drugs, topical and low-dose systemic steroids, and antimalarials (especially hydroxychloroquine). Low-dose methotrexate may be an alternative to systemic steroids. The use of high-dose systemic steroids and immunosuppressive agents, such as mycophenolate mofetil, azathioprine, and cyclophosphamide, is restricted to cases with visceral involvement that might lead to organ (heart, kidney, CNS) damage. Newly developed biologic agents, such as rituximab—a chimeric monoclonal antibody that targets B-lymphocyte surface marker CD20, show promising results for the treatment of lupus. A fully human monoclonal antibody, belimumab, targeted against soluble B lymphocyte stimulator (Blys) has been recently approved by FDA for the treatment of patients with active, autoantibody-positive systemic lupus erythematosus who are receiving standard therapy. This is the first biologic therapy approved for the treatment of lupus and followed a successful clinical trial where belimumab plus standard therapy was shown to reduced SLE disease activity and severe flares (6). Symptomatic treatment of the head and neck manifestations of SLE, as with all systemic autoimmune diseases, is required when the systemic steroids become ineffective. Many patients complain about the loss of salivary flow and the development of oral and pharyngeal lesions, and treatments are varied. Saliva substitutes often prove helpful for this complaint. Steroid-based topical solutions for the treatment of mouth ulcers are effective if administered appropriately. Ointments and creams designed for intraoral use are not effective, but mouthwashes are useful when administered frequently and held in contact with the diseased tissues for several minutes. One such preparation is Klacks solution, which consists of tetracycline, cortisone, diphenhydramine, and nystatin. Postprandial cleansing using mouthwashes with stock hydrogen peroxide solution diluted with equal parts of warm tap water also may help oral lesions. In selected cases, for patients with resistant mucosal disease dapsone and thalidomide can be helpful; however, the side effect profile limits their use (7).

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown cause that primarily presents with inflammation of synovial tissue. Symmetrical involvement of the peripheral joints is the dominant clinical feature. The course of the disease is variable, usually progressive, and may affect nonarticular tissues. RA occurs in 1% of the population, affecting women two to three times more often than men. Although it may occur at any age, and a distinct juvenile variety exists, it is more common in the fourth to fifth decade. The onset of RA may be acute, but more frequently

TABLE 17.3 THE 2010 AMERICAN COLLEGE OF RHEUMATOLOGY/ EUROPEAN LEAGUE AGAINST RHEUMATISM CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS (8)

Target Population

(1) Patients who have at least 1 joint with definite clinical synovitis
(2) Patients with the synovitis not better explained by another disease

Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of 6/10 is needed for classification of a patient as having definite RA)

Joint involvement	1 large joint	0
	2–10 large joints	1
	1–3 small joints	2
	4–10 small joints	3
	>10 joints (at least 1 small joint)	5
Serology	Negative RF and negative ACPA	0
	Low-positive RF or low-positive ACPA (anticitrullinated peptide antibodies)	2
	High-positive RF or high-positive ACPA	3
Acute-phase reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of symptoms	<6 wk	0
	≥6 wk	1

it is insidious, with progressive joint involvement. Morning stiffness lasting more than 30 minutes and stiffness after prolonged inactivity are common symptoms. Tenderness and inflammation in an inactive joint are physical findings specific to RA, and subcutaneous rheumatoid nodules aid in the diagnosis. Nonarticular manifestations include visceral nodules, vasculitis, pleural or pericardial effusions, and Sjögren syndrome. The classification criteria for RA are found in Table 17.3 (8).

Head and Neck Manifestations

Articular involvement predominates in the diverse head and neck manifestations of RA, affecting the ossicles, temporomandibular joints, cricoarytenoid joints, and the cervical spine. Temporomandibular joint dysfunction may be prominent; causing many patients with RA to have temporomandibular joint complaints including pain or tenderness at the joint or in the masseter or temporalis muscles, crepitus, limited mobility, or deviation, and radiographic evidence of joint erosion is often present. Temporomandibular joint dysfunction in patients with RA may be severe and cause contractures of the muscles of mastication, producing an anterior open-bite deformity (9).

RA is the most frequent cause of arthritis in the cricoarytenoid joint. Histologic abnormalities of the cricoarytenoid joints are present in 86% of patients with RA. Clinically, however, only 30% of the patients with RA are hoarse. Cricoarytenoid arthritis may occur with dyspnea on exertion, anterior neck or ear pain, fullness in the throat, dysphagia, and aspiration. Hoarseness in RA is usually the result of cricoarytenoid joint involvement but may be caused by rheumatoid nodules within the cords and ischemic recurrent nerve paresis or paralysis (10). The sudden onset of stridor and dyspnea in a patient with RA is an emergency requiring systemic steroids and possibly a tracheostomy. The oral cavity is not usually involved with abnormalities related to RA unless associated Sjögren syndrome is present or medication side effect develops. In an uncommon variant of rheumatoid vasculitis, oral ulcers similar to those seen in polyarteritis nodosa (PAN) are found.

The middle ear may be involved in severe cases of RA if synovitis develops in the ossicular joints, but this occurrence rarely results in a conductive hearing loss, except during an acute RA flare. Stiffness in the incudomalleolar and incudostapedial joints does not impair sound conduction but does result in stiffness abnormalities detected on tympanometric testing. Autoimmune inner ear disease also has been related to RA, but no definitive mechanism has been proven (11).

Long-standing active RA may lead to cervical spine disease. Recurrent tenosynovitis involving the transverse ligament of atlas results in laxity and/or odontoid process erosion, in which case the ring of C1 can move forward in flexion causing cord compression. Any clinician should be aware about this entity and maintain a high index of suspicion when symptoms such as neck pain, stiffness, or radicular pain are present. Neck manipulation during endoscopic procedures or endotracheal intubation might precipitate atlantoaxial subluxation with subsequent cord compression. Physical examination may reveal abnormal protrusion of the axial arch on the posterior pharyngeal wall, loss of occipitocervical lordosis, and resistance to passive neck motion. Radiographic studies are necessary for the diagnosis.

Treatment

The treatment goal is to effectively control the synovitis and prevent the joint damage. The symptomatic relief

can be achieved using nonsteroidal and/or steroidal anti-inflammatory drugs. Disease-modifying agents should be initiated within the first 3 to 6 months of disease onset. Methotrexate is the most commonly used disease-modifying antirheumatic drug (DMARD) and gastrointestinal mucositis, including mucosal ulcerations and severe pharyngitis, occasionally complicates therapy. Methotrexate may be used alone or in combination with other conventional or biologic DMARDs. Sulfasalazine, hydroxychloroquine, and leflunomide are commonly used conventional DMARDs. If RA cannot be controlled with one or combination of conventional therapy, biologic DMARDs such as tumor necrosis factor inhibitors should be used, alone or in combination with methotrexate. Additional treatment goals include maintaining joint function and prevention of joint deformities. The otolaryngologic manifestations may require therapies directed at the specific symptoms.

Sjögren Syndrome

Sjögren syndrome is a chronic disorder characterized by immune-mediated destruction of exocrine glands, which are predominantly, but not exclusively, the lacrimal and salivary glands. Sjögren syndrome is important to be understood as a slowly progressive, SYSTEMIC autoimmune disease that affects primarily the exocrine glands. Systemic involvement is common; eventually more than three-quarters will develop one or more extraglandular manifestation. Sjögren syndrome occurs in 1% of the general population and in 10% to 15% of patients with RA. A 9:1 female preponderance is noted, and onset occurs between ages 40 and 60 years. Sjögren syndrome occurs in primary and secondary forms. The primary form is a diagnosis of exclusion. The secondary form refers to the sicca complex accompanying any of the systemic autoimmune diseases. The secondary Sjögren syndrome is seen primarily with RA but is also commonly associated with SLE, scleroderma, and primary biliary sclerosis. In one-third of patients with primary Sjögren syndrome, the disorder is systemic with involvement of extraglandular sites (arthritis 70%, Raynaud phenomenon 40% to 50%, pulmonary involvement 25% to 30%). Sjögren syndrome is associated with an increased (33 to 44 times) risk of lymphoma. The greatest risk for degeneration is seen in patients with the primary form, constant parotid swelling, splenomegaly, and lymphadenopathy, low C4 complement level and type II mixed monoclonal cryoglobulinemia. The majority of lymphomas are of mucosal-associated lymphoid tissue type.

The common clinical manifestations of Sjögren syndrome include xerophthalmia with secondary keratoconjunctivitis and xerostomia, with or without salivary gland enlargement. These manifestations are called sicca complex or sicca syndrome. A salivary gland biopsy is the best single test for Sjögren syndrome (specificity 83%, sensitivity 81%). A minor salivary gland biopsy usually demonstrates heavy lymphocyte infiltration, although a parotid biopsy may be more sensitive and specific. Rheumatoid factor and antinuclear antibodies are high in most Sjögren syndrome patients. Antibodies directed toward Sjögren syndrome A (Ro/SS-A) and Sjögren syndrome B (La/SS-B) antigens are noted in 60% and 30% of patients, respectively. These antibody tests lack specificity because they are commonly found in patients with SLE, RA, and polymyositis. Anti-La Ab is more specific than anti-Ro Ab, but less sensitive. Finding anti-La alone is atypical and was found more common in primary biliary cirrhosis or autoimmune hepatitis (12). In many anti-Ro–positive Sjögren syndrome patients, SLE will later develop. The classification criteria for Sjögren syndrome are outlined in Table 17.4 (13).

Confusion often is found between the designations of Sjögren syndrome and Mikulicz disease. The latter is swelling of the salivary glands accompanying nonsystemic autoimmune diseases, such as hyperlipoproteinemia, malnutrition, diabetes, cirrhosis, tuberculosis, and sarcoidosis. In the recent years, Mikulicz syndrome has been increasingly recognized as part of the spectrum of IgG4-related disease and not confined to salivary glands. It is characterized

TABLE 17.4 CLASSIFICATION CRITERIA FOR SJÖGREN SYNDROME (13)

The classification of Sjögren Syndrome will be met in patients who have at least two of the following three objective features:

1. Positive serum anti-SSA/Ro and/or anti-SSB/La or positive rheumatoid factor and ANA titer ≥ 1:320
2. Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥ 1 focus/4 mm^2
3. Keratoconjunctivitis sicca with ocular staining score ≥ 3 (assuming that individual is not currently using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in the last 5 y)

Prior diagnosis of any of the following conditions would exclude participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests: history of head and neck radiation treatment, hepatitis C infection, acquired immunodeficiency syndrome, sarcoidosis, myloidosis, graft versus host disease, IgG4-related disease.

by infiltration of IgG4-positive plasma cells in the salivary glands tissue, raised serum levels of IgG4 and fibrosis or sclerosis. Sjögren syndrome is not related to the divergent group of systemic diseases associated with Mikulicz disease.

The autoimmune diseases of the parotid gland have a unifying histologic pattern of an early lymphocytic infiltrate, followed by thinning and fragmenting of the connective tissue in the terminal or intercalated duct walls with destruction of the acini. The larger ducts are usually uninvolved unless a superimposed infection is present. A diffuse pattern of globular collections of contrast material is observed, originally called sialectasis. It was initially thought that dilatation of the acini and collection of the contrast material within them was noted. It is now known, however, that the weakened acini allow extravasation of contrast material, which forms extramural globular collections. The four progressive radiographic features of autoimmune parotid swelling are punctate, with spherical collections of 1 mm or less; globular, with collections of 1 to 2 mm; cavitary, with large irregular collections of uneven distribution; and destructive, with no recognizable branching. The latter two stages represent superimposed infection.

Head and Neck Manifestations

Exocrine gland pathology dominates the head and neck manifestations of Sjögren syndrome. About 80% of these patients complain of xerostomia, the most prominent symptom of the disease. These patients report difficulty chewing, dysphagia, dysgeusia, fissures of the tongue and lips, and an increased number of dental caries. Oral candidiasis and angular cheilitis are frequent complications of dry mouth. Additionally, diminished secretion of tears leads to keratoconjunctivitis sicca and eye complaints, including dryness, burning, itching, and foreign-body sensation. Loss of glandular secretions in the nasal passages causes crusting and secondary epistaxis in 50% of patients and hyposmia in 40%. Chronic sinusitis may result from inspissated secretions, and occlusion of the nasolacrimal ducts may occur. Other manifestations of primary Sjögren syndrome include sensorineural hearing loss and, in 30% of patients, a painless intermittent unilateral parotid swelling of unpredictable duration that is rarely associated with edema.

Treatment

Symptomatic treatment is the primary approach to patients with Sjögren syndrome because no treatment alters the course of the disease. Patients and their primary care physicians must be made aware of the deleterious effects of decongestants, antihistamines, diuretics, and specific drugs used for the treatment of cardiovascular and psychiatric problems, known to produce a dry mouth. In addition to increasing oral fluid intake, the use of saliva and tear substitutes, pilocarpine and cevimeline may be helpful, but nonsteroidal and steroidal anti-inflammatory medicines fail to improve salivary flow. Antifungal medicines are used to treat oral candidiasis, and close supervision by a dentist and preservative dental treatments are essential. A more recent study showed that human interferon alpha used for dry mouth in 497 subjects had a significant greater mean increase in unstimulated whole saliva flow, compared with placebo (14).

Systemic Sclerosis (Scleroderma)

Scleroderma, also called systemic sclerosis (SSc), is characterized by sclerotic skin changes and is often accompanied by a multisystem disease. Progressive fibrosis of involved organs is the pathologic hallmark of the disease. Scleroderma is usually divided into two main forms: localized scleroderma and SSc. This division has important prognostic implications and allows specific clinical approach. SSc is further divided into limited cutaneous disease (lcSSc) and diffuse cutaneous disease (dcSSc). LcSSc is characterized by skin thickening distal to the elbows and knee, severe Raynaud phenomenon preceding skin disease, anti-centromere antibodies, and later development of visceral involvement (gastrointestinal and lung, pulmonary artery hypertension [PAH] and interstitial lung disease). DcSSc is characterized by proximal skin thickening (thighs, trunk, and arms), significant visceral disease (lung, heart, kidney, and gastrointestinal), absence of anti-centromere antibodies, and a worse prognosis (15). The incidence is approximately 18 to 20 new cases per million per year and the disease has a 3:1 female-to-male preponderance, with 50 years as the median age of onset. Initial presentation includes Raynaud phenomenon, edema of the fingers and hands, and skin thickening. The American College of Rheumatology criteria for scleroderma include one major criterion (sclerodermatous skin changes proximal to the metacarpal–phalangeal joints) and two of three minor criteria: sclerodactyly, evidence of ischemia of the digits (digital pitting scars), and bibasilar pulmonary fibrosis on chest radiograph (16). These criteria were found to have 97% sensitivity and 98% specificity for the diagnosis of scleroderma. Visceral and often fatal manifestations are seen in the gastrointestinal tract, lung, heart, and kidneys. Arthralgias and muscle weakness are common musculoskeletal complaints, and Raynaud phenomenon is almost universal.

Head and Neck Manifestations

Eighty percent of patients with SSc have signs and symptoms involving the head and neck, and in 30% of those patients, the head and neck symptoms are part of the presenting complaints. In the skin, edema precedes epidermal atrophy and loss of appendages. Eventually, in 35% of these patients, facial tightness develops. A decreased ability to open the mouth is the initial complaint in 19% of patients, which is a secondary manifestation to skin changes. Additional skin manifestations include telangiectasias (19%), calcinosis (3%), and linear scleroderma, which usually affect the scalp and limbs. The typical facies associated with scleroderma consists of tight skin, thin lips, and vertical perioral furrows (Fig. 17.3). These skin changes represent a major aesthetic concern for patients (17). These

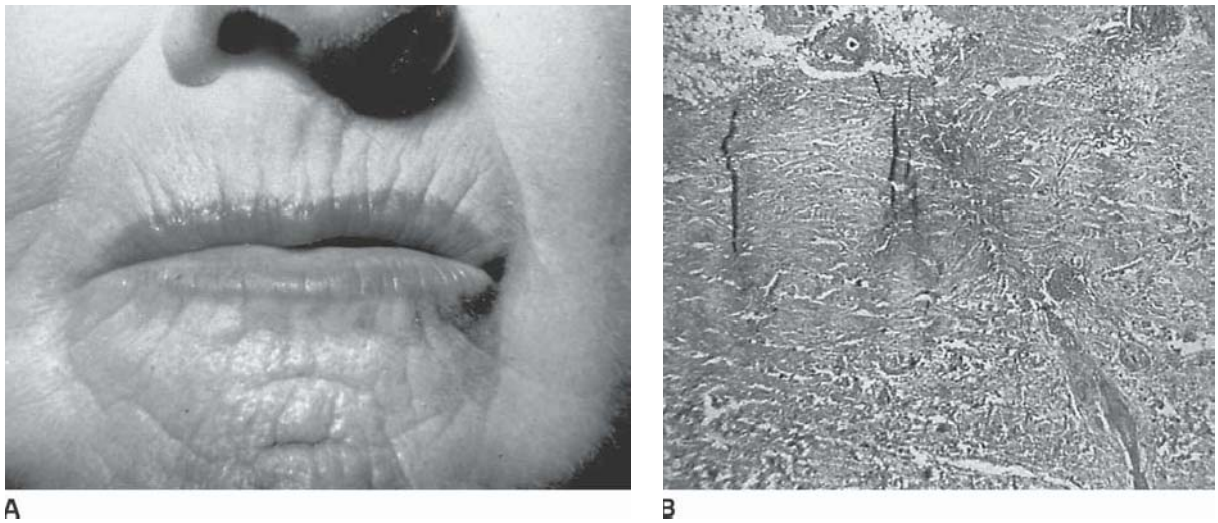


Figure 17.3 **A:** The typical facies of scleroderma: tight skin, thin lips, and vertical perioral furrows. These external facial features are secondary to inflammatory foci in the dermis and subcutaneous tissues. **B:** Infiltrations of lymphocytes, plasma cells, and histiocytes.

skin changes are secondary to the underlying dermal and subcutaneous inflammatory process. Dysphagia is the most common initial complaint. Esophageal problems occur in nearly all patients with this disease; abnormal radiographic findings are observed for the distal two-thirds of the esophagus in 80% of patients with SSc, and 50% of those patients are symptomatic. The dysphagia is due to involvement of esophageal innervation, smooth muscle (the distal two-thirds of esophagus, the portion composed of smooth muscle), esophageal stricture, or combination of all. Upper esophageal involvement does not usually occur unless there is an overlap with inflammatory myopathy, in which case even pharyngeal involvement can be seen, because of the striated muscle structure in the proximal esophagus. Decreased or absent peristalsis in the distal esophagus with mild to moderate dilation also is reported, and hiatal hernias are common.

Scleroderma often involves structures in the head and neck. Gingivitis and periodontal membrane thickening are common. Oral tissues demonstrate edema followed by atrophy and induration of mucosal and muscular tissues. About 25% of patients report xerostomia, xerophthalmia, or both (the sicca complex). A minor salivary gland biopsy will not demonstrate the lymphocytic infiltrate seen with Sjögren syndrome but will demonstrate fibrosis. Involvement of the larynx also occurs, and almost half of the patients with SSc complain of a voice change. The most common cause for laryngeal disease in scleroderma is chronic acid irritation from severe esophageal disease and incompetent lower esophageal sphincter. Raynaud phenomenon of the tongue, an unusual complication, may appear as mucosal blanching associated with dysarthria. Trigeminal neuralgia and facial nerve palsy are infrequent manifestations. Patients with SSc, particularly dcSSc, are at increased risk for development of carcinoma of the tongue (18).

Treatment

Randomized controlled trials in scleroderma have failed to reveal effective disease-modifying therapies (19). Thus, the treatment of SSc is largely symptomatic, although many rheumatologists will use immunosuppressive drugs in patients with active, progressive disease. Calcium channel blockers can be useful in Raynaud phenomenon but can aggravate gastroesophageal reflux. Proton-pump inhibitors are used with life-style modifications to treat gastroesophageal reflex in these patients, as in other patient groups. Dysphagia to solids can be helped by using liquids to clear the esophagus. Angiotensin-converting enzyme (ACE) inhibitors are used in the treatment of scleroderma renal crisis. Important advance has been made in the management of vascular disease of scleroderma, especially the PAH. FDA approved therapies for PAH in the United States include two endothelin-1 receptor blockers, two phosphodiesterase-5 inhibitors, and prostacyclin derivatives (20).

Inflammatory Muscle Disease (Polymyositis and Dermatomyositis)

The inflammatory myopathies are a group of disorders characterized by proximal muscle weakness and nonsuppurative inflammation of the skeletal muscle. Polymyositis, dermatomyositis, and inclusion body myositis are subsets of this group. The incidence of these disorders is estimated to be approximately five new cases annually per million, with a 2:1 female preponderance, and the age of onset is between 40 and 50 years, with a pediatric variant affecting children between the ages of 5 and 15 years. The diagnostic criteria for polymyositis and dermatomyositis are complex and subject to ongoing debate (21–23) (Table 17.5). The most common presentation is that of progressive proximal muscle weakness over a period of months, and fatigue is common.

TABLE 17.5 BOHAN AND PETER CRITERIA FOR THE DIAGNOSIS OF PM AND DM (22,23)

1. Proximal muscle weakness: usually symmetrical
2. Elevated serum muscle enzymes: CK, aldolase
3. Electromyographic abnormalities:
   (a) Common: myopathic potential—low amplitude, short duration, and polyphasic action potentials
   (b) Characteristic triad: (i) myopathic potentials; (ii) fibrillations, positive sharp waves, increased insertional activity; (iii) complex repetitive discharges
4. Muscle biopsy findings typical of PM or DM: necrosis, phagocytosis, regeneration, inflammation
5. Dermatologic features of DM, Gottron sign or papules, or heliotrope rash

Definite DM requires four criteria (including rash) and definite PM requires four criteria (without rash).
Probable disease comprises three criteria (including rash) for DM and three criteria (without rash) for PM.
Possible disease requires two criteria (including rash) for DM and two criteria (without rash) for PM.

The inflammatory myopathies may be isolated or associated with other abnormalities. Polymyositis and dermatomyositis may be associated with other systemic autoimmune disorders, including SSc, SLE, Sjögren syndrome, Churg-Strauss syndrome, and RA. In approximately 20% of patients, the myopathy is associated with a malignancy, particularly ovarian cancer, but non-Hodgkin lymphoma and carcinoma of the lung, prostate, breast, nasopharyngeal areas, and colon have also been implicated.

Head and Neck Manifestations

Head and neck manifestations of polymyositis reflect proximal muscle involvement. Half of the patients report weakness of the neck muscles, which is often manifested by a patient's inability to lift his or her head off a pillow. Difficulty in phonation and deglutition occurs because of diseased tongue muscles, and nasal regurgitation is common because of palatal and pharyngeal muscle involvement. Thirty percent of patients with these diseases have upper dysphagia secondary to the involvement of the upper esophagus, pharynx, superior constrictors or, most commonly in inclusion body myositis, the cricopharyngeus (24). Dysfunction of these muscle groups also results in aspiration and secondary pneumonia. Cutaneous photosensitivity is common in dermatomyositis. The heliotropic rash, seen in some (fewer than 50%) patients with dermatomyositis, is a purplish discoloration in the periorbital area, especially the upper eyelids.

Treatment

The treatment of inflammatory muscle disease starts with steroids to treat symptomatic patients. Methotrexate and azathioprine are commonly used as first steroid-sparing agents; they can be used alone or in combination for refractory myositis (25). Another important therapeutic approach with positive results in several perspective trials is intravenous immunoglobulin (Ig). Recently, rituximab has been used in a pilot study of dermatomyositis (26). Upper gastrointestinal symptoms related to esophageal dysfunction may require omeprazole, cisapride, or referral to a speech therapist. If untreated, the mortality rate from this disease is quite high. Physical therapy plays a role in reducing contractures and loss of function.

Relapsing Polychondritis

Relapsing polychondritis is characterized by episodic recurring inflammation of the cartilaginous structures and other tissues with a high concentration of glycosaminoglycans that are eventually replaced by granulation tissue and fibrosis. Diagnosis is based on chondritis at two of three sites (auricular, nasal, or laryngotracheal) or one of those three sites with two of the following symptoms: ocular inflammation, cochlear or vestibular damage (or both), or seronegative inflammatory arthritis (27). Biopsy of the lesion is not required for diagnosis. The incidence is about 3.5 cases per million.

Head and Neck Manifestations

Auricular chondritis and nonerosive arthritis are the most common presenting symptoms of relapsing polychondritis. Auricular chondritis is characterized by the sudden onset of erythema and pain, sparing the lobule, which lacks cartilage. Chondritis is the feature presentation in 33% of patients and will develop in 90% of those with the disease. Resolution can occur in 5 to 10 days with or without treatment. Conductive hearing loss may develop secondary to collapse of the external auditory canal or eustachian tube chondritis, causing serous otitis media, and 40% have cochlear or vestibular dysfunction, possibly due to vasculitis of the internal auditory artery. Aphthous ulcers are the most common dermatologic manifestations of this disease.

Chondritis of the nasal cartilages develops in 61% of patients and often does not coincide with auricular involvement (27). The nasal cartilage chondritis also has a sudden onset and resolves in several days with or without treatment. Overtime, and with repeated attacks, deformities result from the loss of cartilage. These deformities occur in the pinna, which become soft and flops over, and in the nasal bridge, which can cause a classic saddle deformity of the nose.

Laryngeal involvement is seen early with a nonproductive cough, which progresses to hoarseness and stridor. On physical examination, tenderness over the thyroid cartilage and the anterior trachea can be observed. Inflammation of the tracheobronchial tree damages the cartilaginous rings, which can cause a dynamic obstruction in inspiration. Stricture can form in subglottic space, increasing susceptibility to secondary infection. Of patients with relapsing polychondritis, 53% will have respiratory tract involvement during the course of their disease. Diagnostic endoscopy can be dangerous in these patients because of the risk of tracheal collapse. With extensive airway involvement, management is difficult, even with a tracheotomy. Indications for the need of a tracheotomy include severe edema of the glottic and subglottic regions of the larynx and laryngeal collapse.

Biopsy often reveals a lack of basophilic staining of the cartilage, perichondrial inflammation, with presence of mononuclear cell infiltrate at the fibrochondrial junction, and eventual cartilage destruction and replacement with fibrous tissue. The erythrocyte sedimentation rate (ESR) is often increased with active disease. Serologic evaluation often reveals a positive rheumatoid factor, antinuclear antibody, and anti-type II collagen antibody; however, the first two lack specificity and the last one is not routinely available. The clinical course ranges from mild disease to severe fulminating attacks. Mortality is generally related to respiratory involvement (i.e., laryngeal collapse) or cardiovascular disease (e.g., aneurysms or valvular insufficiency). The cause of relapsing polychondritis is unknown.

Treatment

Because of the relapsing nature of the disease, it is uncertain whether any therapy changes its course. In most cases, corticosteroids are the main form of treatment. Nonsteroidal anti-inflammatory medicines are used for arthritis. Colchicine may be used for auricular chondritis. The anti-leprosy sulfone drug dapsone also has helped in some cases, methotrexate is used when the arthritis component is an important feature, and azathioprine also has a place as a steroid-sparing agent. In the treatment of recalcitrant cases, treatment with infliximab may be successful (28,29). Surgery to correct the collapsed nasal cartilage and subglottic stenosis can be performed when disease is stable. Tracheal stenting is considered but experience is limited. Continuous positive airway pressure ventilation at night time might help to keep airway open while in the recumbent position.

Mixed Connective Tissue Disease

The term *mixed connective tissue disease* (MCTD) was coined in 1972 to describe a distinct entity with coexisting features of SLE, SSc, and myositis. This entity is characterized by high titers of anti-U1 RNP (1:1,600 or higher), a ribonucleoprotein antibody. The prevalence is unknown, and no consensus diagnostic criteria have been developed; the nature and existence of the disease as a unique entity is still debated. Eighty percent of patients are women, and onset usually occurs between the ages of 30 and 60 years, with death resulting primarily from pulmonary fibrosis and hypertension. The most acceptable criteria for diagnosis are those proposed by Alarcon-Segovia (30). Requirements for the diagnosis are anti-U1 RNP antibody positive at titer 1:1,600 or higher plus myositis or synovitis plus two of the following: edema of the hands, acrosclerosis, or Raynaud phenomenon.

Head and Neck Manifestations

Head and neck manifestations are a combination of the features seen in other systemic autoimmune disorders. Mucocutaneous changes include malar rash, discoid lupus, sclerodermatous skin thickening, oral mucosal ulceration, and nasal septal perforation. Sjögren syndrome also has been described in 50% of patients with MCTD, albeit sicca complex is usually less prominent than in those with anti-La antibodies. Esophageal dysfunction is present in most cases, resulting in abnormal peristalsis, heartburn, and dysphagia in 60%, 48%, and 38% of patients, respectively. One interesting clinical manifestation of MCTD that happens on a fairly frequent basis, in about 25% of cases, is trigeminal neuralgia. As with most other systemic autoimmune diseases, corticosteroid and immunosuppressive agents are the mainstays of treatment with the goal of managing the specific organ involvement or disease manifestations on a case-by-case basis.

Vasculitides

The vasculitides are a group of diseases characterized by a noninfectious necrotizing vasculitis and resultant ischemia. Considerable overlap in the clinical manifestations of these diseases makes it difficult to develop categories with strict criteria. A practical approach has been to classify them into groups by the size of vessels involved, the specific anatomic sites involved, clinical manifestations, and the presence or absence of anti-neutrophil cytoplasmic antibodies (ANCAs). Some of the more important categories are discussed herein.

Polyarteritis Nodosa

PAN has been considered the prototype of the vasculitides. This rare disease has an incidence of less than 1 in 100,000 per year. It affects males and females equally and is seen in all racial groups. Patients are usually in the fifth and sixth

decades of life at presentation. PAN is a non-ANCA vasculitis affecting predominantly medium-sized arteries and can be the result of hepatitis B infection. Tissues involved include the gastrointestinal tract, hepatobiliary system, kidneys (vascular nephropathy without glomerulonephritis), pancreas, skin, testicles, peripheral nerves, and skeletal muscles. Symptoms at presentation are primarily constitutional (fever, weight loss, and malaise) with peripheral neuropathy (mononeuritis multiplex).

Despite widespread arterial involvement, otolaryngologic manifestations are few, but sudden bilateral sensorineural hearing loss has been attributed to this disease. Vestibular disturbances also have been reported. The proposed mechanism of cochleovestibular damage is thromboembolic occlusion of the end arteries of the inner ear. Other head and neck manifestations include cranial nerve palsies, in which the seventh nerve is most commonly involved, and skin or mucosal lesions.

Churg-Strauss Syndrome

Churg-Strauss syndrome, also called allergic angiitis granulomatosis, is a disease characterized by the triad of systemic small-vessel vasculitis, asthma, and hypereosinophilia. Mean age at onset is 50 years, with a male preponderance and an incidence rate of approximately three per million. Three phases of this disorder exist. The prodromal phase consists of asthma, atopy, and allergic rhinitis; the latter symptom is present in 70% of cases. The second phase is marked by hypereosinophilia and eosinophilic tissue infiltration, leading to peripheral neuropathy or pulmonary infiltrates. Systemic necrotizing vasculitis constitutes the final phase, including renal, gastrointestinal, cardiac, and CNS involvement. Progression from asthma to vasculitis occurs over a period of 3 years to decades, and diagnosis of Churg-Strauss syndrome is suggested if four of six criteria (asthma; eosinophilia greater than 10%; neuropathy, mononeuritis multiplex, or polyneuritis; non-fixed pulmonary infiltrates; paranasal sinus abnormality; and extravascular eosinophilia) are present. Seventy percent of patients have nasal involvement, with polyps, resultant obstruction, rhinorrhea, secondary rhinosinusitis, and crusting. Asthma is nearly universal, and the ANCA serology (usually perinuclear or p-ANCA detected by IF and myeloperoxidase (MPO)-ANCA detected by enzyme-linked immunosorbent assay [ELISA]) is detected in 50% of the cases. Otologic manifestations of Churg-Strauss syndrome include sensorineural hearing loss and conductive hearing loss due to eosinophilic infiltration into the mastoid and middle ear with otorrhea. The middle ear and mastoid disease is reversed by steroid treatment (31). High-dose corticosteroids are the treatment of choice, but some patients with severe systemic involvement require cyclophosphamide. Deaths occur most commonly from cardiac and CNS involvement. Before the use of steroids, the mortality rate was 50% within 3 months of onset of the systemic vasculitis.

Granulomatosis with Polyangiitis (Wegener Granulomatosis)

Granulomatosis with polyangiitis (GPA) which is new nomenclature for the disease previously known as Wegener granulomatosis, is a rare (incidence of less than 1 in 100,000 per year) form of vasculitis characterized by the triad of upper and lower respiratory tract granulomas, vasculitis, and glomerulonephritis (Wegener triad), which could have been included in the granulomatous disease section of this chapter. No gender predilection is seen. Most patients are white and present in the fifth decade of life. The typical clinical features include bilateral pneumonitis (95% of patients), chronic sinusitis (90%), mucosal ulceration of nasopharynx (75%), and evidence of renal disease (80%). Nasal symptoms usually occur early in the disease and include crusting, epistaxis, and rhinorrhea. Erosion of the septal cartilage with saddle-nose deformity and nasal stenosis may occur after cartilage is destroyed by the vasculitis and granulomas. The sinusitis associated with GPA is difficult to treat. *Staphylococcus aureus* is often cultured from these patients.

The most common oral cavity findings of GPA include hyperplasia of the gingiva and gingivitis (strawberry gums). Edema and ulceration of the larynx are seen in 25% of patients. Significant subglottic stenosis develops in up to 23% of patients and is a poor prognostic sign. Salivary glands also may be involved.

Otologic problems develop in 20% to 25% of patients and include conductive hearing loss secondary to serous otitis media; suppurative otitis media, with or without granulation tissue in the middle ear; sensorineural hearing loss, often profound and bilateral; and pinna changes similar to those seen with polychondritis. Facial nerve palsies also have been documented, and is believed to be secondary to compression due to inflammation in the middle ear.

Diagnosis is based on clinical, pathologic, and laboratory findings. The hallmark pathologic lesion in GPA is necrotizing, granulomatous, small and medium vessel vasculitis with an inflammatory infiltrate. Often, upper-airway biopsies are nondiagnostic because the inflammatory infiltrate obscures the vasculitis, so that multiple upper-airway biopsies or lower-respiratory biopsies are required before histologic diagnosis is ultimately made. The discovery of cytoplasmic staining ANCA (c-ANCA) has revolutionized the diagnosis of GPA. The sensitivity of c-ANCA for GPA ranges from 65% to 96% for patients with an active, generalized disease, and the specificity is quite high, although this test may be positive in patients with microscopic polyangiitis (MPA) and Churg-Strauss Syndrome. ELISA provides target antigen-specific characterization of ANCA and enhances the specificity and sensitivity of IF. The c-ANCA pattern usually corresponds to detection of proteinase-3 ANCA (PR3-ANCA) by ELISA. Finding c-ANCA by IF in combination with PR3-ANCA by ELISA carries a sensitivities and specificities >95% for GPA

(32). Tissue diagnosis should be reserved for cases with high clinical suspicion but a negative PR3-ANCA or low clinical suspicion but positive PR3-ANCA. Classical clinical findings in conjunction with positive PR3-ANCA may be sufficient for diagnosis. The ESR varies with disease activity. Left untreated, generalized GPA is fatal within 2 years in 93% of all cases. However, symptomatic control of the disease is achieved in most patients with corticosteroids and low-dose daily cyclophosphamide (2 mg/kg/day). Some experts prefer regimens of monthly intravenous (IV) cyclophosphamide. Induction of remission with monthly IV cyclophosphamide was shown to be as effective as daily oral cyclophosphamide with fewer side effects (33). Azathioprine or methotrexate may be alternatives to cyclophosphamide and are used for the maintenance of remission or for patients with limited disease. Recently, the RAVE study has shown that rituximab therapy was not inferior to daily cyclophosphamide treatment for induction of remission in severe ANCA-associated vasculitis and may be a better option for recurrent disease. (34). Approximately 20% of patients, even with therapy, eventually succumb to the disease or to the therapy. Isolated sinus disease may be treated with low-dose steroids, topical nasal steroids, saline irrigations, or antibiotics when bacterial superinfection is suspected. Additionally, airway compromise may be alleviated with systemic steroids, although significant subglottic stenosis may require a tracheostomy.

Microscopic Polyangiitis

MPA is fairly recently described vasculitis, coined in 1994 by a group of experts during an international consensus conference. MPA essentially branched out from PAN as a small vessel disease. Vasculitis in the arterioles, capillaries, and venules, which involves primarily the lung and the kidney, are characteristic to MPA and absent in PAN. In addition, MPA patients commonly are ANCA positive unlike PAN. GPA, MPA, and Churg-Strauss syndrome comprise a category of small vessel vasculitis related to ANCA and are characterized by pulmonary and renal involvement. MPA and GPA have a similar clinical spectrum and are often hard to distinguish. Histopathologically, MPA is characterized by pauci-immune, necrotizing, small vessel vasculitis without evidence of granulomatous inflammation, in contrast with GPA where granulomatous vasculitis is the hallmark of disease. The prevalence is about 2 cases per 100,000 with white males being slightly more commonly affected than females; usual onset of disease is around 50 years.

The clinical presentation is similar with GPA. One of the most important differentiating factors between GPA and MPA is the severity and timing of upper respiratory tract involvement. MPA may affect the upper respiratory tract but is usually limited to a mild sinusitis, rhinitis, and mucosal lesions, and does not typically precede the disease onset. Fever, malaise, fatigue, myalgia, and weight loss is found in about 50%. Pulmonary involvement is common with infiltrates, hemoptysis, dyspnea, and cough. Renal disease in MPA is similar with GPA, but tends to present earlier in the disease. The most dreadful clinical presentation is with rapid progressive glomerulonephritis and kidney failure. Other organs and systems involvement are frequently found; patients with MPA might have gastrointestinal tract vasculitis, nervous system manifestations, more commonly mononeuritis multiplex (57%) but CNS involvement with seizure may be found in 11% of patients. Skin involvement (palpable purpura 40%, livedo reticularis, skin ulceration, and necrosis), ocular manifestation, myalgia, and arthralgia are part of the MPA clinical spectrum. Laboratory studies reveal elevated acute-phase reactants, anemia, and renal involvement (elevated BUN and creatinine, proteinuria, hematuria, and urinary casts). Eighty percent of the patients are ANCA positive and, in contrast with GPA, MPA typically exhibit a p-ANCA pattern on IF with MPO-ANCA reaction by ELISA. GPA typically has c-ANCA pattern on IF with PR3-ANCA by ELISA.

Treatment is identical for MPA as for GPA. The prognosis is relatively similar and the disease course is slightly different with a higher relapse rate for GPA (40%) and more frequent renal morbidity for MPA. In a retrospective study of 246 patients, 18% mortality was observed at 1 year and 76% survival at 5 years (35).

Giant Cell Arteritis/Polymyalgia Rheumatica

Giant cell (temporal) arteritis is characterized by focal granulomatous inflammation of arteries of medium and small size. Histologically, a panarteritis is seen with giant cell granuloma formation near the internal elastic lamina, which is often disrupted and concentric intimal hyperplasia. Giant cell arteritis is the most common of the vasculitides, and its incidence increases with age to approximately 20 cases per 100,000 persons aged 50 years and older in Northern European descent, 6 cases per 100,000 in Southern European and 1 to 2 cases per 100,000 in blacks and Hispanics. Giant cell arteritis is actually a general arteritis, of which temporal arteritis is only one local manifestation. Many rheumatologists believe this disease also encompasses polymyalgia rheumatica. Polymyalgia rheumatica is a clinical syndrome of muscular pain and morning stiffness in the proximal muscle groups without inflammatory joint or muscle disease. Patients with polymyalgia rheumatica have histologic changes in their arteries like those in temporal arteritis. In addition, polymyalgia rheumatica is seen in 50% of patients with classic giant cell arteritis. Systemic symptoms, such as low-grade fever, weight loss, and malaise, may precede localized symptoms in all manifestations of the disease. Polymyalgia rheumatica alone is usually self-limiting and responds well to low-dose prednisone therapy.

The symptoms of classic giant cell arteritis reflect involvement of the cranial blood supply by the vasculitis.

Headaches of variable character (throbbing, sharp, or dull) are the initial and the most common symptom in 47% of patients, and occur in as many as 90% of patients. Despite the name, the temporal artery is erythematous and tender in only 50% of patients with giant cell arteritis. The scalp, however, is often very tender. Other manifestations are presumably due to involvement of other arteries in the head and neck. Jaw claudication occurs in as many as 67% of these patients with prolonged talking or chewing, 25% have lingual claudication and cases of tongue infarction have been reported. Vertigo and hearing loss also have been reported. Involvement of the ascending pharyngeal artery can lead to dysphagia. Additionally, cranial nerve deficits, hemiparesis, vertebrobasilar insufficiency, and psychosis reflect intracranial disease. Blindness occurs in one-third of untreated patients and may be heralded by field defects, diplopia, or amaurosis fugax reported as fleeting visual blurring induced by exercises or sudden orthostatism. Sore throat and odynophagia may indicate ischemia of the pharynx and dry cough has been reported in the setting of vasculitis of the bronchial tree.

In giant cell arteritis, as with several of the vasculitides, the ESR is usually more than 50 mm/h. Although cases with normal or slightly elevated ESRs have been reported, those results usually lead the clinician away from the diagnosis. Confirmation of diagnosis of giant cell arteritis is accomplished with a biopsy of the temporal artery on the most symptomatic side. The false-negative results, however, range from 5% to 40% because of skip lesions and the frequently small foci of the disease in the artery. The American College of Rheumatology requires that three of five criteria (age older than 50 years at onset, new headache, temporal artery abnormality (tenderness or decreased pulsation), ESR more than 50 mm, and temporal artery biopsy showing vasculitis) be present to make the diagnosis. Thus, the role of temporal artery biopsy is to confirm the diagnosis when it is in doubt, although a negative biopsy does not rule out the disease. A positive biopsy is helpful if, after treatment, a question remains about the diagnosis. Because of the seriousness of the ophthalmologic consequences, treatment should not be delayed for the biopsy, as it is most useful within 24 hours of initiation of treatment (36).

Treatment for giant cell arteritis is corticosteroids. Using pulse IV corticosteroids (15 mg/kg/day) for the first 3 days allows a faster steroid taper and has a greater chance for a sustain remission (37). Normalization of the ESR or C-reactive protein and loss of symptoms are the therapeutic guidelines. The purpose of treatment is both the elimination of pain and prevention of blindness or other vascular complications and may be required for 5 years or longer.

Immune Complex–Mediated Vasculitis

The immune complex–mediated vasculitis are a heterogeneous group of small-vessel vasculitides that universally involve the skin, arteritic involvement of small vessels (particularly postcapillary venules), and leukocytoclasis. Diseases in this group include hypersensitivity angiitis, Henoch-Schönlein purpura, and cryoglobulinemia vasculitis. These syndromes appear to be immune complex–mediated and may be triggered by a foreign antigen, which is often not identified. Therapy is concentrated on identification and elimination of inciting antigens. Glucocorticoid and immunosuppressive drugs and plasmapheresis are commonly used in treatment.

Behçet Disease

Behçet disease is a systemic vasculitis affecting mostly East-Asian and Mediterranean populations and usually presents with oral and genital ulcers in the third decade of life. Ocular inflammation, such as anterior uveitis or panuveitis with posterior chamber involvement typically follows mucocutaneous symptoms. These aphthous-like ulcers are characteristically punched out, with or without surrounding erythema, and covered with a pale pseudomembrane. They are frequently the first symptom of the disease. Primarily, these painful lesions occur singly or in clusters on the lips, gingiva, buccal mucosa, and tongue and less frequently on the palate and in the oropharynx. The genital ulcers are similar but are deeper and larger. Healing occurs in a few days to weeks and some scarring results. Uveitis is seen in 50% of patients, and loss of sight occurs in 25%. Genetic studies have shown a strong association with human leukocyte antigen (HLA)-B51 gene. The diagnosis is also supported by positive pathergy test (an erythematous papule larger than 2 mm at the prick site 48 hours after the application of a 20- to 22-gauge sterile needle, which obliquely penetrated avascular skin to a depth of 5 mm). Aseptic neutrophilic infiltration causes the papule and is due to neutrophil hyperreactivity.

The cause of the disease is not known, but a genetic component exists, and vessels of all sizes can be involved. Large vessel involvement occurs in about a quarter of patient with Behçet disease and constitutes the number one cause of mortality (38). Symptoms may occur simultaneously or months apart, and diagnosis is made by exclusion of other similar diseases. Local treatment for oral and genital ulcers is primarily through the use of corticosteroid creams. Fever is treated with antipyretics or nonsteroidal anti-inflammatory medicines. Oral colchicine is a first-line systemic treatment for mucocutaneous involvement. Oral dapsone is used if colchicine fails. Local treatment for eye involvement includes topical mydriatic agents. Systemic steroids, cytotoxic immunosuppressive agents, and interferon alpha-2b are reserved for systemic disease, severe mucosal disease, and eye involvement. Antitumor necrosis factor α block agents have been used with success in severe and refractory eye inflammation (39) and mucocutaneous disease (40).

Cogan Syndrome

Cogan syndrome is a rare disease of young adults (median age, 22 years) characterized by Ménière-like auditory and

vestibular dysfunction, interstitial keratitis, and nonreactive tests for syphilis. Interstitial keratitis is a mononuclear cell corneal infiltrate resulting in eye irritation, erythema, and photophobia. The symptoms frequently begin after an upper respiratory infection. Histopathologic analysis of the inner ear has shown lymphocytic and plasma cells infiltrate in the spiral ligament and endolymphatic hydrops, degeneration in the organ of Corti, new bone formation and demyelination of cranial nerve VIII branches. Auditory and vestibular manifestations are usually bilateral and can include fluctuating hearing loss, vertigo, tinnitus, and aural pressure. These symptoms may resolve spontaneously and reappear months later. The hearing loss is progressive and severe and usually associated with decreased or absent vestibular responses on caloric testing. Bilateral deafness results in 50% of the cases. The ear symptoms may precede or follow the ocular disease by several years. Cogan syndrome is accompanied by a large- or medium-vessel systemic vasculitis in about 10% of the cases. Proximal aortitis with valvular involvement was found in up to 10% of the patients with Cogan syndrome. Pathologic features suggest end-organ–specific autoimmune mechanisms rather than vasculitis damage to the inner ear. Hearing outcomes are improved with early initiation of systemic corticosteroid treatment, so early diagnosis is critical. Permanent visual loss rarely results from this disease unless ocular inflammation involves the posterior segment. Interstitial keratitis is treated with topical steroids. Systemic steroids and occasionally immunosuppressive agents are used to treat the otologic symptoms. Cochlear implantation is successful after loss of hearing.

Kawasaki Disease

Kawasaki disease, also known as mucocutaneous lymph node syndrome, is a disease involving the pediatric age group, and it is the most common cause of acquired heart disease in children in the developing world. The cause is unknown, but epidemiologic data suggest an infectious cause. Clinical characteristics include fever, conjunctivitis, red and dry lips, erythema of the oral mucosa, strawberry tongue, polymorphous truncal rash, desquamation of the fingers and toes, and cervical lymphadenopathy. Although cervical adenopathy is the least common clinical feature in US cases, though it is more common in Asia (US occurrence is roughly 40%, in Asia cervical adenopathy is seen in 50% to 75% of patients), this disease must be considered in febrile children with cervical lymphadenopathy unresponsive to antibiotics without an alternative diagnosis. In 20% to 25% of untreated children, coronary artery dilation or aneurysms develop, and a small percentage die of myocardial infarction due to thrombosis or rupture of coronary aneurysms, usually within 2 to 12 weeks after the onset of the disease. Treatment with IV Ig and aspirin in the first 10 days of illness reduces the incidence of coronary abnormalities by 10-fold. Addition of methylprednisolone as a third therapy may be used if coronary artery abnormalities are still a possibility.

Kikuchi Disease (Histiocytic Necrotizing Lymphadenitis)

Kikuchi-Fujimoto disease is a histiocytic necrotizing lymphadenitis, is a rare, idiopathic, usually self-limited disease characterized by cervical lymphadenopathy and constitutional symptoms. The pathogenesis of Kikuchi disease is unknown; however, infectious and autoimmune etiologies have been proposed. The clinical course and histology favors an immune response of cytotoxic T cells and histiocytes to an unidentified infectious agent. Multiple agents were proposed, such as Epstein Barr virus, human immunodeficiency virus (HIV), parvovirus B19, human herpesvirus VI, human herpesvirus VIII, *Yersinia enterocolitica*, and *Toxoplasma*. Kikuchi disease has similar histologic features with SLE. In addition, both diseases share gender and age distribution. Kikuchi disease has been reported in association with SLE or before a diagnosis of SLE is made. The typical patient is a young Asian female. The prevalence of Kikuchi disease among patients with lymphadenopathy ranges between 0.5% in Saudi Arabia and 34.7% in Korea, with female to male ratio ranging from 1.26:1 to 1:4. The most common presentation is acute cervical lymphadenopathy (80%) associated with low-grade fever and flu-like prodrome. Fatigue and joint pain was reported in 7% of the cases, skin rash (10%), hepatosplenomegaly, leukopenia (43%), elevated acute-phase reactants (40%) and anemia (20%) (41). The lymph nodes are firm and mobile and about 2 cm in diameter; they are not fluctuant or draining. The course is usually benign and can last anywhere between a couple of weeks to 6 months. Few cases of complication from heart failure, infection, meningitis and macrophage activation syndrome have been reported. Kikuchi disease is diagnosed by excisional lymph node biopsy done after more common causes for cervical lymphadenopathy are excluded, such as mononucleosis, sarcoidosis, syphilis, SLE, tuberculosis, and hematologic malignancies. Laboratory tests might reveal granulocytopenia, atypical lymphocytes, elevated acute-phase proteins and LDH. Appropriate radiographic studies to look for tuberculosis, malignancy, or other possible disease are reasonable. The histology of the lymph node typically follows three phases: proliferative phase with follicular hyperplasia and paracortical expansion of lymphocytes (B and T), monocytes, and histiocytes; followed by a necrotizing phase that shows extensive necrosis with distorted lymph node architecture without neutrophilic infiltrate and with histiocytes dominance; and the last phase, the xanthomatous phase or foamy cell phase, with the resolution of necrosis. The first-line of treatment is supportive with nonsteroidal anti-inflammatory drugs. Corticosteroids, IV Ig, and hydroxychloroquine have been used in recurrent or severe forms of disease (42,43).

GRANULOMATOUS DISEASES

A granuloma is a lesion produced by a defensive immunopathologic process. Initially, a circulating monocyte

acquires additional cytoplasm and organelles in the process of removing inflammatory debris. If the phagocytic mechanism fails, the cell becomes inert and immobile (i.e., epithelioid) and then becomes a relatively functionless multinucleated Langerhans giant cell with lymphocytes and eosinophils surrounding it. Fibroblastic proliferation occurs around the involved cells, forming a granuloma. Although some granulomatous diseases have known, and often infectious, causes, the cause of others remains poorly understood.

If a patient is first seen with a nonhealing ulcerative lesion, mucosal tumor, or mass in the head or neck, a biopsy is frequently performed to rule out neoplastic disease. The pathologist often reports only the presence of granulation tissue consistent with acute and chronic inflammation. The differential diagnosis may be lengthy, and the physician's first task is to determine whether the lesion is a localized disease process or a regional presentation of a systemic disease. The investigation begins with a thorough history, with special reference to fever, night sweats, weight loss, loss of appetite, malaise, arthralgia, and other factors suggesting systemic disease. A history of recent travel to developing countries and the possibility of compromised immunity also are important factors.

A physical examination comes next and includes a search for cervical, axillary, or inguinal lymphadenopathy or hepatosplenomegaly. If the first biopsy is inadequate, a subsequent specimen should be obtained from the superficial margins or the depth of the lesion. Tissue also is sent for special stains and cultures. Preoperative consultation with the pathologist or microbiologist ensures proper collection and transportation of specimens. Further laboratory and radiologic workup depends on the findings of the history and physical examination. However, shotgun ordering of multiple studies targeted at rare diseases in a "rule out" fashion is not cost-effective.

Neoplastic Disorders

Langerhans Cell Histiocytosis (Histiocytosis X)

Langerhans cell histiocytosis (LCH) is the preferred term for these disorders of proliferation of mononuclear phagocytic cells. The unifying feature of the disorders classified under LCH is their histopathology. Histologically, LCH lesions are granulomatous and contain histiocytes, eosinophils, and lymphocytes. Giant cells, neutrophils, and plasma cells also may be present. In the early stages, the lesions are dominated by histiocytes, including Langerhans cells. As the lesions mature, necrosis, phagocytosis, and ultimately xanthomatous changes and fibrosis occur, and Langerhans cells are less common. The identification of Langerhans cells is necessary for diagnosis, and electron microscopy may be required to identify the characteristic inclusions known as Birbeck granules, X granules, or Langerhans bodies. On light microscopy, the pathologic Langerhans cells are similar to those found in the skin, in which these cells are involved in delayed hypersensitivity. The presence of Langerhans cells in the lesion of LCH with eosinophils and lymphocytes suggests an immunologic mechanism for the disease. By light microscopy, these lesions do not appear malignant; however, cells in the lesions have been shown to be clonal. Whether this is a reactive or malignant disease is still debated.

LCH has a number of recognized variants and can present a continuum of disease severity. The term *histiocytosis X* was coined in 1953 to unify the diagnoses of eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease and to emphasize the unknown cause of these disorders. Other variants have been described, but this discussion is limited to the more common ones.

Traditional naming of this collection of disorders is based on the history of their first description in medical literature. Hand-Schüller-Christian disease, described in 1921, is the chronic disseminated form of LCH. Some investigators describe this process as the polyostotic form of eosinophilic granuloma. This entity occurs in children past infancy and in young adults, but it also is reported in the elderly. A classic triad, occurring in 10% of cases, consists of skull lesions, exophthalmos, and diabetes insipidus. Letterer-Siwe disease, described in 1933, is the acute disseminated form of LCH, which affects infants and children, age 3 years or younger. Extraskeletal involvement predominates. Eosinophilic granuloma, the localized form of LCH described in 1940, occurs in children and young adults. This disorder is characterized by osteolytic lesions in one bone (i.e., monostotic) or several bones (i.e., polyostotic), with a predilection for the frontal and temporal bones. The distinction between eosinophilic granuloma and the disseminated forms is helpful, but the distinction between Hand-Schüller-Christian disease and Letterer-Siwe disease does not affect treatment. Modern studies on LCH use classification schemes based on organ systems and sites of disease involved, rather than the traditional, historic classifications (44).

The annual incidence of LCH is about four per million, with the median age at diagnosis approximately 2 to 3 years. LCH is more common in males, and cases with multisystem involvement generally are initially seen in the first 2 years of life and are rare in adults. Half of the cases appear as a single bony lesion in patients older than 5 years old. Evidence exists that LCH is associated with a predilection to malignancy.

Many organ systems can be involved in LCH. As bone is the most commonly involved organ, with a predilection for the skull, the most common manifestation of the disease in the head and neck is skull lesions. The bony lesions of LCH are lucencies of the medullary bone, which look punched out on radiography, with no surrounding sclerotic reaction. Otitis media is the most frequent otologic finding in patients with LCH and is due to temporal bone involvement, particularly in the petrous ridge. Dental symptoms are due to mandibular involvement. Mandibular lesions

may be painful and cause swelling. The maxilla is involved less often. Gingival swelling is associated with cervical adenopathy. Skin involvement is common in the disseminated form and as a seborrheic rash that often involves the scalp and postauricular areas. Diabetes insipidus is common because of hypothalamic or pituitary involvement, and the thyroid also may be involved. Other organ symptoms commonly involved include the liver, lung, CNS, lymph nodes, and spleen.

Treatment depends on the extent of the disease. For isolated, accessible lesions in older children and young adults (eosinophilic granuloma), surgical excision is preferred. Radiation therapy is reserved for recurrences or inaccessible lesions. Isolated eosinophilic granulomas carry an excellent prognosis. Patients with systemic disease are generally treated with systemic chemotherapy. Vincristine, etoposide, and corticosteroids have proven to be effective chemotherapeutic agents, and with treatment, the mortality rate is approximately 20% (44).

Fibrous Histiocytoma

Fibrous histiocytoma most often develops as a painless mass lesion and is commonly found in sun-exposed skin and orbital tissues in the dermis and hypodermis but also can be found in deep soft tissues. In the head and neck, it has been found in the upper aerodigestive tract, salivary glands, and deep layers of the scalp and face. Age range is 1 to 70 years, with a male-to-female ratio of 2.5:1. The most common symptoms include nasal obstruction, epistaxis, dysphagia, and dyspnea. The lesions of fibrous histiocytoma are slow-growing nodules, and roughly one-third of tumors are multiple and metachronous.

The basic histopathology of fibrous histiocytoma consists of a biphasic cell population of fibroblasts and histiocytes with spindle-shaped cells with elongated nuclei arranged in a storiform (cartwheel) pattern. Some lesions show atypia and mitotic activity, although the histologic appearance does not completely correlate with clinical behavior. Metastasis is rare. Treatment of fibrous histiocytoma is local excision with clear margins.

Pyogenic Granuloma

Pyogenic granuloma is a polypoid capillary hemangioma, sometimes called lobular capillary hemangioma, which is seen on skin and mucosal surfaces. Histologically, pyogenic granuloma consists of circumscribed aggregates of capillaries arranged in lobules. These lesions are seen on the gingiva, most commonly the fingers, lips, face, nasal cavities, and tongue. Sixty percent of nasal lesions arise on the septum and can appear with epistaxis. Surgical excision is the treatment of choice; incomplete resection can lead to recurrence. These lesions are benign, and although they characteristically bleed intermittently, they are painless. In patients younger than 18 years, pyogenic granulomas occur predominantly in boys (82%), but a female predominance (86%) is found among patients 18 to 39 years old. It is probable that gender distribution is based on hormonal factors, as pyogenic granuloma is common, particularly in the gingiva, in pregnant women and shows marked regression with delivery. In this setting, these tumors are known as granuloma gravidarum.

Reparative Granuloma

The cause of reparative granuloma is unknown, but it is probably secondary to local trauma, such as a tooth removal. The peripheral form is a sessile or pedunculated mucosa-covered reddish or bluish mass arising from the gingiva or alveolar mucosa, and it is most commonly found on the anterior mandible. The central form is endosteal, usually anterior to the first molar in the mandible. Radiographically, the lesion appears as a lytic, expansile, unilocular cavity with well-demarcated nonsclerotic margins and a bony cortex, which is thinned but intact. Treatment consists of curettage.

Necrotizing Sialometaplasia

Necrotizing sialometaplasia is a lesion characterized by metaplastic epithelial cells lining small salivary gland ducts with the preservation of lobular architecture, unlike squamous cells or mucoepidermoid carcinoma. This process may be found wherever salivary tissue is present, but it occurs most often in the oral cavity, and the junction of the hard and soft palate is the most frequently involved site. This lesion is first seen as a deep-seated and sharply demarcated ulcer, but a nonulcerated swelling may be the only manifestation. Spontaneous resolution over the course of weeks to months is the rule. This entity is more common in persons who smoke and these lesions are often mistaken for oral carcinoma.

Sarcoidosis

Sarcoidosis is a systemic, idiopathic disease characterized by noncaseating granulomas in the afflicted areas. The disease usually occurs in the third to fifth decade, rarely before age 15 years, and is more common in women. It is relatively more common in African-Americans (annual incidence, 35 per 100,000) than in white Americans (11 per 100,000) and for unclear reasons the highest prevalence is estimated in Sweden (60 to 80 per 100,000), although this disease seen throughout the world. Sarcoid granulomas most often deposit in the lungs and intrathoracic nodes. Thirty to sixty percent of patients with sarcoidosis are asymptomatic, and incidental discovery by radiograph is a common presentation. One-third of patients have constitutional symptoms including weight loss, night sweats, fatigue, myalgia, and low-grade fevers. Symptomatic patients also may complain of dry cough, dyspnea, skin rash, arthralgia, or nervous system symptoms including vision changes. Generalized adenopathy occurs in 25% to 50% of the cases, and splenomegaly in 10%. Neural involvement occurs in 4% to 6% of these

cases, and 15% to 25% involve the orbit. Sarcoid may deposit in the subcutaneous "Darier-Roussy" nodules and can show isolated involvement or multiple system involvement. Sarcoidosis may present acutely with bilateral hilar adenopathy, erythema nodosum, and arthritis (poly- or oligoarthritis with periarticular soft tissue inflammation), this triad is called Lofgren syndrome, fever and uveitis may be associated. Lofgren syndrome is more common in Caucasians and has a good prognosis. Cardiac involvement is clinically present in 5% of sarcoidosis patients, but is considerably more common at autopsy, 67% of patients in Japan and 20% in United States (45). The most common clinically evident manifestations of cardiac involvement are conduction abnormalities, sudden death, and infiltrative cardiomyopathy. Diagnosis depends on the correlation of symptoms with radiographic, pathologic, or biochemical indicators.

The pathologic hallmark, the noncaseating epithelioid granuloma, is compact and demonstrates multinucleated giant cells, lymphocytes, and mononuclear phagocytic cells wrapped by fibroblasts and mast cells (Fig. 17.4). Typically no necrosis (caseation) is found. The predilection of the granulomas for lymph nodes and connective tissue can lead to the typical radiographic findings of hilar adenopathy, thickening of the septae between lobules, nodules, and generalized attenuation by diffuse interstitial lung involvement.

Diagnosis of sarcoidosis involves exclusion of other granulomatous diseases, particularly tuberculosis, and finding the typical granulomas on open or fine-needle biopsy. Laboratory evaluation includes chest radiography and skin tests for anergy and tuberculosis. When the diagnosis is established, it is important to evaluate the patient for the extent and severity of the disease, including possible CNS, cardiac, or ophthalmologic involvement (46). ACE has previously been used to monitor the course of the disease, but many physicians who treat these patients question the value of this test. ACE is elevated in 40% to 90% of sarcoidosis patient and it correlates with active pulmonary disease. It is produced by alveolar macrophage and epithelioid cells present in granulomas as a response to an ACE-induced factor released by T lymphocytes. More recently, serum and bronchial washing levels of interleukin (IL)-12 and bronchial washing levels of macrophage inflammatory protein 1α and 1β have shown promise as markers of disease severity (47). Nuclear scanning is occasionally used; it may reveal the typical pattern of uptake in sarcoidosis: the "panda sign" due to increased uptake in lacrimal and parotid glands and the lambda sign due to increased uptake in paratracheal and hilar lymph nodes.

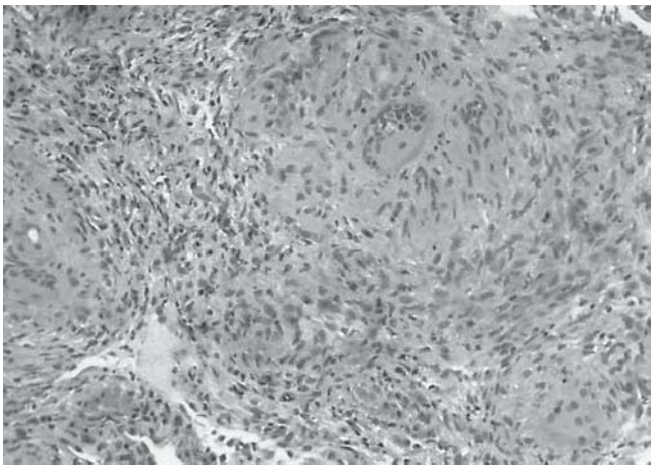


Figure 17.4 Sarcoidosis. Lung biopsy shows noncaseating granulomas with giant cells (hematoxylin and eosin stain; original magnification, 310×).

Although the cause of sarcoidosis is not known, recent evidence suggests a fivefold increased familial relative risk and possible linkage to chromosome 6 and specific HLA genes. Sarcoidosis is thought to be a result of host and environmental factors interacting to create an overexuberant T-cell–mediated response, but neither the host susceptibility nor the environmental triggers have been defined (46). The immunopathogenesis of noncaseating epithelioid granuloma, the hallmark of sarcoidosis, is believed to be a three-step event. The first step is lymphocytic alveolitis, a process driven by CD4+ Th1 lymphocytes being activated by antigen presenting cells. The second step is granuloma formation by local proliferation of Th1 lymphocytes, accumulation of macrophages and Langerhans-type cells surrounded by fibroblasts, and collection of more lymphocytes interweaved in bands of collagen. The third step is granuloma resolution.

Head and neck manifestations occur in 10% to 15% of patients, and the various manifestations may be the presenting disorder (48). Cervical adenopathy is present in nearly half of the patients with sarcoidosis. The typical yellow submucosal nodules or polyps of sarcoidosis may deposit anywhere in the upper respiratory tract. In the larynx, they usually deposit in the supraglottic larynx. Dysphonia, dyspnea, and dysphagia are the usual symptoms. Pathognomonic of laryngeal sarcoid is a diffusely enlarged, pale-pink, turban-like epiglottis. Lesions in the orbit include orbital masses, lacrimal swelling, and uveitis. Parotid swelling occurs in approximately 6% of patients, with or without facial nerve involvement. Parotitis, uveitis, facial paralysis, and fever are known as Heerfordt disease or uveoparotid fever. Sinonasal tract symptoms include nasal obstruction, edema, epistaxis, crusting, and nasal mass (49). Additionally, epiphora from lacrimal obstruction and anosmia have been described. Lupus pernio describes a purplish rash involving primarily the nose and cheeks, and it is a poor prognostic sign. Otologic involvement is rare, but sarcoidosis can involve structures of the ear. Middle ear dysfunction is usually due to eustachian tube involvement. Sensorineural hearing loss has been reported, likely due to meningeal inflammation, and tonsillar, pharyngeal, and cranial nerve involvement are other reported head and neck manifestations.

The natural history of the disease is variable. Most patients regress spontaneously (60%) or with corticosteroid treatment (20%); the severity of the disease can wax and wane, yet some succumb to the disease, particularly the pulmonary, CNS, and cardiac manifestations. Negative prognostic factors include age older than 40 years, chronic uveitis, nasal mucosal involvement, hypercalcemia, nephrocalcinosis, decline in pulmonary function, and cardiac and CNS involvement. Other negative prognostic factors include chronic disease (more than 2 years of systemic disease) and chest radiograph findings beyond hilar adenopathy (46). In the United States, the prognosis for those of African descent is worse than that for whites. In Japan, the patients die of cardiac sarcoidosis, whereas in United States pulmonary disease is the number one cause of mortality. Treatment is the use of oral corticosteroids, which improve pulmonary function and radiographic appearance, yet this treatment does not change long-term disease progression. Thus corticosteroid treatment is used sparingly to avoid long-term side effects. Steroid-sparing effect was showed with methotrexate and chloroquine. A relatively recent phase II trial demonstrated mild improvement in pulmonary function tests in patients treated with infliximab (50).

Gout

The arthritis of gout is episodic, self-limited, usually monoarticular, and a result of monosodium urate crystals deposition in and around the tissues of joints usually in association with hyperuricemia, a common metabolic abnormality. Definitive diagnosis is by microscopic examination in either joint fluid or a tophus that reveals negatively birefringent monosodium urate needles. According to the Third National Health and Nutrition Examination Survey, the prevalence of gout is 2.7 cases per 100 and rises to 9% in men older than 80 years (51). Head and neck involvement, although rare, usually is manifest as gouty arthritis or tophaceous deposits. The most common site of gouty arthritis in the head and neck is the cricoarytenoid joint that, depending on the position of fixation, produces pain, dysphagia, hoarseness, aspiration, stridor, and possible airway compromise. Tophi in the head and neck are usually painless and classically involve the helical rim of the pinna. Treatment of gout involves two major considerations: (a) treatment of acute attacks and (b) prophylaxis to prevent flares and long-term sequelae, such as chronic tophaceous gout. In the absence of contraindication, nonsteroidal anti-inflammatory drugs are the first-line therapy for acute attacks, although more often than not corticosteroids, regional or systemic, are necessary to control the attack. Colchicine in low dose (0.6 mg daily or BID) is an appropriate treatment for prophylaxis of recurrent attacks. Uric acid lowering therapy should be initiated only after total resolution of the acute inflammatory phase. Otherwise, it can worsen acute gout by mobilizing urate crystal from tophi. Allopurinol (most popular) and febuxostate (newer) are two commonly used urate lowering therapy.

Infectious Diseases

Bacterial Infections

Cat-Scratch Disease and Bacillary Angiomatosis

Although cat-scratch disease and bacillary angiomatosis are caused by the bacteria *Bartonella henselae* (belonging to the Rickettsiaceae family), they are associated with different histopathologic lesions and clinical pictures. *B. henselae* can be recovered from about 50% of cats, which may serve as the reservoir. This agent is an intracellular, pleomorphic, gram-negative bacterium, turning black or dark brown on the Warthin-Starry silver stain.

Cat-scratch fever is generally a self-limited regional disease, often seen in children. Fifty percent of patients first present with axillary, cervical, or submandibular lymphadenopathy that usually involve only one lymph node with erythema of the overlying skin. A mild fever is common. Fifty-five to ninety-four percent of patients exhibit a cutaneous lesion at the site of inoculation by a cat scratch or bite 3 to 14 days after exposure. A less common presentation occurs after conjunctival inoculation, causing Parinaud oculoglandular syndrome (red, tender, inflamed eye, possible conjunctival nodules, fever, and a preauricular lymphadenopathy). Uncommonly, the disease is complicated by liver, spleen, bone marrow, or lower respiratory involvement. CNS complications, including neuroretinitis, can also occur but are generally self-limiting. Approximately 25,000 cases of cat-scratch disease are diagnosed per year and are seen in the United States. Diagnosis is based on a history of cat exposure, the presence of a primary inoculation site, regional adenopathy, and histologic features of cat scratch (supportive and necrotizing granulomatous lymphadenitis with stellate microabscesses) in an excisional biopsy. Warthin-Starry silver staining of the tissue may reveal intracellular bacilli. Two types of serologic tests are available, indirect fluorescence assay and enzyme immunosorbent assay. Titers greater than 256 (titer is the reciprocal of the dilution) are highly suggestive of an active infection. Lower titers can be associated with false-positive results due to cross reactivity with other *Bartonella* species. Culturing the organism from tissue samples remains very difficult. Some centers use DNA detection of the organism after polymerase chain reaction (PCR) signal amplification for diagnosis.

Treatment is supportive, with incision and drainage reserved for abscesses that form in 5% to 10% of patients. Azithromycin is usually used as a 5-day therapy, but disappearance of the lymphadenopathy within 1 to 2 months is expected regardless of therapy. Rifampin and trimethoprim–sulfamethoxazole are often used as an alternative therapy.

Bacillary angiomatosis occurs predominantly in patients infected by the HIV. This disease presents as vascular

cutaneous papules and subcutaneous nodules or masses. Bacillary angiomatosis can involve other organs, causing hepatic peliosis, splenitis, osteomyelitis, and bacteremia. The clinical lesions can be confused with Kaposi sarcoma.

Bacillary angiomatosis may involve the mucous membranes of the nose, oral cavity, pharynx, larynx, bronchi, or conjunctiva. The causative agent is believed to be *B. henselae* and, to a lesser degree, *Bartonella quintana*. The disease caused by *B. henselae* is associated with exposure to cats and cat fleas, whereas the *B. quintana* cases are associated with louse exposure, poverty, and homelessness. The histopathology of bacillary angiomatosis is somewhat different from that of cat-scratch disease. In bacillary angiomatosis, lesions show ectatic vessels lined by plump, cuboidal endothelial cells that may show marked pleomorphism and mitotic activity that may be confused with malignancy. The organisms are best observed within the lesion Warthin-Starry or Grocott methenamine silver staining (52). The lesions respond well to erythromycin, clarithromycin, or doxycycline; rifampin is added for CNS involvement and life-threatening situations. If untreated, this disease is progressive and can prove fatal.

Brucellosis

Brucellosis (undulant fever, Mediterranean fever, Malta fever) is caused by an aerobic gram-negative coccobacillus. It is a zoonotic disease transmitted to humans from infected cattle, pigs, goats, elk, and bison, or from their dairy products. In the United States, most reported cases are due to ingestion of unpasteurized goat milk products from Mexico, or occupational exposure to infected animals. After exposure, the *Brucella* sp. bacteria enter the lymphatic system and replicate intracellularly in regional lymph nodes before disseminating hematogenously. The bacteria proliferate in the reticuloendothelial system and cause noncaseating granulomas in the involved tissues. Fatigue, sweating, chills, malaise, headache, backache, and arthralgia are common ailments, and this disease should be considered in the diagnosis of fever of unknown origin. Diagnosis is based on exposure history and serology using ELISA or agglutination tests. Newer PCR techniques are very sensitive, but culture of the organism remains the gold standard. The microbiology laboratory must be notified because long incubation periods are required (53). Doxycycline and rifampin for 6 weeks or doxycycline with 2 weeks of streptomycin/gentamicin are the treatments of choice (54). It is important to monitor patients closely after treatment completion as up to 10% of them will relapse.

Rhinoscleroma

Rhinoscleroma, sometimes called as "Balkan leprosy," is caused by *Klebsiella rhinoscleromatis*, a gram-negative bacterium. This disease is uncommon in the United States but is seen in the Middle East, Latin America, and Eastern Europe. It usually involves the nose and paranasal sinuses, but the larynx, ear, trachea, and bronchi can also be involved (55). The natural course of the disease is progression through three stages: catarrhal or atrophic, characterized by purulent rhinorrhea and mucosal crusting; granulomatous or hypertrophic, characterized by nasal mucosal granuloma and hyperplasia with bleeding and cartilage destruction; and fibrotic, which leads to nasal, laryngeal, and tracheobronchial tree stenosis. Diagnosis is based on finding the characteristic "honeycomb-color" crusting in the nose of patients, history of travel to endemic countries, and culturing of the organism; although only 50% of lesions will be culture positive (56).

Histologically, the submucosa demonstrates mixed inflammation, including characteristic Mikulicz cells (histiocytes with clear to foamy cytoplasm) during the granulomatous stage, when diagnosis is usually made. If numerous, the bacteria can be seen by hemalum-eosin staining, but a tissue Gram stain (e.g., Brown-Brenn) or a silver stain may be required to confirm the diagnosis. Long-term tetracycline is the standard treatment and occasionally surgical intervention is warranted for laryngeal obstruction during the florid or fibrotic stage.

Tuberculosis

Members of the genus *Mycobacterium* are a group of aerobic, nonsporulating, bacteria that are slow growing and have high cell-wall lipid content that makes them acid-fast on staining. *Mycobacterium tuberculosis* causes the vast majority of human tuberculosis. Tuberculosis is the second leading cause of infectious death in the world, leading to 2 million deaths per year. Up to one-third of the world's population is infected, and 9 million new cases occur annually (57). In the United States, the incidence has fallen every year since 1993. In 2009, 11,545 cases were reported, with a risk 11-fold higher in the foreign-born citizens compared to US-born individuals. Eighty percent of these cases were pulmonary. This disease is most frequent in geographic and demographic groups where AIDS is prevalent, notably among inner city African-American and Hispanic males between 25 and 45 years of age. An estimated 11% of the tuberculosis patients in the United States are coinfected with HIV. *Mycobacterium tuberculosis* is generally transmitted by inhalation of airborne droplets, which can remain aerosolized for hours. Other modes of transmission are rare. Tuberculosis is relatively rare in the head and neck. About 5.6% of people in the United States are tuberculin (partial-purified derivative—PPD) skin test positive, suggesting exposure to the bacteria. Almost 90% of these patients are asymptomatic, but the disease may develop at any time during their lives if left untreated. In many of these cases, the bacteria lie dormant in small numbers, unless the person becomes immunocompromised. This population represents the natural reservoir for the disease.

The pathogenesis is highly variable, and latency from exposure to clinical symptoms can be long. Initial pulmonary infections occur largely unchecked after inhalation until cell-mediated immunity is established from

3 to 9 weeks. At this point, the tuberculin skin test becomes positive, and the bacteria may have spread both regionally to lymph nodes and systemically. Granuloma formation results from the cell-mediated response to the infected loci and the original pulmonary lesion (Ghon focus) often heals. Reactivation later occurs in approximately 10% of these patients, mostly during the 1st year after exposure and often because of a reduction in host immunity. Infectivity is greatest in patients with positive sputum samples, lung cavitary disease, or tuberculosis of the larynx. Health care workers should be aware of the occupational risk of exposure; early identification of infected individuals is necessary for appropriate isolation precautions to be implemented.

A PPD skin test is considered positive if it causes a 15 mm or larger induration in normal hosts, a 10 mm or larger induration in high-prevalence groups (inmates, homeless, recent immigrants, etc.), and a 5 mm or larger induration in HIV-positive individuals, organ transplant recipients, or other groups of patients with defects of cell-mediated immunity. Unless a patient has been treated, a positive PPD test implies the presence of a few viable bacilli and the potential for reactivation. In addition to tuberculin skin testing, the diagnosis of latent tuberculosis can now also be made with one of two *in vitro* assays; the QuantiFERON-TB Gold In-Tube and the T-Spot.TB assays. These assays use the patient's whole blood and measure the lymphocytes release of interferon gamma in response to tuberculosis antigens. They are specific and sensitive, avoid the need for a follow up visit, and notably are not affected by BCG vaccination, but they are expensive (58).

Fine-needle aspiration cytology is useful in evaluating tuberculous lymphadenitis, but this technique has limitations, particularly when acid-fast bacilli cannot be found on smears. Nucleic acid amplification can identify mycobacterial DNA or RNA from specimens, particularly sputum, but also from tissue aspirates, with better sensitivity and specificity than direct microscopy (59). These tests take approximately 6 hours. All patient specimens should be sent for mycobacterial culture. Culture takes longer than a nucleic assay to give a result, but it is essential for drug susceptibility testing, especially with the rising multidrug resistant tuberculosis cases.

Tuberculosis has many different manifestations, which may include constitutional symptoms. Cervical lymphadenopathy is the most common form of head and neck involvement. Nodes are multiple, matted, bilateral, firm, and generally nontender. They frequently involve the posterior triangle and supraclavicular area. If a nonanergic patient with cervical lymphadenitis has a negative PPD test, tuberculosis is unlikely because 98% of patients with cervical lymphadenitis due to tuberculosis have a positive skin test. Fine-needle aspiration is helpful in reaching a diagnosis. A chest radiograph should always be obtained, and a neck computed tomography (CT) scan and ultrasound should be considered. CT findings include a multiloculated low-density nodal mass with enhancing rims and normal fascial planes. The walls of the nodal mass also are thicker than those found in malignant disease. As necrotic caseation and suppuration continue the ultrasound image changes to a low echogenic mass with nonhomogeneity and with further progression, abscess formation spreads into adjacent subcutaneous tissues. Excisional biopsy should also be considered and will reveal the characteristic granulomas (Fig. 17.5). The most common laryngeal symptom is hoarseness, but odynophagia, dysphagia, and stridor are not uncommon. A high index of suspicion must be maintained for laryngeal tuberculosis in patients infected with HIV. Before the antibiotic era, laryngeal involvement was common, but now it is rare and seen in less than 1% of all tuberculosis cases. In these patients, lesions can be seen throughout the larynx and can vary in appearance such as edema, hyperemia, nodularity, ulcerations, and obliteration of anatomic landmarks. Specifically, the epiglottis can be markedly edematous (turban-shaped), and can resemble polypoid corditis. Exophytic lesions can often be mistaken for laryngeal carcinoma.

Otologic involvement begins with granulomas appearing as thickened hyperemic spots on the tympanic membrane, which coalesce to form multiple perforations. These perforations painlessly drain a thin watery discharge. Granulation tissue then increases, with the discharge becoming thick and cheesy, often because of pyogenic bacterial superinfection. Mastoiditis may ensue, with intracranial extension. Mastoid imaging typically does not show bony destruction and sclerosis as the process is relatively acute. Generally, examination reveals middle ear granulation with erosion of the ossicles. Postauricular fistula may occur, and preauricular adenopathy is common (60). Mastoidectomy should be reserved for concurrent mastoiditis.

Other head and neck sites can be involved. Nasal infection is manifested by obstruction and rhinorrhea. Mucosal

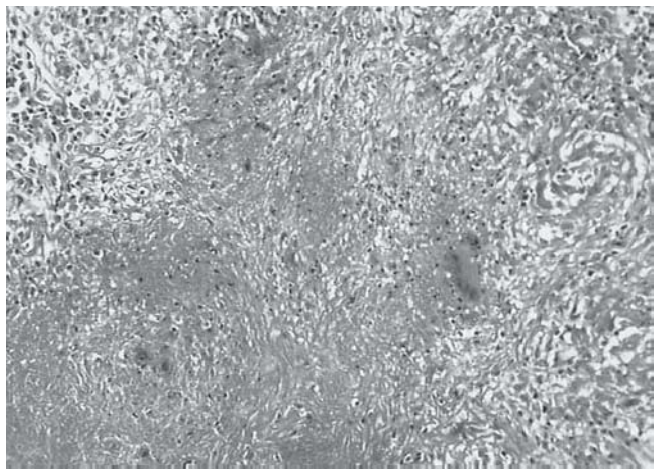


Figure 17.5 Tuberculosis. Lymph node reveals necrosis surrounded by Langerhans giant cells, epithelioid histiocytes, and lymphocytes (hematoxylin and eosin stain; original magnification, 310×).

granulomas are seen, and septal perforation can occur. Tuberculosis can cause oral ulceration. Nasopharyngeal and oropharyngeal tonsillar tissue may be infected, and salivary glands may become involved (62).

Treatment for tuberculosis is directed by organ site involved, culture, and drug susceptibility. Patients with suspected or confirmed pulmonary or laryngeal tuberculosis must be placed in respiratory isolation until no longer infectious. There are currently four recommended regimens for patients with confirmed or suspected tuberculosis. The usual first option is a four drug daily regimen of isoniazid, rifampin, pyrazinamide, and ethambutol for the first 2 months (the intensive phase). A repeat smear and culture at the end of the intensive phase of treatment will determine the regime used in the continuation phase of treatment, which is usually a 4-month course of isoniazid and rifampin. In certain cases, the treatment could be extended to a total of 9 months (61). The current incidence of resistance to at least one drug in the United States is 12%, and 1% for multidrug resistance (resistance to at least isoniazid and rifampin). This makes following cultures and susceptibility testing important to make sure that the usual drug combinations are effective. All tuberculosis cases should be reported to the local public health department, and patients with tuberculosis should be tested for HIV (62). Lymph node excisions *en bloc* may be necessary for fluctuant or chronically draining nodes.

Nontuberculous Mycobacteria

Nontuberculous mycobacteria are usually less virulent than *M. tuberculosis*; however, they also are less responsive to standard antituberculous drugs. They are generally free living, ubiquitous organisms in the environment, and can colonize the upper respiratory tract making repeated positive cultures more significant than a single culture. The usual routes of transmission are from soil to the oral cavity, the respiratory tract, or the eye. Incubation periods are long, up to 5 years. The prevalence and virulence of nontuberculous mycobacterial disease, especially the *Mycobacterium avium-intracellulare* complex (MAC), have increased in the HIV population in whom these pathogens are considered opportunistic. In AIDS patients with low CD4 lymphocyte counts, the disease can become systemic. Oral ulcerative lesions, fever, and weight loss are common features of disseminated disease. *Mycobacterium kansasii* is the second most common atypical mycobacteria affecting the pulmonary system especially in the elderly, and is often recovered from tap water.

Mycobacterium scrofulaceum most often cause lymphadenitis (scrofula) in children younger than 6 years. The lymphadenopathy is most commonly cervical, predominantly in the preauricular, submandibular, or anterior cervical areas. Enlargement is slow, and eventually the skin becomes involved, and a draining tract develops. Scrofula in children also can be commonly caused by MAC (more than 80%) and less commonly by *M. kansasii*. Tuberculosis itself as a cause for cervical lymphadenopathy is rare (less than 10%) in the United States. Nontuberculous mycobacteria like *Mycobacterium fortuitum*, *Mycobacterium abscessus*, and *MAC* are rare causes of parotitis and mastoiditis, with a presentation similar to that of tuberculous mastoiditis, including chronic painless otorrhea, and exuberant middle ear granulation tissue.

Diagnosis is usually by culture and sensitivity testing of a biopsy specimen; typical detection of growth in cultures takes about 2 weeks, but identification of the species can take up to 4 weeks. Acid-fast staining may provide a presumptive diagnosis before positive culture results are available. Susceptibility testing is strongly desirable, but developing standard techniques have been difficult and unreliable. The use of nucleic acid probes and the PCR are becoming more common for both the rapid identification of mycobacterial species and the identification of drug-resistant strains. These novel techniques may shorten laboratory diagnostic time to days. Furthermore, a positive culture is seen only in about 50% of patients with scrofula, so a high index of suspicion is necessary for diagnosing a child with a pathologic diagnosis of granulomatous inflammation. A PPD test is often weakly positive (induration ranging from 5 to 12 mm).

Pediatric patients with scrofula are treated by excisional biopsy when the nodes involved can be safely resected. Complete resection is usually curative and preferable because the time course of the disease is shortened (63). For fluctuant lesions, lesions with severe skin necrosis, and lesions close to the facial nerve or other critical structures, excisional surgery may have an unacceptable risk of complication. Conservative treatment with combination antimycobacterial drugs and wound care may be preferred. MAC infections with or without HIV is often treated with clarithromycin, rifabutin, and ethambutol. Even without treatment, localized disease will resolve, but the usual course of illness is long, and may result in undesirable scarring (64). Incision and drainage or multiple biopsies are contraindicated. Nontuberculous mastoiditis should be treated with mastoidectomy as they are less responsive to antibiotics.

Leprosy

Leprosy (Hansen disease) is still a worldwide problem, but less than 100 cases per year are reported in the United States, mostly in immigrants. The mode of transmission of leprosy is still unclear but is thought to be through a respiratory route. Cutaneous transmission appears to require prolonged contact to open lepromatous wounds. Leprosy is caused by *Mycobacterium leprae*, an acid-fast bacillus, which is an obligate intracellular parasite. Table 17.6 lists the common manifestations of leprosy (65). The bacteria are thermolabile, growing optimally between 27°C and 33°C, and divide slowly; thus the disease evolves slowly and involves primarily cooler peripheral tissues such as in the fingers, nose, testicles, feet, and earlobes. It leads to loss of peripheral sensation

TABLE 17.6 COMMON MANIFESTATIONS OF LEPROSY (65)

Hypopigmented or erythematous macules
Tuberculoid skin and nerve involvement with muscle wasting and anesthesia
Anesthetic plaques
Nerve thickening in the plaque vicinity
Mucosal nodules in the mouth and nose that ulcerate (especially anterior inferior turbinate)
Keratitis
Laryngeal ulcerations
Lymphadenopathy
Hyposmia
Atrophy of the anterior maxillary spine and maxillary alveolar process
Nasal collapse
Fish-mouth deformity
Facial nerve paralysis
Eyebrow and eyelash loss

and eventually traumatic mutilation. Early skin lesions vary from hypopigmented to erythematous macules with well-defined margins. Biopsy of the lesions is required to make the diagnosis. Involvement of the nasal cavity and paranasal sinuses may manifest before the clinical skin lesions (56). The Ridley-Jopling classification identifies different forms of the disease that are important to recognize for treatment purposes. They range from the tuberculoid form characterized by a few anesthetic, well-delineated macules or plaques and common peripheral nerve involvement to the lepromatous form with multiple nonanesthetic, symmetrical macules or papules, and neurologic involvement only late in the disease. The tuberculoid form is associated with a strong local T cell reaction that causes a positive lepromin skin test, and a low bacillary density. In contrast, the lepromatous form is characterized by a negative skin test and a heavy bacillary load. This latter form is associated with damage to various end organs, which for some of them can be the result of an immune complex–mediated reaction called erythema nodosum leprosum. Eye involvement causes pain, photophobias, glaucoma, and blindness. Laryngeal involvement results in stridor and hoarseness. The characteristic saddle-nose deformity is seen with involvement of nasal cartilages. Nasal congestion and epistaxis are common. PCR diagnostic techniques can be run on nasal smears, skin biopsy and blood specimens. Depending on the severity and type of disease dapsone alone or in combination with clofazimine and rifampin are used for a long duration.

Actinomycosis and Nocardia

Actinomycosis is a granulomatous infection caused by anaerobic or microaerophilic gram-positive filamentous bacteria called *Actinomyces* species. At least 30 different species have been described with *Actinomyces israelli* being the most common cause of human disease. *Actinomyces naeslundii*, *Actinomyces odontolyticus*, *Actinomyces meyeri*, and *Propionibacterium propionicum* are seen as well. Infection may follow dental manipulation, trauma, or gingival infection in patients with poor oral hygiene. Bacterial growth is facilitated by the presence of necrotic tissue and a foreign body. The three commonly described clinical forms are cervicofacial, thoracic, and abdominopelvic with about 50% of all actinomycosis being cervicofacial. Actinomycosis may occur virtually anywhere in the head and neck and has been described in the sinuses, mastoid, major salivary glands, and thyroid (66). Sixty-one percent of patients with cervicofacial infection have visible sinus tracts, and 40% have lymphadenopathy. Concurrent dental, sinus, and perimandibular disease is common, with or without pain and fever. The course of actinomycosis is typically indolent but progressive. Symptoms are often present for months before diagnosis is made or erroneously attributed to tuberculosis or cancer. Actinomycosis may also present as an acute suppurative infection with rapid progression to abscess formation. A suggestive purplish discoloration of the overlying skin may be seen in some patients. The infection does not respect fascial planes. Granuloma formation and frank suppuration of the larynx have also been reported with cicatricial scarring as noticeable possible long-term sequelae.

"Sulfur granules" are usually seen in exudates or on histologic examination, although this finding is not present in every case (Fig. 17.6). These granules are concretions of the organisms and neutrophils. They are hard, yellow particles measuring about 0.1 to 5 mm in diameter. Diagnosis is confirmed by culture incubated for 1 to 2 weeks in thioglycollate broth in a microaerophilic environment. On smear, Actinomyces are branching, filamentous organisms and should be differentiated from fungal hyphae, which are much thicker and less delicate (56).

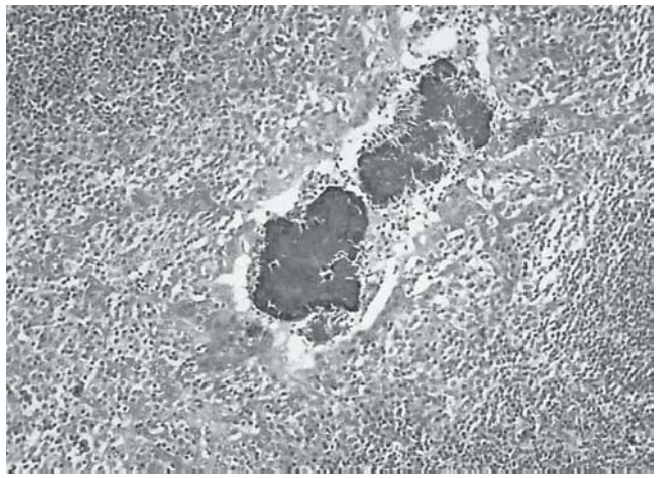


Figure 17.6 Actinomycosis. Tonsil exhibits colonies of *Actinomyces* organisms in the crypts (hematoxylin and eosin stain; original magnification, 310×).

The genus *Nocardia* includes more than 80 species. It is a member of the family Actinomycetaceae and shares morphologic features with *Actinomyces*. *Nocardia* spp. are opportunistic pathogens most commonly causing pulmonary disease in an immunocompromised host, although about 33% could be immunocompetent. It is not a part of the normal flora. The most common route of transmission is inhalational but, cutaneous *Nocardia* infection can be seen after trauma to the skin. This disease can appear as a localized pustule, cellulitis, abscess, or mycetoma. Actinomycetoma, usually caused by *Nocardia brasiliensis* are localized, chronic, indolent lesions that can grow quite large if untreated and should be differentiated from eumycetoma which are caused by fungi (67). The granules in a *Nocardia* actinomycetoma are white, in contrast to the yellow "sulfur granules" of actinomycosis.

Treatment of actinomycosis is by surgical debridement plus aqueous penicillin G administered intravenously for 2 to 6 weeks followed by 6 to 12 months of oral penicillin. Penicillin-allergic patients respond well to tetracycline or clindamycin. Wide excision is not required. Nocardia is treated by trimethoprim–sulfamethoxazole or imipenem but susceptibility testing should be requested as different species have variable resistance patterns.

Syphilis

Syphilis is a sexually transmitted disease caused by the spirochete *Treponema pallidum* and is reportable in the United States. On the decline since 1990, the disease incidence rebounded since the past decade, especially in the young men who have sex with men population. There were 11,181 reported cases in 2007. The disease passes through three stages. The primary stage is characterized by the development, typically on an average of 3 weeks after exposure (range 10 to 90 days) of a small red papule that gradually enlarges and evolves into a painless ulceration with indurated edges, the syphilitic chancre. Secondary syphilis develops about 4 to 10 weeks after the primary lesion. Patients often complain of malaise, fever, myalgias, and arthralgias. Lymphadenopathy and a maculopapular rash, especially on the palms and soles, can be seen (56).

An asymptomatic stage known as the latent phase, which can last up to 30 years, is characterized by a positive serologic reaction. The 1st year of the secondary stage is called early latent, and subsequently is the late latent phase. In about a third of patients, the latent stage can evolve into the tertiary stage of the disease with three main presentations: gummas, late neurosyphilis, and cardiovascular disease. Gummas are inflammatory granulomas characterized by an *intervening zone* containing epithelioid cells with indistinct borders and multinucleated giant cells, and a *peripheral zone* of fibroblasts and capillaries. They appear as soft masses that usually develop in the skin, bones, and liver on average 15 years (range 1 year to more than 40 years) after the initial infection; any organ can be affected. General paresis, a peculiar form of psychosis, and tabes are now very rare, but are classic manifestations of neurosyphilis. Aortitis is the characteristic form of cardiovascular syphilis. A devastating congenital form can be seen as a result of transplacental transfer. The multiple manifestations in the head and neck depend on the stage of the disease (68).

Syphilis is associated with otologic disease. Sensorineural hearing loss from either congenital or tertiary syphilis accompanied by fluctuating tinnitus and vertigo is termed otosyphilis. The exact pathologic mechanism is not known. The hearing loss starts in the high frequencies but can progress to bilateral profound deafness, with absent vestibular function. Screening patients with sensorineural hearing loss for syphilis is controversial. Although the yield is low, the potential reward is high because syphilis is a treatable cause of sensorineural hearing loss. Even though the spinal fluid is seldom positive for syphilis, often patients with otosyphilis are treated as neurosyphilis patients. In one study, 83% of treated patients preserved their hearing (69). Involvement of the middle ear with destruction of the ossicles can occur. The development of nystagmus upon the application of pressure to a sealed external auditory canal (Hennebert sign) suggests the presence of a fistula in patients with syphilis, presumably from fibrosis between the stapes footplate and the membranous labyrinth.

Mucosal head and neck structures also can be involved. Chancre formation in the oral cavity results from primary inoculation. Lesions of secondary syphilis can present as mucosal erosions on the nasal cavity, tongue and lips, hairy leukoplakia, oral lichen planus, or oral erythema multiforme. Gummas can be located in the oral cavity, pharynx, or larynx. Congenital syphilis can cause otosyphilis and radial scars (rhagades) of the tongue, palate, and lips. Nasal discharge is an early sign of congenital syphilis, while "Hutchinson teeth," which are notched, lack enamel, and are underdeveloped, occur in late congenital syphilis.

The diagnosis of syphilis is established by either direct visualization of the spirochete or more commonly by serology testing, as the organism does not grow in culture. Dark-field examination of tissue from lesions of primary, secondary, or tertiary syphilis demonstrates thin, delicate, corkscrew-shaped organisms but this study is only performed in a few laboratories now. Histologic examination, although not pathognomonic for syphilis, reveals a dense chronic inflammatory infiltrate with an abundance of plasma cells (Fig. 17.7). Early nodular lesions of tertiary syphilis can have minimal necrosis and sparse plasma cells with granulomas thus mimicking tuberculosis, sarcoidosis, or a deep mycosis (70). Two types of test are used for the serologic diagnosis of syphilis, nontreponemal tests such as the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR), and treponemal tests like the fluorescent treponemal antibody absorbed test, the *T. pallidum* passive particle agglutination assay, and various enzyme immunoassays. Due to their high sensitivity, the nontreponemal tests are used as primary screening tests; the RPR on serum and the VDRL on cerebrospinal fluid

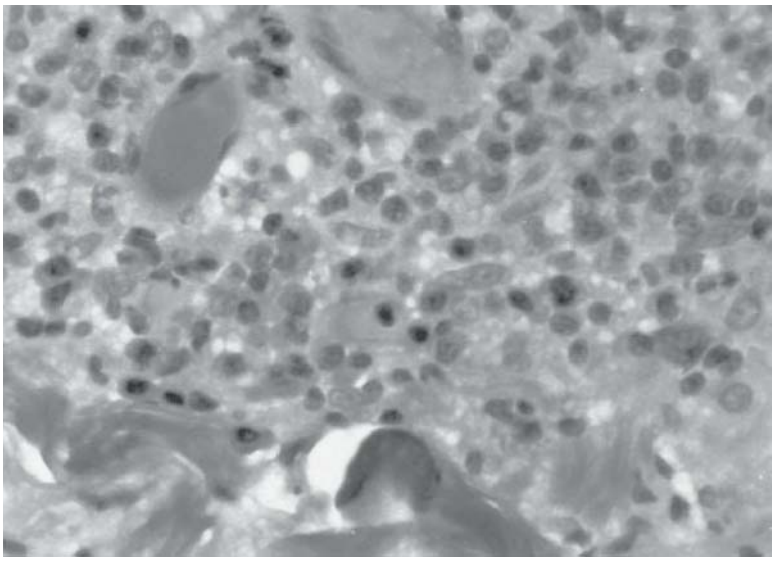


Figure 17.7 Syphilis. The skin of the neck shows typical, chronic, dense inflammatory infiltrate with abundant plasma cells (hematoxylin and eosin stain; original magnification, 340×).

(CSF). Because they usually correlate with disease activity, the results are reported quantitatively. However, many conditions can result in false-positive reactions, and a positive result needs to be confirmed with a treponemal test, which offers greater specificity. The magnitude of the seroreactivity with the nontreponemal tests tends to decrease or even disappear after treatment, while treponemal tests remain positive for the remainder of the patient's life in most instances (71). Clinical signs of neurosyphilis (i.e., cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, loss of vibration sense, and auditory or ophthalmic abnormalities) warrant further investigation and treatment. Laboratory testing is helpful in supporting the diagnosis of neurosyphilis; however, no single test can be used to diagnose neurosyphilis in all instances. CSF laboratory abnormalities are common in persons with early syphilis.

Benzathine penicillin given intramuscularly is the treatment of choice and curative in a single dose for the primary disease and early latent syphilis. Three weekly injections are recommended for the treatment of late latent syphilis or latent syphilis of unknown duration. Tertiary syphilis such as otosyphilis and neurosyphilis requires 10 to 14 days of IV penicillin. Steroids are used for improvement of hearing and reduction of vestibular symptoms. However, treatment differs for each stage and consideration should be given to sexual partner management (71). All positive cases should be reported to the state health department.

Tularemia

Tularemia is a rare disease caused by the gram-negative pleomorphic rod, *Francisella tularensis*. It is a complicated, highly virulent zoonotic agent. The natural reservoirs include hundreds of animals; especially important in human disease are ticks, cats, rabbits, and deer. Infection is due to direct inoculation by contamination of a wound or ingestion of uncooked meat or an arthropod bite. After an incubation period of 2 to 10 days, the patient exhibits severe illness with fever, chills, headache, and myalgia. Almost 60% to 80% have ulceroglandular disease. Isolated lymphadenopathy may be present in 3% to 15%. One distinct form of the disease is oropharyngeal tularemia due to ingestion of animal meat or contaminated water (72). These patients have fever, exudative pharyngitis, and cervical adenopathy. Diagnosis is confirmed with a serum agglutination test or ELISA tests to detect antibodies to the organism. A titer of 1:160 or higher is supportive of the diagnosis and patients are treated with a short course of streptomycin or gentamicin.

Fungal Infections

Histoplasmosis

Histoplasma capsulatum, a dimorphic fungus, is the causative organism of histoplasmosis. This entity most commonly occurs in the Ohio and Mississippi River valleys. It is spread by airborne particulate dissemination of soil contaminated with bird or bat guano, which supports luxurious growth of this mold. Pulmonary histoplasmosis may present as acute pneumonitis with mediastinal lymphadenopathy or a chronic cavitary infection. Progressive disseminated forms may involve the heart and CNS. Most infections are subclinical and have benign clinical courses. In endemic areas, by adulthood almost 80% have had this disease. However, infants, elderly or those who are immunocompromised (e.g., HIV infection) can often have the progressive disseminated form, which consists of granulomatous lesions spread throughout the body. Head and neck mucosal sites, including the lips, gingiva, tongue, pharynx, and larynx, are involved in 25% of disseminated cases (73). These lesions show firm, slowly enlarging, painful ulcers with heaped-up edges or a verrucous appearance and sometimes mimic carcinoma or tuberculosis. Sore throat, painful mastication, hoarseness, gingival irritation, dysphagia, and weight loss may

result. Granulomatous mediastinitis is characterized by massive enlargement of multiple lymph nodes that are often matted together and undergo caseation and necrosis. Diagnosis is facilitated by two types of tests, the detection by enzyme immunoassay of *Histoplasma* antigens in the urine, and the detection of specific serum antibodies by complement fixation and by immunodiffusion. The pathology often shows lymphohistiocytic aggregates and diffuse mononuclear cell aggregates forming granulomas. Methenamine silver or periodic acid-Schiff staining best demonstrates the ovoid shape yeast phase of the organism with narrow based budding. The culture of a swabbing of an ulcer centers or any tissue sample after 4 to 6 weeks of incubation will grow the mycelial phase of the fungus. Itraconazole is the usual treatment of choice for mild disease and the severe and CNS forms are treated with liposomal amphotericin B (74).

Blastomycosis

The causative organism of blastomycosis is the dimorphic fungus *Blastomyces dermatitidis*, which is contracted by inhaling the conidia of the organism disseminated in soil dust, or sometimes present in the home (attic, basement). Fungal reproduction of the yeast form occurs in the lungs and can cause an acute or a chronic form. Direct inoculation is a rare mechanism of infection. The endemic area for blastomycosis includes the entire central United States from the Gulf Coast to the Canadian border and extends into the southern parts of Manitoba, Saskatchewan, and Alberta. Manifestations range from the patient being asymptomatic to having acute pneumonitis with disseminated infection involving the skin, bones, and genitourinary system (esp., prostate, epididymis, and testes). Skin lesions exhibit proliferative verrucous growth with scarring. A common triad consists of cutaneous disease, pulmonary involvement, and constitutional symptoms. The face and extremities are common sites for skin lesions. Subcutaneous nodules are cold abscesses in the disseminated form. Oropharyngeal and laryngeal involvement is much less common than in histoplasmosis, although case reports of blastomycosis involving multiple sites in the head and neck such as the larynx, parotids, and paranasal sinuses can be found. The diagnosis of pulmonary blastomycosis is confirmed by sputum culture and microscopic examination of skin scrapings or biopsy of other involved sites. Unlike *Candida* and *Aspergillus* species, colonization does not occur with this fungus and hence visualizing this fungus is diagnostic of an infection. It grows well within 1 to 4 weeks. On a tissue methenamine silver stain, it appears as thick walled budding yeast with a broad base. Urine and serum antigen detection tests are sensitive and appear to correlate with disease activity and/or recurrence (75). Itraconazole is the treatment of choice for most cases of blastomycosis. Amphotericin B is reserved for immunosuppressed patients or CNS involvement (76).

Coccidioidomycosis

Coccidioides immitis, the agent of coccidioidomycosis, is a fungus endemic in southern Arizona, southern and central valley of California, southwestern New Mexico, west Texas and parts of Central and South America. As with histoplasmosis, most residents in endemic areas become infected as children. The disease is contracted by inhalation of the arthroconidia. In the lungs, the arthroconidia changes to a spherule which enlarges over time, matures and eventually ruptures releasing endospores, which can lead to hematogenous dissemination (77). A subacute illness known as Valley fever is seen with respiratory and systemic involvement, often lasting for weeks to months. Manifestations in the head and neck are rare but most commonly, as a result of dissemination, involve the skin, where lesions are first seen as nodules or erosions and can form draining sinus tracts. The mucous membranes, thyroid, eyes, orbit, trachea, temporal bones, facial skeleton, and larynx can also be involved (78). Some of the more severe forms of extrapulmonary infections are meningitis and vertebral osteomyelitis, which can have an acute presentation. Diagnosis is established by histology (the methenamine silver stain is the most sensitive), serology, and culture (the organism may take many weeks to grow). Patients are treated with fluconazole or itraconazole whereas amphotericin B is reserved for severe disease and azole failures (79).

Paracoccidioidomycosis, also called South American blastomycosis, is a disease primarily found in South America with almost 80% of infections occurring in Brazil. This disease is rare in healthy adults but can be serious in immunocompromised patients. The infective agent is the dimorphic fungus *Paracoccidioides brasiliensis*. Head and neck manifestations include the common involvement of the oral mucosa. The oral lesions are generally granulomatous in appearance but can be ulcerated (80), and the larynx also can be involved in the disease. Diagnosis is usually based on visualization of the organism in a biopsy of the involved tissue, culture of enlarged lymph node aspiration or serology. Histologically, the lesions are suppurative granulomas with lymphocytes, epithelioid cells, and giant cells. Azole antifungal agents and amphotericin B are effective treatments.

Parasitic Infections

Leishmaniasis

Leishmaniasis is a disease distributed worldwide, except Antarctica, caused by various species of *Leishmania*, obligate intracellular protozoans belonging to the family of Trypanosomatidae, and divided into subgenera *Leishmania* and *Viannia*. These parasites are transmitted as promastigotes by the bite of female sand flies (genus *Lutzomyia* in the Americas, *Phlebotomus* elsewhere). The promastigote enters mononuclear phagocytes in the skin, and multiplies and transforms in the macrophage cytoplasm into amastigotes. The infection can then remain asymptomatic or progress to one of the three characteristic forms of the disease: visceral

(causing kala-azar in its full blown form), cutaneous (the commonest), and mucocutaneous (about 1% to 5% of primary cutaneous forms can advance to this stage). The patterns of illness in large part depend on the tissue tropism of the particular *Leishmania* species. Lesions are the result of the cell-mediated immune response to the organism in targeted tissues. The cutaneous form most commonly occurs on the extremities, although the head and neck may be affected. Papules that progress to wet or dry ulceration with indurated borders and encrustation are characteristic. Mucocutaneous leishmaniasis, mainly associated with *Leishmania braziliensis* infection is also called espundia. Mucocutaneous leishmaniasis exhibits an initial lesion on the extremities and months to years later due to hematogenous or lymphatic dissemination, new lesions occur on the mucosal surfaces. Progressive inflammation and destruction of the soft tissues of the mouth, nose, pharynx, epiglottis, larynx, and trachea may occur with attendant disfiguration. Ulceration can lead to nasal septal perforation and mucosal bleeds. Internal destruction can be considerably more extensive than the external damages. This form of the disease is seen primarily in South America (81).

Diagnosis of all forms is established by microscopic visualization of the intracellular organism in a biopsy or skin scrapings. The histology findings range from well-formed granulomas with numerous lymphocytes and a few identified amastigotes to an abundance of parasite-containing tissue macrophages and few lymphocytes. The organism can be revealed with Giemsa, hematoxylin-eosin or Wright stain. The organism can also be cultured in special media and newer PCR-based assays are now available (82). Patients traditionally have been treated with pentavalent antimonial (Sb^V) compounds: sodium stibogluconate and meglumine antimonite. Liposomal amphotericin B and pentamidine are alternate agents. Miltefosine has been a promising oral agent. All these drugs can be associated with substantial toxicities. Various azole antifungal agents appear efficacious as well in cutaneous leishmaniasis (83,84).

Myiasis

Myiasis, often seen in a returning traveler, is a condition caused by the infestation by maggots transmitted in Mexico, Central and South Americas by the botfly (*Dermatobia hominis*) and in tropical Africa by the tumbu fly (*Cordylobia anthropophaga*). Myiasis may be nonfuruncular when present in the oropharynx or nasopharynx, or furuncular when in the skin. Patients typically note an insect bite which enlarges to a nodule (1 to 3 cm in diameter) that can be associated to a serosanguineous discharge and a crawling sensation. Diagnosis is made clinically or by microscopic examination. Treatment consists of surgical removal of the entire larva (85).

Toxoplasmosis

Toxoplasma gondii is a widely distributed intracellular protozoan parasite that infects various mammals, including sheep, pigs, cats, rodents, cows, deer, and humans, and causes toxoplasmosis. The cat is the primary host, where sexual reproduction of the parasite occurs. Human infection with *T. gondii* occurs through ingestion of oocyst-containing cat feces or poorly cooked infected lamb or pork. In the human intestine, the sporozoites from the oocysts or the bradyzoites from the tissular cysts are released, and invade various tissues (especially muscles, heart, liver, spleen, lymph nodes, and CNS) where their intracellular reproduction yields tachyzoites that further disseminate throughout the tissues of the body where they eventually form bradyzoites-containing cysts. In the United States, almost 11% of adults have been exposed to this organism. Primary infection is asymptomatic in 80%. Congenital toxoplasmosis can occur from vertical transmission of tachyzoites from an infected mother, while in the immunocompromised host, secondary disease can result from the reactivation of the cysts particularly in the CNS, but also in the lungs and myocardium. This is a feared opportunistic infection in the AIDS population with very low lymphocyte count and is suspected whenever a patient with prior evidence of toxoplasmosis infection presents with multiple nodular or ring-enhancing brain lesions with edema or mass effect. Primary toxoplasmosis most commonly presents as bilateral painless cervical adenopathy. Pharyngitis, rash, fever, fatigue, and hepatosplenomegaly can be seen. The likelihood of transmission and the severity of disease in congenital toxoplasmosis is greater as the pregnancy advances. Although generally normal at birth, the majority of children with congenital toxoplasmosis will have chorioretinitis, hearing loss, and/or developmental delays unless treated. Enzyme immunoassays are essential for the diagnosis of toxoplasmosis. Acute illness is confirmed by anti-*T. gondii* antigens IgM rise in the acute phase and a fourfold increase in IgG 3 to 4 weeks after the acute illness. A past infection, thus the possibility of reactivation, is established by the lifelong presence of specific IgG. A lymph node biopsy will show follicular hyperplasia and irregular clusters of tissue macrophages with eosinophilic cytoplasm. Granulomas and abscesses are not seen and hence it is important to differentiate this illness from acute cytomegalovirus or Epstein-Barr virus infections. Parasite DNA may also be detected by PCR techniques and may be useful in diagnosis in ocular disease. Pyrimethamine, sulfadiazine, and folinic acid is the treatment regimen of choice.

Rhinosporidiosis

Rhinosporidiosis is caused by *Rhinosporidium seeberi*, a protest belonging to the mesomycetozoea family of aquatic parasites. The disease is most prevalent in Southern India and Sri Lanka and causes "strawberry" lesions (pink lesion with whitish specs which are the chitinous walls of *Rhinosporidium* sporangia). In the nose, it produces painless mucosal papules that evolve into large and hyperplastic polypoidal masses, which characteristically bleed on touch. Other mucosal sites involved include the palpebral

conjunctiva, oropharynx, nasopharynx, maxillary antrum, larynx, external ear canal, and the parotid duct. Diagnosis is confirmed by histopathologic demonstration of the characteristic thick-walled giant sporangia containing up to 10,000 sporangiospores (86).

BONY LESIONS

Some of the more common idiopathic bone lesions of the head and neck are discussed in this section. Although their radiographic appearance may be similar (Figs. 17.8 and 17.9), these bony lesions can be differentiated by a thorough history and physical examination and radiographic evaluation.

Fibrous Dysplasia

Fibrous dysplasia (Table 17.7), a genetic but nonfamilial skeletal disorder wherein medullary bone is replaced by fibro-osseous tissue, manifests itself in three clinical forms: monostotic fibrous dysplasia, polyostotic fibrous dysplasia, and McCune-Albright syndrome. Monostotic fibrous dysplasia, the term applied when the disease is confined to one bone, accounts for 75% to 80% of all cases. Polyostotic fibrous dysplasia, which accounts for 20% to 25% of patients, is applied when two or more bones are involved. If polyostotic fibrous dysplasia is associated with abnormal skin pigmentation, precocious puberty, and other nonskeletal diseases, it is called McCune-Albright syndrome, which accounts for 20% to 25% of all polyostotic fibrous dysplasia patients.

Fibrous dysplasia occurs almost exclusively before age 30 years. Polyostotic fibrous dysplasia and McCune-Albright syndrome tend to occur in the first decade, and monostotic fibrous dysplasia usually manifests in the second or third decade. The disease is usually quiescent after puberty. Polyostotic fibrous dysplasia has a 3:1 female predominance. Monostotic fibrous dysplasia occurs with equal frequency in both sexes. The cause of the disease has been localized to postzygotic missense mutations in the *GNAS*1 gene, which is found on chromosome 20q13.2.

Most patients (90%) with fibrous dysplasia are asymptomatic. The most commonly affected bones are the ribs and femur for monostotic fibrous dysplasia and the femur and tibia for polyostotic fibrous dysplasia. About 25% of patients with fibrous dysplasia have head and neck involvement. The ethmoid, sphenoid, frontal, maxillary, and temporal bones are the most commonly affected. Head and neck symptoms include sinusitis, proptosis, diplopia, compression of the cranial nerves in foramina, facial pain, facial asymmetry, headache, and hearing loss.

The typical radiographic finding is an expanded osseous lesion with a poorly defined margin covered by an eggshell-thin cortex. Fibrous dysplasia also may appear radiographically as a pagetoid lesion or sclerotic lesion. When the paranasal sinuses are involved, radiographic studies show a calcified, thick, enlarged sinus margin and a ground-glass appearance of the mass inside the sinus.

Histologically, the fibrous dysplasia lesion reveals normal marrow-space bone replaced by irregular spindle-shaped mesenchymal cells. The mesenchymal cells form whorled patterns, and the bony trabeculae are poorly developed. One differentiating feature of fibrous dysplasia is the lack of "osteoblastic rimming," in which osteoblasts rim the fibro-osseous tissue.

The differential diagnosis for fibrous dysplasia often depends on the location and radiographic characteristic of the lesion. Although the fibrous dysplasia lesion may appear pagetoid radiographically, it can easily be differentiated clinically. When located along the sphenoid ridge, it may look radiographically like a meningioma. Fibrous dysplasia also may be difficult to differentiate from osteomyelitis, and the two conditions may coexist. Osteosarcoma must always be considered, as 1 in 200 cases undergo malignant degeneration. Biopsy should be performed if

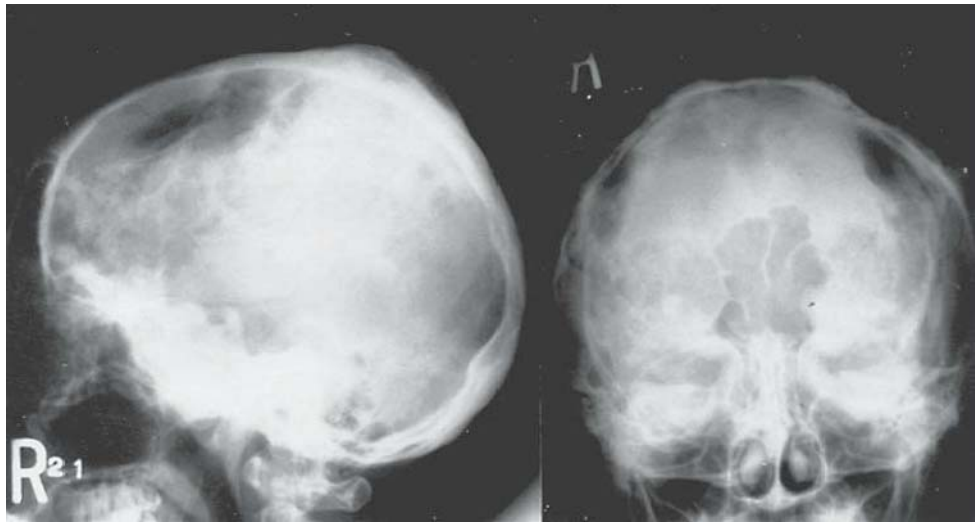


Figure 17.8 Fibrous dysplasia.



Figure 17.9 Paget disease. Note the pattern of thickened bone surrounding lucent bone.

the diagnosis is in doubt or if malignant degeneration is suspected. Surgical treatment for decompression of cranial nerves (typically the optic, cochleovestibular, or facial nerves) helps restore function but should not be performed prophylactically because of the risk of iatrogenic injury. Surgical curettage can help with diplopia and relieve sinus obstruction, although with this procedure, recurrence rates reach 20% to 30%. In recent years, refinements in surgical instrumentation and craniofacial surgical techniques have made more aggressive nondisabling procedures possible. Additionally, bisphosphonates may reduce the bony pain and risk of fractures (87).

Ossifying Fibroma

Ossifying fibroma is similar to fibrous dysplasia, but its onset, on average, is 10 years later. Its radiographic appearance is homogeneously dense in head and neck locations, similar to the appearance of fibrous dysplasia. The ossifying fibroma is usually more discrete. Histologically, it resembles fibrous dysplasia, but osteoblastic rimming is present. Treatment consists of excision, and recurrence is rare.

Paget Disease

The demographics and clinical manifestations of Paget disease (osteitis deformans) differ from those of fibrous dysplasia (Table 17.7). Paget disease rarely occurs before age 40 and most often occurs between ages 55 and 70. Most patients (85%) have polyostotic disease, and the lumbosacral region is the area most frequently involved. Patients with Paget disease are often asymptomatic but are more commonly symptomatic than are those with fibrous dysplasia. The classic symptoms are enlarging skull, dorsal kyphosis, and bowing of the legs. The most common symptom is bone pain. Other symptoms that occur as complications of the disease include spinal root compression, normal-pressure hydrocephalus, and repeated fractures with nonunion. Increased bone metabolism results in heightened vascularity of bone that has been reported to cause vascular steal syndrome and high output heart failure.

The classic radiographic findings of Paget disease follow the underlying histologic process. Initially, a lytic phase is associated with increased osteoclastic activity with replacement with vascular stroma, followed by a mixed phase, with increased osteoblastic activity in addition to the osteoclastic activity, resulting in a mosaic pattern of bone. The metabolic activity of the disease produces the typical "cotton wool" appearance on the radiograph. During the final phase, the osteoblastic activity is preeminent, and the radiographic picture becomes one of sclerosis. Calcium and parathyroid hormone levels may be elevated secondary to the increased bone turnover but are usually normal. Patients with Paget disease often have elevated alkaline phosphatase levels secondary to increased osteoblastic activity and increased urinary hydroxyproline levels secondary to increased osteoclastic activity. Recently, several

TABLE 17.7 FIBROUS DYSPLASIA COMPARED WITH PAGET DISEASE

Characteristic	Fibrous Dysplasia	Paget Disease
Age	≤30 y	≥40 y
Presentation	Monostotic	Polyostotic
Most commonly	Ribs, femur	Lumbar sacrum, affected bones
Most commonly	Maxilla	Skull affected, head and neck region
Treatment	Curettage	Bisphosphonates

studies suggest different markers to evaluate for rate of bone formation with bone-specific alkaline phosphatase or procollagen type 1N-terminal propeptide and bone resorption N-telopeptide (NTx). NTx is a sensitive way to assess for response to antiresorptive therapy (88).

In the head and neck, Paget disease occurs more commonly in the skull than in the face, as seen in fibrous dysplasia. The skull is the third most frequently involved bone. In the skull, lesions are typically lytic (i.e., osteoporosis circumscripta) and only slowly progress to the mixed phase. Paget disease of the jaw rarely occurs before age 40 and is usually bilateral. In contrast, fibrous dysplasia is usually unilateral and is rare after age 30.

Hearing loss is a common complaint by patients with Paget disease. This hearing loss includes a high-frequency sensorineural component and a low-frequency conductive component. The pathogenesis of the hearing loss has not been resolved (87).

The differential diagnosis for Paget disease includes fibrous dysplasia, osteomyelitis (which can coexist with Paget disease), osteitis fibrosa from primary hyperparathyroidism, and osteosarcoma. Like fibrous dysplasia, Paget disease can undergo malignant transformation. Approximately 5% of cases degenerate to an osteosarcoma, with the 5-year survival rate lower than that of other osteosarcomas. More rarely, Paget disease degenerates to giant cell tumor, which typically involves the skull and is less aggressive than other giant cell tumors, which rarely involve the skull and are seen almost exclusively in the long bones.

Usually the clinical and radiographic picture is classic, but a biopsy may help if diagnosis is in doubt. The patient with Paget disease also is at risk of serious sequelae developing, including hypercalcemia, polycythemia, neurologic compression, malignant transformation, and congestive heart failure. These patients need close follow-up. Medical treatment becomes necessary with impending hypercalcemia, repeated fractures and nonunion, compression of nerves, and intractable bone pain.

Calcitonin has been widely used; however, due to waning efficacy, absence of durable remission, and availability of better therapeutic options, it is currently used in rare circumstances. It decreases bone turnover and alkaline phosphatase levels, urinary hydroxyproline, and the risk for heart failure. In the last decade, bisphosphonates were developed. They are potent inhibitors of bone resorption and showed sustained clinical remission. These drugs have become the mainstay therapeutic option in Paget disease. Disodium etidronate was the first bisphosphonate studied, however, due to its negative effect on bone mineralization it was soon replaced by newer and better aminobisphosphonates (alendronate, pamidronate, risedronate, ibandronate, and zoledronic acid). This newer generation of bisphosphonates reflects a trend toward more potent suppression of bone resorption without impaired mineralization (89). All the bisphosphonates are generally well tolerated. Occasionally, they may cause flu-like symptoms and gastrointestinal distress. Rarely, and mostly with IV therapy for malignancy-associated bone metastasis, osteonecrosis of the jaw has been reported (90).

AMYLOIDOSIS

Amyloidosis is considered a rare disease, but autopsy studies suggest a higher incidence of subclinical disease than previously thought. In 1854, the term *amyloidosis* was coined by Virchow, who was describing a starch-like substance in a patient who died of multiorgan failure. Amyloidosis is characterized by the deposition of extracellular fibrillar proteins in various tissues. It manifests in several different forms: primary systemic, secondary systemic, localized, myeloma associated, dialysis associated, senile, and hereditary-familial amyloidosis. However, amyloidosis is extremely rare in the pediatric age group.

Of the two forms of amyloidosis, the AL amyloidosis (formerly primary systemic), which predominantly affects mesenchymal tissues (e.g., heart, tongue, and gastrointestinal tract) and AA amyloidosis (formerly secondary systemic amyloidosis), which is associated with chronic inflammatory destructive diseases such as tuberculosis, RA, juvenile RA, spondyloarthritis, autoinflammatory syndromes, and osteomyelitis. AA amyloidosis primarily affects the kidneys, adrenals, liver, or spleen and occurs after 10 to 20 years of inflammatory disease. Although amyloidosis develops in only 12% of patients, myeloma-associated amyloidosis is the second most common form. This form is deposited primarily in mesenchymal tissues. Localized amyloid may be primary or secondary, but it is limited to one site in the body and occurs in several neurodegenerative diseases such as Alzheimer disease, Parkinson disease, and Huntington chorea.

Although the mechanism of deposition is different, all fibrils in amyloidosis are of β-pleated sheet conformation. With light microscopy, all forms of amyloid are identical. Chemical analysis reveals that primary amyloid and myeloma-associated amyloid are composed of light-chain immunoglobulins (AL); this disease is a plasma cell dyscrasia. AL amyloidosis results from deposition of protein fragments that have been generated by aberrant proteolytic cleavage of normal Ig. Secondary amyloid is composed of amyloid protein A (AA). AA amyloidosis is the result of overproduction and deposition of serum amyloid A protein. Localized and familial amyloid may be composed of several different types of protein; the vast majority of familial amyloidosis is caused by deposition of transthyretin (TTR) variants. The dialysis-associated protein is β_2-macroglobulin. Nephrotic syndrome is the most common manifestation of systemic amyloidosis, either alone or with other organ system involvement, particularly restrictive myocardiopathy, hepatomegaly, peripheral neuropathy, and macroglossia. Ecchymosis due to capillary wall infiltration, bleeding due to factor X deficiency, carpal tunnel syndrome, arthropathy, lymphadenopathy, and gastrointestinal dysmotility are

all seen in systemic disease. Cardiac evaluation provides important clues in the diagnosis of systemic amyloidosis. In cases with cardiac amyloid infiltration it is common to observe a pattern of low QRS voltage on electrocardiogram (91). Echocardiographic features of amyloidosis include nondilated ventricles with concentric left ventricular thickening and increased echogenicity of the myocardium with a "granular sparkling" (92). Cardiac MRI is able to demonstrate myocardial late gadolinium enhancement with global and subendocardial localization and correlates with classical histologic changes observed in cardiac amyloidosis (93). The diagnosis of amyloid is established by biopsy, which is characterized by extracellular proteins that are green and birefringent under polarized light after staining with Congo red. Reversibility of the birefringence with potassium permanganate implies secondary amyloid. Crystal violet also is used to stain for amyloid. Biopsy for systemic amyloidosis is often accomplished by needle aspiration of abdominal fat, although biopsies of the tongue, minor salivary glands, and buccal mucosa have all been advocated (94). Diagnosis of the myeloma-associated form is diagnosed based on findings of plasma cells in bone marrow biopsies and monoclonal Ig light chains on plasma and urine electrophoresis.

Generalized amyloid has a worse prognosis than localized amyloid. As a result, these patients must be evaluated for generalized disease by a rectal biopsy or a fine-needle aspiration of the anterior abdominal wall fat. Eighty to ninety percent of patients with generalized amyloid show positive results with these tests.

Amyloid may deposit in several sites in the head and neck. The tongue is the most commonly involved area. Of those with AL amyloidosis, 50% have lingual involvement, but macroglossia is present in only 5% of patients, although it is considered pathognomonic. The orbit is another common site of deposition for localized amyloid in the head and neck. Typically, it is seen as a painless mass in the superior orbit. The true vocal cord is the most common site of deposition in the respiratory tract, although the supraglottis, subglottis, trachea, and bronchial tree also may be involved. In the larynx, the typical firm gray, red, or yellow deposits are usually localized. The nodules tend to be diffuse in the subglottis. Surgical reduction of amyloid lesions is the treatment of choice, and multiple procedures over a number of years may be required (95). Laryngeal amyloidosis tissue is relatively fragile and bleeds readily if traumatized. Anesthetists should be cautious when intubating patients with laryngeal amyloid involvement. Otologic manifestations of the disease are extremely rare and involve the external auditory canal and concha. Other head and neck sites of deposition reported include the parotid gland, oral and pharyngeal mucosa, minor salivary glands, the paranasal sinuses, cervical lymph nodes, the nasopharynx, and the skin. Treatment for amyloidosis comes in two parts, direct treatment of the underlying disease, if possible, and supportive treatment for the involved organs. AL is the most serious among the amyloid disorders with 18 to 24 months survival. Treatment with melphalan and autologous stem cell transplant extends the survival to 40 months (96). Treatment of AA amyloidosis is directed towards controlling the inflammatory disease process.

HIGHLIGHTS

- Rheumatologic diseases result from immunologic or autoimmune reactions.
- The tissue distribution of the inflammatory response, the pattern of organ involvement, and the presence of specific autoantibodies are the factors that differentiate one systemic autoimmune disease from another.
- Mucocutaneous and musculoskeletal involvement are the most common manifestations of SLE.
- Sudden unexplained onset of erythema and pain over the cartilages of the nose or ear suggests a diagnosis of polychondritis.
- It is possible that a significant overlap in the clinical presentation of the systemic autoimmune diseases exists, and if one patient exhibits distinct clinical characteristics of several of these diseases, the diagnosis of overlap syndrome or undifferentiated connective tissue disorders should be considered.
- LCH is the preferred term for the collection of disorders of proliferation of mononuclear phagocytic cells previously known as histiocytosis X.
- Sarcoidosis, characterized by noncaseating granulomas, most often involves the lungs and intrathoracic nodes; the cervical nodes are often involved when sarcoid appears in the head and neck.
- Cervical lymphadenitis, frequently involving the posterior triangles, is the most common head and neck manifestation of tuberculosis
- Although radiographically similar, bony lesions of the skull can be differentiated by their most common site of involvement and the patient demographics of those involved.

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18 Geriatric Otolaryngology

David E. Eibling *Sarah H. Kagan*

Health care in our aging society is widely acknowledged as the force substantially altering current and future health needs, demand for services, and provision of primary and specialty care. Otolaryngologists, as specialists best prepared to treat senescent functional sensory loss and many age-related diseases and syndromes including dysphagia and malignancies of the head and neck, hold a unique role in provision of specialty care for older adults. Addressing health care needs of an aging society through provision of general otolaryngology and specialized otology, rhinology, and laryngology care, as well as head and neck surgery, requires knowledge of several specialized topics in aging and geriatrics. This chapter reviews central concepts relevant to an aging society. It then proceeds to detail aspects of clinical care for older adults relevant to the practice of otolaryngology as it relates to the future of health care. This discussion includes consideration of geriatric competence for the generalist and specialist otolaryngologist. The chapter concludes with consideration of the subspecialty of geriatric otolaryngology in health care for our aging society.

CONCEPTS IN AGING

Terms and Definitions

Language used to define and discuss issues of aging and health care for older Americans is often diverse and difficult to understand. Even terms of reference to older Americans themselves are somewhat controversial. Current conventions acknowledge the slightly pejorative connotation of the grammatically incorrect appellation elderly as a noun. The only accepted use of *elderly* is as an adjective; however, *older* is preferred in America and across most international scholarly literature in aging. While American scholars and clinicians often say "*older adults*," those in the European Union may prefer "*older people*." Interestingly, older adults themselves rank "elderly" among the most negative terms of reference (1). Words and phrases like "senior" or "50+" may be preferable to older adults, especially combined with individually and generationally expressed forms of address that avoid diminutives and informality. *Gerontology* is the name of the discipline that studies aging, health, and function from biologic, psychological, and social perspectives. *Senescence* refers to the process of aging and generally refers to cellular processes. Chronologic age is often subdivided into three categories. The *young-old* are ages 65 to 75. The *old* are generally considered aged 75 to 85. The *old-old*—or alternatively, *oldest old*—are those individuals aged over 85 and are currently the fastest-growing demographic (2). *Centenarians*—those over 100 years—and *supercentenarians*—those aged 110 years or older—while few in number are extensively studied to better understand extreme longevity (3). *Geriatric* is both the term used to define the biomedical study of age-related disease, dysfunction, and disability as well as being the name of the medical specialty of caring for older adults (4). Use of the word geriatric also delimits the subspecialty within other medical disciplines dedicated to care of older adults and to that within other professional groups. Examples of this use of term include geriatric otolaryngology, geriatric nursing, and geriatric social work.

Demographics and Disability

Emphasis on aging demographics and implications for health care are now commonplace in health care literature. Proportional change in the number of older Americans draws most attention. The current projection is that one in five Americans are expected to be aged 65 and older by 2030 (2,5). In some regions, the percentage of older Americans may rise to one in four or more. Significant

growth in the old-old, those individuals aged 85 and over, compounds this demographic shift (2). Current trends in population aging are the result of improved disease prevention and control and of extended longevity (2). Improved health status and declining disability in late life are also apparent (6).

Two concepts, existing in balance, explain health and social care burdens in an aging society. *Compression of morbidity*, classically defined by Fries (7), is the possibility of compressing illness and functional loss as close as possible to the time of death. The *elder dependency ratio* measures the number of older people against working adults. The elder dependency ratio, like the total dependency ratio that includes dependent children, evaluates care needs at a population level. These population measures are critical to understanding health care needs and projecting necessary services in any society.

Compression of morbidity, once only a concept yet to be realized within our population, is a current reality. Cutler and Landrum (6) offer current analyses reflecting significantly improved health and declining disability of our aging population overall. Notably for otolaryngology, Cutler and Landrum (6) suggest that sensory impairment is declining as elder health status is improving. Nonetheless, they also show stable use of nursing homes, implying potential persistence of unaddressed disability in the old-old. Cai and Lubitz (8) show older Americans are indeed increasingly experiencing compression of morbidity and disability in the time before death. However, in more discrete analyses, differential patterns of functional disability that signal commensurate health and social care needs remain a reality within the aged population.

Concerns about elder dependency ratios persist despite gains made in limiting disability and extending life (9). Some of these concerns lie in the accuracy of projections. Tuljapurkar et al. (9) suggest elder dependency ratios are in fact underestimated in most developed nations including the United States. Thus, in comparing research reported from different disciplines, some debate over projections of morbidity and consequent disability exists and warrants continued analysis to draw clinically relevant conclusions. While overall health status of older Americans is improving, dependency and specific forms of disability continue to drive improved health care education and workforce recruitment to address these needs in our aging population (5)

AGING, DISEASE, AND DISABILITY

Much science investigates interrelationships among aging, disease, and disability (10–14). However, these entities and their interactive and correlative effects in health and function remain incompletely understood, particularly in translating basic science into clinical contexts. *Frailty* is the state of declining functional reserve in which response to stressors is diminished, resulting in proportionally more severe sequelae and limited recovery after an insult (14). Fundamentally, study of processes like senescence and inflammation shed increasing light on frailty as a phenomenon of function understood now in physiologic dimensions, differentially expressed in late life (15,16). *Epigenetics* is the study of both heritable and nonheritable genetic expression and cellular transcription potential that is generally stable but may be modified by interactions with physiologic, pathologic, and environmental factors over a lifetime (17,18). Rising interest in epigenetics complements growing evidence in frailty (19). Evidence in epigenetics increasingly elucidates critical aspects of age-related diseases like dementia and cancer (18,20). Epigenetics may eventually clarify the triad of disability, frailty, and comorbidity outlined by leading frailty researcher Fried et al. (11).

Disability, frailty, and comorbidity are almost certainly causally related, manifesting in overlapping and difficult-to-distinguish patterns in late life (11). As molecularly mediated understandings of frailty and epigenetics frame translational science of aging and disease, investigation of frailty, age-related disease, and functional disability increasingly delimit related aspects of clinical geriatrics. Fried et al. (11) highlighted interchangeable use of these three terms, proceeding to outline overlapping prevalence and intercurrent sequelae. Comorbidity—diagnosis of two or more acute or chronic diseases—is highly prevalent in the old-old. The old-old bear proportionally more disability, presence of physical or mental impairment, than younger counterparts do. Both comorbidity and disability are commonly present in the case of clinical frailty. Accruing evidence continues to disentangle the clinical manifestations and consequences of these entities in prognosis, care needs, and health care costs (15,21–26).

Age-related disease and geriatric syndromes commonly coexist and may increase as frailty escalates (14). Frailty likely mediates age-related disease though exact mechanisms, beyond epigenetic influences and possible inflammatory processes, remain relatively obscure (18). Geriatric syndromes, unlike diseases with identifiable pathology at hand, are more complex. A geriatric syndrome, such as delirium, falls, or incontinence, manifests in a singularly identifiable presentation (27). However, manifold etiologic factors and interacting pathogenesis are at hand in any single syndrome (27). Unlike disease, there is not an authoritative and comprehensive list of geriatric syndromes. Some like sarcopenia and frailty draw debate and remain controversial. Other syndromes like delirium, falls, incontinence, malnutrition, or geriatric failure-to-thrive are more widely accepted.

Age-related disease and geriatric syndromes may interact, creating risk for complications and increasing care needs (14,28,29). A classic example exists in the older person with dementia who is then at greater risk for delirium. Once delirium emerges, this older person

may have a more complicated presentation and less predictable recovery (30). Both presentation—which is often atypical—and recovery may risk excess disability and poor outcomes (11,27,31). *Atypical presentation* describes unexpected signs of illness—such as delirium instead of fever as the presenting sign of pneumonia occurring in an older adult—that often conflict with typical signs and symptoms in diagnosis for a younger adult (31). Many authors contend that frailty is the element of declining functional reserve that undergirds age-related disease and geriatric syndromes (11,14,15,27). Others argue that frailty itself is a clinically identifiable geriatric syndrome (10,23). As biologic evidence accrues, the import of relationships between and among frailty, age-related disease, and geriatric syndromes for clinical medicine is clear. These interconnections require parallel investigation of prevention, treatment, and outcomes in the context of medical, surgical, and rehabilitative treatment (22,24,32–34).

CLINICAL CARE OF OLDER ADULTS

Geriatric competence optimizes care of older adults across specialties and settings (5,29,31,35). Specifically, geriatric competence limits risk of errors in high-risk settings and in hand-offs and transitions in care (31). Otolaryngologists of the 21st century will need geriatric competence to optimize the discipline's contribution to our aging society and to ensure best practices and outcomes for individual patients. Competence implies the possession of specific skill sets and a working knowledge of critical concepts, as well as understandings of current and future implications of an aging society.

Otolaryngologists are specialists in the diagnosis and treatment of disabling sensory and functional impairments, including presbycusis, presbystasis, presbynosmia, presbyphonia, and dysphagia (36). Such impairments beget often debilitating limitations in daily function and quality of life (6,36). Additionally, otolaryngologists lead surgical and interdisciplinary treatment of head and neck cancer. Along with diagnosis and treatment of other otolaryngologic conditions seen across the life span, otolaryngology residency training equips otolaryngologists with the knowledge and skill necessary to manage and collaborate in optimal interdisciplinary care of older adults. However, in the process of that care, otolaryngologists confront geriatric concerns that risk convoluted processes of care and poor clinical outcomes. Frequently, matters of atypical presentation intersect with comorbidities and geriatric syndromes to generate resultant questions of frailty, functional reserve, and rehabilitative potential. These geriatric concerns drive needs for specific knowledge regarding care of older adults. Conversely, such concerns also draw into question anecdotal reliance on a general sense of older adult patient outcomes, especially the false confidence of "I take care of older people and they do OK."

Possession of specific geriatric competence is vital to enhancing the domains of assessment, decision making, complications, and care in advanced, life-limiting disease. Assessment of older adults, given inherent complexity of frailty with comorbid disease and conditions along with geriatric syndromes, is among the most active research topics in clinical geriatrics (33,37,38). Nonetheless, many recommended protocols require extensive training and time unsuited to most specialist practices. Treatment decision making coalesces concerns about health care for the individual juxtaposed against comparative effectiveness and outcomes. Increasing evidence suggests that geriatric focused assessment alters decision making (32,39–41). Emerging understanding of links between geriatric assessment and decisions that employ assessment data potentially improves clinical management, resulting in improved patient outcomes and reduced postoperative complications (32,37,40).

Specific assessment, complex decision making, and risk of complications are all heightened in the older adults with advanced, life-limiting diseases such as dementia, cancer, and heart failure. The contributions of otolaryngology are particularly valuable to these individuals and their families. For many older adults diagnosed with advanced, life-limiting diseases, the presence of sensory and functional impairments makes daily life limited and quality painfully circumscribed. Diagnosis and treatment of these impairments fall precisely within the practice domain of otolaryngology. Consequently, otolaryngologists can markedly improve quality of life for such individuals, as consultants to primary treatment teams in community-based and institutional long-term care.

Geriatric Assessment

Geriatric assessment is the foundation for medical and interdisciplinary care of older adults. As such, specialized assessment targets the unique needs of older adults and accounts for manifestations of frailty with specific indicators (22,32,33,38). Accumulating evidence progressively reveals which frailty criteria are the most robust indicators in assessment (42), and clinical investigation highlights specific indicators and assessment protocols that are most clinically relevant (32,42). Classically, geriatric assessment protocols relied on a formal assessment technique called Comprehensive Geriatric Assessment (CGA). This global, multifocal, expert multidisciplinary process is time consuming and often requires hours to complete (43). Though CGA is clinically useful in identifying needs and risks, early work failed to establish its value in enhancing outcomes and comparative cost effectiveness definitively. As a result, there is no current standard to assess functional status and reserve of older patients facing serious, life-limiting diagnoses as well as standard interventions and procedures for primary and comorbid conditions (44).

Current CGA research is most robust in medical oncology. More recently, geriatric assessment is the focus of some investigations of frailty and outcomes in surgical and other medical specialties (33,37–39,44). Current investigations apply CGA principles in one of two ways. Investigations entail either a geriatric consultation team to complete assessments or application of specific assessment indicators that may be clinically feasible without geriatric expertise. Translation of consultation teams and targeted assessments to clinical practice remains limited. Interventions that rely on consultation teams are often not feasible for all but large medical centers with geriatric services or departments in place. Frailty phenotype indicators may be more useful. Makary et al. (32) and Robinson et al. (33) report findings that suggest clinical utility in the near future for easily assessed frailty parameters such as walking speed and weight loss. Conversely, Aparicio et al. (43) report a competing model, called Mini-Geriatric Assessment (MGA), that relies on assessment of geriatric syndromes and physiologic indicators. Both frailty phenotype indicators and MGA overcome some of the limitations of CGA and promise tangibly better clinical assessment. While evidence to shape future practice continues to accrue, critical clinical appraisal of frail-appearing patients and judicious use of geriatric consultation services augment current thorough otolaryngologic assessment and communication with primary care providers and referring physicians.

Substantial evidence exists confirming that utilizing assessment data that target frailty, comorbidity, and disability improves decision making and clinical outcomes (32,38,39,43,45). Yet, decision-making preferences among older adults are difficult to predict (46–48). Executing an *advance directive* is an important adjunct to improved decision making. Silveira et al. (49) suggest that those who have directives are more likely to receive the care they desire at end of life. Advance directives offer benefit in generating discussion among older individuals, their family members, and treating clinicians as much as in documenting wishes for the type and extent of care in serious illness and injury. Nevertheless, population prevalence of completed directives is generally low with higher numbers found in frail institutionalized older adults. Scalable solutions to improve adherence are, as yet, untested (49–51). Best practices in care of older adults, for specialists such as otolaryngologists and primary care providers alike, include eliciting patient and family preferences and recording advance directives in addition to geriatric assessment and communication between specialists and primary care providers (52–57).

Clinical Management

Effective clinical management of older patients, beyond the foundation of otolaryngologic and geriatric assessment and individualized decision making, requires a clear, goal-directed plan of care. Care of older patients is inherently interdisciplinary and implies cognizance of actual needs and potential complications (28,31,40). Inpatient care escalates risks, vulnerability, and opportunity for medical error and complications. Proactive prevention and treatment potentiate improved outcomes in medical management and perioperative care of older patients (31,58–61). Hospital regulatory, credentialing, and institutional quality edicts generally closely correlate with best geriatric practices. As a result, initiatives in patient safety, satisfaction, and centered care offer a familiar platform for improving care for older adults.

Patient safety for older adults implies discrete, nuanced risk related to confluent senescent and pathologic changes creating the potential for unexpected effects in the course of treatment. Polypharmacy, delirium risk, and fall-related injuries are among the most consequential potential events for any hospitalized older adult (27). These geriatric syndromes and their cascade of interconnections serve to illustrate how patient safety and geriatric best practices coincide.

Polypharmacy is the geriatric syndrome in which older adults are prescribed many drugs without due consideration of altered metabolism, drug–drug and drug–food interactions, and patient and family education (62). Senescent and pathologic changes in drug metabolism, distribution, and response complicate prescribing as does the presence of multiple prescribers (62). Careful medication management with consideration of alternate agents and pharmacist consultation offers the means to limit polypharmacy and adverse drug events when combined with routine and new prescription *medication reconciliation*.

Delirium, a syndrome of acute confusion with multiple etiologic factors, is prevalent among medically ill older adults and often complicates postoperative recovery (27,37,40). Undetected and hence unmanaged delirium poses a host of consequences from infection to death (63). While scant evidence and limited instruments limit composite screening for delirium risk, well-established research is revealing identifiable risk factors for delirium. Among the most common events likely to lead to delirium among older adults are presence of infection or other acute illness, metabolic derangement, and use of deliriogenic medications (63). Outcomes of care in delirium are improved by identifying risk, avoiding deliriogenic events when possible, detecting actual delirium early, deleting contributing drugs, correcting pathology when feasible, avoiding physical and chemical restraints, and employing early rehabilitation (63).

Falls and fall-related injuries result from manifold factors among community-dwelling, institutionalized, and hospitalized older adults, leading to substantial morbidity (58,64–66). Delirious patients are at increased risk of

falls given altered sensorium, impaired judgment, and the presence of acute illness. Detecting and treating delirium while providing rehabilitation to restore function may reduce or avoid fall risk. Preventing falls and resultant injury among older adults, regardless of setting, is difficult (66). Falls are prevalent among both community-dwelling and institutionalized older adults, and many intervention programs are relatively ineffective at preventing either falls or related injuries (64,66,67). Through ongoing research in presbystasis and other balance disorders, otolaryngology offers the potential to impact the epidemic of falls and consequent injuries among older adults (67,68).

Patient satisfaction receives ever more attention in our aging society. Measures of satisfaction drive a wide variety of initiatives from hospital incentive programs to hospital accreditation (55). Patient satisfaction is a monolithic icon of health care in the 21st century—gratefully accepted when reported measures are high and puzzled over when low. Care of older adults offers substantive anchors for analyzing and improving patient satisfaction. Assumptions about older adult and family needs and preferences along with ageism persist in health care and in society (69,70). Careful attention to older patients as they ask questions, express preferences, and request assistance in making decisions enhances opportunities to understand expectations and offer satisfaction (55). Avoiding ageist assumptions and actions by measuring functional status instead of delimiting care by chronologic age launches patient-centered decisions with realistic goals of care (44,55).

Communication, coordination, and collaboration facilitates care of older adults who have comorbid conditions and use health care services frequently. Clinicians who provide care to older adults find communication and collaboration improve both processes and outcomes of care (47,56,71). While older adult and family preferences for communication and involvement in decision making are difficult to predict, older adults almost certainly value care coordination (46,52). As a result, clear understandings of locally available geriatric and related specialists in addition to resources for community-based services for older people serve otolaryngologists well.

Identifying geriatric and related specialists and available resources in advance offers advantages in achieving collaborative, coordinated care for older adults. Academic medical centers are most likely to offer geriatric fellowship training and to have board-certified *geriatricians* on staff. *Geriatric nurse practitioners* often collaborate with geriatricians and may offer independent geriatric assessment in many settings. While geriatricians are primary care physicians, they also serve as effective specialist consultants for older adults who wish to remain in the care of a family physician but have complicated comorbidities and multiple geriatric syndromes. Geriatric and medical *social workers* function in many roles in community settings and in health care agencies serving older people. Geriatric social workers offer direct counseling and care coordination in addition to accessing community-based services for older people. *Area Agencies on Aging*, nongovernmental organizations located in each county in the United States (http://www.n4a.org/), are important gateways to these local resources. In addition to clinicians with specific expertise in care of older adults, colleagues such as physical and occupational therapists, speech language pathologists, and clinical nurse specialists possess particular skills useful in interdisciplinary care of older adults. For example, physical therapists assess gait and walking speed as part of their initial assessments, useful in determining frailty. Occupational therapists and speech language pathologists complete various aspects of cognitive assessment, proving further data important in frailty and rehabilitative potential. Clinical nurse specialists frequently direct inpatient safety and quality initiatives, providing programmatic information about delirium and falls prevention, for instance. In the absence of colleagues who can easily collaborate, a variety of useful handbooks, software, and applications are available for clinical guidance. Among the valuable is the American Geriatrics Society publication *Geriatrics at Your Fingertips*, a pocket-sized clinical guidebook updated each year and available in hard and soft copy (www.geriatricsatyourfingertips.org).

UNIQUE CONTRIBUTIONS OF OTOLARYNGOLOGY TO HEALTH CARE IN OUR AGING SOCIETY

Future contributions of otolaryngology to health care in our aging society entail balancing competence and specialization and building discipline specific science and models of care. Otolaryngology supplies essential specialization in alleviating functional and sensory impairments as well treating malignancies of the head and neck that otherwise would diminish longevity and quality in the lives of older Americans. Otolaryngologists require geriatric competence to realize these potential contributions fully. The need for otolaryngologic science and care of older adults will grow dramatically as our society continues to age and demographic and health projections are attained. Recent efforts to define opportunities and advance the unique contribution of otolaryngology claim two published research agendas developed in collaboration with the American Geriatrics Society (72,73), a textbook (74), and the nascent organization *The American Society of Geriatric Otolaryngology* (http://geriatricotolaryngology.org/). Continued work must fulfill the research agendas and help demarcate the subspecialty of geriatric otolaryngology with respect to the discipline of otolaryngology.

HIGHLIGHTS

- Changing demographics will lead to dramatic increases in numbers of older adults seeking care for otolaryngologic disorders.
- Possession of specific geriatric knowledge and skills will enable otolaryngologists to optimize the management of these older adults.
- Specific geriatric syndromes such as dementia, polypharmacy, and delirium will represent comorbidities for ever-increasing numbers of patients.
- Assessment of frailty can inform decision making for patients requiring surgical intervention.
- Attention to collaborative care paradigms, medication reconciliation, and reliable hand-offs have the potential to reduce medical error and adverse events.
- Shared decision making is enhanced when older patients complete an advance directive.
- Management of otolaryngologic disorders can dramatically improve quality of life for older adults.
- A goal of interdisciplinary geriatric care is *compression of morbidity* into the shortest period of time prior to death possible.

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Headache and Facial Pain

19

Chase H. Miller *Alfredo S. Archilla*

Headache and facial pain are a common complaint in the otolaryngologist's office. Ninety percent of Americans experience headache in their lifetime. Referral is often made to determine if headache is sinus in origin, but in this chapter we see that sinogenic causes of headache and facial pain are infrequent. Primary headache disorders are much more common. Secondary causes of headache and facial pain comprise an extensive list. The otolaryngologist should be able to identify sinus pathology and diagnose and treat other common causes of headache.

Headache and facial pain can be grouped into primary, secondary, and other etiologies. Primary headaches include migraines, tension-type, cluster headaches, and chronic daily headaches (CDHs). Other primary headache disorders are beyond the scope of this chapter. Secondary headaches include those that have specific etiologies identified. This group can include trauma, vascular disorders, infections, neuralgias, neoplastic causes, and others. Facial pain can be divided into peripheral or central causes. Peripheral facial pain makes up the larger of the two and includes disorders of the head and neck that refer pain to this region. Examples include temporomandibular joint (TMJ) syndrome and various neuralgias. Central facial pain is secondary to intracranial pathology like neoplasms or vascular disorders. For simplicity, secondary headache and peripheral facial pain disorders have been grouped together in this chapter.

ANATOMY AND PHYSIOLOGY

The brain is not a sensory organ and therefore does not perceive pain, but the surrounding structures in the brain have nociceptive fibers that recognize pain. Intracranial structures that are pain sensitive include major venous sinuses, large cerebral vessels, upper cervical nerves, and cranial nerves (CNs) V, VII, IX, and X. The trigeminal nerve and its branches provide the majority of the somatosensory innervation to the head and face region. The trigeminal nerve is a mixed nerve containing sensory and motor components. The nerve exits the ventrolateral aspect of the pons and divides into three main branches from the Gasserian ganglion; the ophthalmic V1, maxillary V2, and mandibular V3 divisions. Disease in the anterior or middle cranial fossa refers to the scalp or face anterior to the coronal suture. Lesions of the posterior fossa structures refer to the back of the head and upper neck. The sphenoid sinus and sella refer to the vertex of the head. Pain from diffuse intracranial disease may cause both anterior and posterior head pain (1).

Electrical stimulation of the trigeminal ganglion causes a cascade of events that are thought to cause headache. These electrical impulses trigger neurogenic plasma extravasation. This initiates a sterile inflammatory response, which leads to pain. There is also an increase in extracerebral blood flow and release of calcitonin gene-related peptide (CGRP) and substance P (SP) (2). CGRP is the most potent peptide vasodilator and its release causes vasodilation, mast cell degranulation, and plasma extravasation. SP is involved in inflammatory processes and pain perception. Pain impulses from the dilation and inflammation are transmitted from the trigeminal nerve to the trigeminal nucleus caudalis (TNC) in the brain stem. Because activation of the TNC can result in referred migraine pain to the ophthalmic and maxillary regions, patients may present with pain or pressure felt around the eyes and sinuses. The superior salvatory nucleus (SSN) that carries cranial parasympathetic fibers lies in close proximity to the TNC. Stimulation of the TNC can cause parasympathetic symptoms of rhinorrhea, congestion, and lacrimation. A form of central sensitization takes place during migraine, which is evident by symptoms of allodynia. Allodynia is a common finding of pain from non-noxious stimuli like touching the scalp or hair (Fig. 19.1).

V_1- Ophthalmic n.
V_2- Maxillary n. and foramen rotundum
V_3- Mandibular n.
VII- Facial n.
N.C. - Nucleus Caudalis
L.G. - Lacrimal gland
SSN - Superior Salivatory Nucleus
TG - Trigeminal ganglion

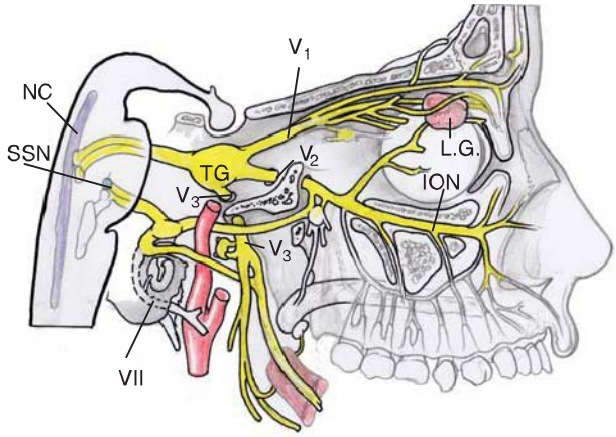


Figure 19.1 Trigeminal nerve. V1, ophthalmic nerve;V2, maxillary nerve and foramen rotundum; V3, mandibular nerve; VII, facial nerve; NC, nucleus caudalis; LG, lacrimal gland; SSN, superior salivatory nucleus; TG, trigeminal ganglion; ION, infraorbital nerve.

Depicted is the trigeminal nerve with its three major branches; ophthalmic, maxillary, and mandibular. The TNC is close to the superior salivary nucleus (SSN), which houses parasympathetic fibers. Activation of the TNC can cause reflex activation of the SSN giving rise to rhinorrhea, congestion, and lacrimation.

PRIMARY HEADACHES

Migraine is the most common primary headache and one of the leading causes of chronic illnesses and disability. Its prevalence is estimated at 18% of the US female population and 6% of the US male population (3). Two-thirds of women experience migraine before or during menses and these can worsen early in pregnancy. There is a significant decrease in episode frequency after menopause. About 70% of sufferers have a first-degree relative with migraines.

Migraine headaches are recurrent attacks lasting 4 to 72 hours. They are usually unilateral, pulsatile in nature, and of moderate to severe intensity. Attacks are often aggravated by physical activity. They are associated with nausea and/or photophobia and phonophobia. Most patients report at least one trigger of their migraine headaches. Common precipitating factors are emotional stress, hormonal changes in women, fasting, weather changes, sleep disturbances, odors, and alcohol (4).

Patients with migraine often have prodromal symptoms such as neck stiffness, euphoria, depression, fatigue, anorexia, food cravings, fluid retention, drowsiness, and enhanced alertness that begin 24 to 48 hours before the onset of headache. Fifteen to thirty percent of migraine sufferers have an aura preceding the pain. Auras are focal neurologic symptoms presenting as visual, motor, and sensory disturbances. Most auras develop slowly and may follow one another in succession starting with visual symptoms followed by sensory disturbances. Visual auras are most common and often present as zigzag figures near the point of fixation (fortification spectrum), moving geometric patterns, flashes of light, and scotomas. Sensory disturbances are frequently described as pins and needles affecting a small or large area of one side of the body and face. Numbness may also occur alone or in conjunction with other visual and sensory auras. Some patients experience a postdromal period where sudden head movements may precipitate short lasting pain in the location of the antecedent migraine headache. During this period, some patients feel tired and others have a sense of euphoria.

The diagnosis of migraine is clinical and relies on efficient history taking skills and detailed physical exam. The International Headache Society (IHS) divides migraines into two major subtypes; migraine without aura and migraine with aura. The latter is further subdivided into (i) typical aura with migraine headache, (ii) typical aura with nonmigraine headache, (iii) typical aura without headache, (iv) familial hemiplegic migraine, (v) sporadic hemiplegic migraine, (vi) basilar-type migraine. Each subtype has specific diagnostic criteria (Table 19.1). There are no diagnostic tests for migraine and neuroimaging is not necessary in most patients. A head computed tomography scan (CT) or magnetic resonance image (MRI) should be obtained if there are unexplained abnormal findings on neurologic examination, rapidly increasing frequency of headaches and atypical headaches that do not fulfill the strict diagnostic criteria established by the IHS.

Treatment for migraine headaches consists of acute headache resolution, avoidance of known triggers, and prevention of subsequent events. For mild to moderate nondisabling pain, oral nonsteriodal anti-inflammatory drugs (NSAIDs), acetaminophen, and aspirin are appropriate first choice agents. Caffeine may enhance the effect of the medications. Some patients do not respond to mild analgesics and need specific abortive therapies for acute migraine attacks. The triptans are serotonin 1b/1d agonists that inhibit the release of vasoactive peptides, promote vasoconstriction, and block pain pathways in the brainstem. They are used in outpatient situations because they are available in oral preparations, nasal sprays, and subcutaneous injections (Table 19.2).

Ergotamine and dihydroergotamine are other abortive therapies with similar pharmacology to the triptans, which are commonly used in emergency rooms and hospitalized patients. Ergots are serotonin 1b/d receptor and alpha-adrenergic receptor blockers that cause arterial and venous vasoconstriction. Dihydroergotamine is preferred over ergotamine for its safety profile. It is available for intravenous, intramuscular, subcutaneous, and intranasal use. Antiemetics are also used, alone or in combination with analgesics, for the treatment of acute migraine attacks. Commonly used agents include intravenous metoclopramide, intravenous and intramuscular chlorpromazine,

TABLE 19.1 DIAGNOSTIC CRITERIA FOR SELECTED MIGRAINE DISORDERS (5)

Migraine without aura

A. At least five attacks fulfilling criteria B–D
B. Headache attacks last 4–72 h (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. unilateral location
   2. pulsatile quality
   3. moderate-to-severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity
D. During headache at least one of the following:
   1. nausea and/or vomiting
   2. photophobia and phonophobia
E. Not attributed to another disorder

Migraine with aura

1. Typical aura with migraine headache:
   A. At least two attacks fulfilling criteria B–D
   B. Aura consisting of at least one of the following, but no motor weakness:
      i. Fully reversible visual symptoms including positive features (e.g., flickering lights, spots,
      or lines) and/or negative features (e.g., loss of vision)
      ii. Fully reversible sensory symptoms including positive features (e.g., pins and needles) and/or negative features (e.g., numbness)
      iii. Fully reversible dysphasic speech disturbance
   C. At least two of the following:
      i. Homonymous visual symptoms and/or unilateral sensory symptoms
      ii. At least one aura symptom develops gradually over ≥5 min and/or different aura symptoms occur in succession over ≥5 min
   D. Headache fulfilling criteria B–D for *Migraine without aura*
   E. Not attributed to another disorder
2. Basilar-type migraine
   A. At least two attacks fulfilling criteria B–D
   B. Aura consisting of at least two of the following fully reversible symptoms, but no motor weakness:
      i. Dysarthria
      ii. Vertigo
      iii. Tinnitus
      iv. Hypacusia
      v. Diplopia
      vi. Visual symptoms simultaneously in both temporal and nasal fields of both eyes
      vii. Ataxia
      viii. Decreased level of consciousness
      ix. Simultaneously bilateral paresthesias
   C. At least one of the following:
      i. At least one aura symptom develops gradually over ≥5 min and/or different aura symptoms occur in succession over ≥5 min
      ii. Each aura symptom lasts ≥ or ≤60 mins

TABLE 19.2 AVAILABLE TRIPTANS AND MODE OF DELIVERY

1. Sumatriptan—subcutaneous injection, nasal, oral
2. Eletriptan—oral
3. Naratriptan—oral
4. Rizatriptan—oral
5. Zolmitriptan—nasal, oral
6. Almotriptan—oral
7. Frovatriptan—oral

and prochlorperazine. Abortive therapy is more effective if given early in the course of the headache. Patients should be treated with the safest, least expensive medications and advance to migraine-specific alternatives if the initial treatment fails.

Preventive treatment for migraine headache is indicated when headaches become recurrent (greater than four headaches per month), long lasting (>12 hours), and interfere with daily activities. Commonly used therapies include antihypertensives, antidepressants, anticonvulsants, herbal remedies, and acupuncture. Botulinum toxin injection to

trigger points (6) and surgical resection of trigger points like glabellar muscles and zygomaticotemporal branch of the trigeminal nerve are effective therapies for selected patients with moderate recurrent migraine that are difficult to manage with standard therapy (7).

TENSION-TYPE HEADACHE

Tension-type headache (TTH) is the most common type of primary headache in the general population. Epidemiologic studies have shown prevalence as high as 80% between 20- and 40-year-olds. Women are affected more than males. TTH tends to peak in the fourth decade with decreasing prevalence with increasing age. Sustained contraction of pericranial muscles was believed to be the cause of TTH, but studies have failed to prove a causative relationship. Terms like stress headache and muscle-contraction headache have been abandoned. The pathogenesis of TTH is unclear and is likely multifactorial. In the episodic form there is activation of peripheral nociceptors around blood vessels in muscles and tendon insertion resulting in increased muscle tenderness and headaches. In the chronic form, general pain sensitivity in the central nervous system is increased due to repetitive and sustained pericranial myofascial nociceptor activation (8).

TTH attacks are mild to moderate in intensity and are usually less debilitating than migraine attacks. The pain is constant, nonthrobbing, and localized to the occipitonuchal or bifrontal regions bilaterally. It is often described as tightness, fullness, or "viselike." Attacks are variable in duration, lasting from 30 minutes to 7 days. They are not associated with prodromal periods or auras. Nausea and vomiting are extremely uncommon. Muscle tenderness in the head, neck, and shoulders are usually associated with the headaches and its intensity will parallel that of the attack.

The IHS divides TTHs into an episodic and chronic form, each with specific diagnostic criteria (Table 19.3).

TABLE 19.3 INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS 2ND EDITION DIAGNOSTIC CRITERIA FOR EPISODIC AND CHRONIC TTHs (5)

Episodic TTHs

1. Infrequent episodic TTH
   - A. At least 10 episodes occurring on <1 d/mo on average (<12 d/y) and fulfilling criteria B–D
   - B. Headache lasting from 30 min to 7 d
   - C. Headache has at least two of the following characteristics:
     1. bilateral location
     2. pressing/tightening (nonpulsating) quality
     3. mild or moderate intensity
     4. not aggravated by routine physical activity such as walking or climbingstairs
   - D. Both of the following:
     1. no nausea or vomiting
     2. no more than one of photophobia or phonophobia
   - E. Not attributed to another disorder
2. Frequent episodic TTH
   - A. At least 10 episodes occurring on ≥1, but ≤15 d/mo for at least 3 mo (>12 and <180 d/y) and fulfilling criteria B–D
   - B. Headache lasting from 30 min to 7 d
   - C. Headache has at least two of the following characteristics:
     1. bilateral location
     2. pressing/tightening (nonpulsating) quality
     3. mild or moderate intensity
     4. not aggravated by routine physical activity such as walking or climbingstairs
   - D. Both of the following:
     1. no nausea or vomiting
     2. no more than one of photophobia or phonophobia
   - E. Not attributed to another disorder

Chronic TTH

- A. Headache occurring on ≥15 d/mo on average for >3 mo (≥180 d/y) and fulfilling criteria B–D
- B. Headache lasts hours or may be continuous
- C. Headache has at least two of the following characteristics:
  1. bilateral location
  2. pressing/tightening (nonpulsating) quality
  3. mild or moderate intensity
  4. not aggravated by routine physical activity such as walking or climbing stairs
- D. Both of the following:
  1. no more than one of photophobia, phonophobia, or mild nausea
  2. neither moderate or severe nausea nor vomiting
- E. Not attributed to another disorder

Patients with episodic TTH have fewer than 15 attacks per month and do not cause a significant impact in quality of life or performance. They are further subdivided into infrequent episodic TTH (less than one episode a month) or frequent episodic TTH (more than one, but less than 15 attacks per month). Individuals with chronic subtypes have more than 15 attacks per month. Chronic forms evolve from episodic forms and are associated with greater economic and personal costs.

Although TTHs are the most common primary headache, patients do not routinely seek medical attention. The history will reveal the quality and duration of the attacks. Physical exam will reveal normal blood pressure, oxygen saturation, and no neurologic deficits. Tenderness may be elicited in the scalp or neck muscles. As for all primary headaches there are no diagnostic tests available for TTH. Imaging of the brain is indicated if the pain is sudden and severe in order to exclude other conditions such as subarachnoid hemorrhage. Stress has been reported to be the most common precipitant of TTHs. Anxiety, poor posture, and depression have also been associated with the development of attacks. Attacks are not precipitated by food, weather changes, or exposure to noxious odors.

The treatment of TTHs ranges from nonpharmacologic therapies to use of potent analgesics. Over-the-counter analgesics (NSAIDs, aspirin, and acetaminophen) are considered first-line therapies and have been shown to be beneficial in most cases (9). NSAID in combination with caffeine works better than NSAIDs alone, but carries a greater risk of side effects. Patients often try a number of medications before seeking medical attention. These medications should not be used more than 10 days a month to decrease the risk of medication overuse headaches. Preventive treatment of TTHs is indicated if the attacks are frequent, long lasting, or they have a significant impact on quality of life. Tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors, and anticonvulsant medications have been tried with variable success.

CLUSTER HEADACHES

Cluster headache is a type of primary headache that belongs to the trigeminal autonomic cephalagias, characterized by short-lasting attacks accompanied by autonomic symptoms. The pathophysiology of cluster headache is not completely understood. The most accepted theory is activation of the trigeminal–hypothalamic pathway causing central disinhibition of nociceptive and autonomic pathways. The prevalence of cluster headache is estimated to be less than 1% and affects mostly men. It is most common in the third decade of life. Most patients are chronic cigarette smokers and a small proportion have a history of recent head trauma.

Cluster headache attacks are short lasting (15 to 180 minutes) and may occur up to 8 times a day. Attacks may occur daily for several weeks followed by a period of remission. The headache is severe and frequently described as stabbing, sharp, and excruciating. The pain is unilateral in the orbital, supraorbital, or temporal regions. Auras, nausea, vomiting, and photophobia are rare. Sympathetic impairment and parasympathetic hyperactivity are found on the ipsilateral side. Autonomic symptoms, such as ptosis, myosis, lacrimation, sweating, rhinorrhea, and nasal congestion, are commonly described during an attack. In contrast to migraineurs, patients become agitated and restless, scream in pain and crawl on the floor in desperation, and hit their head against hard surfaces. Attacks may be evoked by alcohol consumption, nitroglycerin, and histamine. Other commonly described triggers include stress, extreme temperatures, glare, and sexual activity.

The diagnosis of cluster headaches does not require extensive laboratory testing or imaging. CT or MRI of the head is recommended for initial evaluation of patients with cluster headaches and when the exam reveals atypical features or neurologic deficits. The IHS published specific diagnostic criteria for cluster headaches and divides them into episodic, more than 1 month of remission, and chronic, less than 1 month of remission (Table 19.4).

As with other primary headaches, treatment of the attacks are divided into abortive and preventive. First-line therapies for the treatment of acute cluster headaches include 100% oxygen at 12 L/min via nonrebreather mask and/or subcutaneous sumatriptan. Other commonly used abortive medications include intranasal sumatriptan, intranasal and oral zolmitriptan, subcutaneous octreotide, and intranasal lidocaine. Preventive therapy is recommended at the onset of an attack in order to avoid future attacks over the expected cluster period. Verapamil 240 to 320 mg/day is the drug of choice for preventive therapy. Glucocorticoids, lithium, ergotamine, valproic acid, and topiramate are other pharmacologic therapies that have been used with mixed results. Surgical procedures directed at the trigeminal nerve are rarely employed and only recommended for attacks refractory to all available pharmacologic intervention. Gamma knife radiosurgery, nerve sectioning, radiofrequency thermoregulation, and deep brain stimulation have been described.

CHRONIC DAILY HEADACHES AND MEDICATION OVERUSE HEADACHE

CDHs are a common problem affecting 4% of the population. Headache clinic-based studies find 80% of patients have CDH (10). Most CDH sufferers have a primary headache disorder that has been transformed into a chronic form. Classification of CDH requires headache on 15 or more days per month. Classification is then further broken down by average daily headache duration (less than or greater than 4 hours). Workup requires determining if there is a secondary disorder underlying the frequent headaches. Patients in chronic pain often overuse medication, which can play a role in initiating or sustaining pain.

TABLE 19.4 INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS 2ND EDITION DIAGNOSTIC CRITERIA FOR EPISODIC AND CHRONIC CLUSTER HEADACHES (5)

Cluster headache diagnostic criteria:
- A. At least five attacks fulfilling criteria B–D
- B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15–180 min if untreated
- C. Headache is accompanied by at least one of the following:
  1. ipsilateral conjunctival injection and/or lacrimation
  2. ipsilateral nasal congestion and/or rhinorrhea
  3. ipsilateral eyelid edema
  4. ipsilateral forehead and facial swelling
  5. ipsilateral meiosis and/or ptosis
  6. a sense of restlessness or agitation
- D. Attacks have a frequency from one every other day to 8 per day
- E. Not attributed to another disorder

1. Episodic cluster headache diagnostic criteria:
   - A. Attacks fulfilling criteria A–E for cluster headache
   - B. At least two cluster periods lasting 7–365 days and separated by pain-free remission of ≥1 mo
2. Chronic cluster headache diagnostic criteria:
   - A. Attacks fulfilling criteria A–E for cluster headache
   - B. Attacks recur over >1 y without remission periods or with remission periods lasting <1 mo

Medication overuse headaches have previously been known as rebound headache. Approximately 5% to 10% of headache sufferers have medication overuse headache. Medication overuse can exacerbate a primary headache disorder, interfere with effectiveness of preventive medications, or cause tolerance. This is a behavioral disorder and fulfills the criteria for physical dependency. Overuse medications include analgesics, opioids, ergotamine, and triptans. The International Headache Society Classification requires headache for 15 days per month with medication usage 3 months or greater.

Treatment of CDH can be difficult. Acute medications should be limited and prophylactic medications can be started realizing that they may not be effective until the abused medications have been removed. During the withdrawal of acute medication, patients may need psychological support. Encourage regular sleep, exercise, and meals. Patients may have severe exacerbations of their migraines during removal of the acute agents. Additional treatment called headache terminators may be needed to break the cycle of CDH (10,11).

SECONDARY HEADACHE AND FACIAL PAIN

Initial evaluation of the headache patient requires a careful history, physical and neurologic exam. A search should be made for certain "red flags" that increase the suspicion of a secondary headache disorder. Table 19.5 lists concerning findings that should be further evaluated.

In addition to the complete ENT exam further evaluation should include the retina (papilledema), cerebrovasculature (temporal arteries or carotid bruits), cervical paraspinal muscles, and TMJ. Red flag findings or positive findings on exam should be clarified with additional diagnostic tests if indicated. Neuroimaging should include preferably MRI, if available, or CT scan. A complete review of all secondary headache causes is beyond the scope of this chapter. Table 19.6 is a list of possible causes of secondary headaches. Following is a review of the more pertinent otolaryngology diagnoses.

SINOGENIC PAIN

True sinus causes of headache are uncommon. Sinogenic causes can include allergic rhinitis, acute rhinosinusitis, mucocele, mucosal contact headaches, or neoplasm. Other common nasal conditions like nasal polyps and mucus retention cysts rarely cause pain. Sinus headaches are most commonly a primary headache disorder. A study performed in 2002 questioned 100 consecutive patients responding to the symptom of sinus headache. Among them, 86% met criteria for

TABLE 19.5 SECONDARY HEADACHE RED FLAGS

- New onset severe headache/thunderclap headache
- Rapidly increasing headache frequency
- Headaches after trauma
- Headache with systemic symptoms of fever, chills, mental status changes
- Headache in immunocompromised individual
- New onset headache in age >50
- Focal neurologic signs
- Headaches associated with increases in ICP (cough, sneezing, valsalva)
- Headache awakening one from sleep

TABLE 19.6 SECONDARY CAUSES OF HEADACHE

Vascular: temporal arteritis, HTN, cavernous sinus thrombosis, cerebral aneurysm, AV malformation
Musculoskeletal: neck and shoulder muscle contraction, strain of extraocular or intraocular muscles, cervical spondylosis, temporomandibular arthritis
Infections: meningitis, encephalitis, brain abscess, sepsis, sinusitis, osteomyelitis, parotitis, mastoiditis, herpes zoster
Neoplasm: cerebral neoplasms, pheochromocytoma
Subdural hematoma
Cerebral hemorrhage/infarct
Pseudotumor cerebri
Normal pressure hydrocephalus
Post LP
Trauma
Dental: abscess, periodontitis, poorly fitting dentures
Neuralgia: sphenopalatine, glossopharyngeal, Sluder's, occipital
Eye: glaucoma
Metabolic: uremia, carbon monoxide inhalation, hypoxia, hypoglycemia
Endocrine: hypothyroidism
Drugs: alcohol, nitrates, histamine antagonists
Paget disease of the skull
Effort induced: exertional, cough induced, coital cephalagia
Emotional/psychiatric

migraine or probable migraine. Only 3% were diagnosed with rhinosinusitis (12). This can be confusing to the patient and the clinician especially because it is not unusual for migraine referred to the distribution of the trigeminal nerve to have parasympathetic symptoms of rhinorrhea, congestion, or lacrimation. Those patients who do have headache and facial pain from rhinosinusitis often have associated symptoms of nasal obstruction, hyposmia, or purulent nasal drainage. The American Academy of Otolaryngology Head and Neck Surgery includes headache as only a minor factor in the diagnosis of acute rhinosinusitis (Table 19.7). Facial pain alone does not constitute rhinosinusitis without another major factor.

TABLE 19.7 CRITERIA FOR DIAGNOSIS OF RHINOSINUSITIS—2 MAJOR OR 1 MAJOR AND 2 MINOR (13)

Major Factor	Minor Factors
Facial pain/pressure	**Headache**
Facial congestion/fullness	Fever (chronic)
Nasal obstruction/blockage	Halitosis
Nasal discharge/purulence/discolored postnasal drainage	Fatigue
Hyposmia/anosmia	Dental pain
Purulence in the nasal cavity on exam	Cough
Fever (acute rhinosinusitis only)	Ear pressure/pain/fullness

TABLE 19.8 HEADACHE ATTRIBUTED TO RHINOSINUSITIS (5)

Diagnostic criteria
A. Frontal headache accompanied by pain in one or more regions of the face, ears, or teeth and fulfilling criteria C and D
B. Clinical, nasal endoscopic, CT and/or MRI imaging and/or laboratory evidence of acute or acute-on-chronic rhinosinusitis
C. Headache and facial pain develop simultaneously with onset or acute exacerbation of rhinosinusitis
D. Headache and/or facial pain resolves within 7 d after remission or successful treatment of acute or acute-on-chronic rhinosinusitis

The IHS has specific criteria for headache due to rhinosinusitis. Diagnosis requires a history of associated symptoms and clinical evidence via examination or radiologic studies. Nasal endoscopy, CT, or MRI can be used to determine the presence of rhinosinusitis. The IHS classifies sinus headache as a secondary diagnosis as illustrated in Table 19.8.

Headache from paranasal sinus disease is characterized by deep, dull pain that may or may not pulsate. Typical referral patterns exist as recorded in Table 19.9. Based on the studies by Wolff most pain emanating from the sinuses is related to inflammation and engorgement of the turbinates, ostia, and nasal frontal ducts. Anatomical narrowing can create contact points between mucosal surfaces. These trigger points cause referred pain.

Other causes of headache include rhinitis, mucoceles, neoplasm, and contact points. Nasal mucoceles or neoplasms often reach a notable size before symptoms of obstruction of the ostia cause pain and symptoms. Nasal mucosal swelling and anatomical abnormalities like concha bullosa or septal deflections can cause contact points and theoretical pain. Release of SP can occur locally and centrally through the trigeminal pathways.

TABLE 19.9 HEADACHE AND FACIAL PAIN LOCATION IN ACUTE SINUSITIS (14)

Paranasal Sinus	Location of Pain
Frontal	Frontal region Vertex
Maxillary	Over the antral area Radiate to upper teeth Forehead
Ethmoid	Nasion Retro-orbit Radiate to temporal
Sphenoid	Occipital Vertex Frontal region Retro-orbit

Various studies have been performed to evaluate the validity of contact points between membranes as the cause of rhinogenic headache. Palpation of the contact point or injection of Xylocaine with 1:100,000 epinephrine to contact point during a headache has been tried. Jones has, however, found that 50% of these contact areas are on the side opposite the side of the pain (15). Case reports and series exist showing improvement in headache pain from 30% to 90% after surgical treatment of these areas. Treatment varies from turbinate reduction, septoplasty, to directed endoscopic ethmoidectomy. Long-term studies by Welge-Luessen have been performed with almost 10-year follow up revealing 65% improvement (16). No controlled or randomized studies have been performed to investigate the validity of surgical treatment.

NEUROPATHIC PAIN

Neuropathic pain is nerve-type pain affecting any CN with sensory division or sensory nerve in the head and neck. The most common nerves affected include the trigeminal nerve and cervical roots 1, 2, and 3. Common disorders include trigeminal, glossopharyngeal, or occipital neuralgia. Pain is described as electric shock, sharp, or burning. Triggers often include non-noxious stimuli like touching of the scalp. Causes can include inflammation, trauma, vascular compression due to tumors or bone projections as seen in Eagle syndrome.

TRIGEMINAL NEURALGIA

Trigeminal neuralgia is the most common cranial neuralgia. Pain is unilateral, brief, lancinating pain limited to the distribution of CN V. The maxillary and mandibular branches of CN V are most commonly affected. Typical triggers include washing, shaving, talking, or brushing teeth. Women are more commonly affected than men during the fifth to seventh decade. Workup should include MRI to rule out other diagnoses. Vessel compression is best visualized on magnetic resonance angiogram (MRA). Table 19.10 lists the differential diagnosis of trigeminal neuralgia.

TABLE 19.10 DIFFERENTIAL DIAGNOSIS OF TRIGEMINAL NEURALGIA

Multiple sclerosis
Basilar artery aneurysm
Arterial or venous compression
Tumor
Postherpetic neuralgia
Temporal arteritis
Temporomandibular syndrome

Treatment of trigeminal neuralgia is directed toward prophylactic treatment most commonly using the antiseizure medication carbamazepine. Other medications include gabapentin, baclofen, phenytoin, sodium valproate, and chlorphenesin. Surgical treatment is reserved for medical failures. Extracranial peripheral denervation involves treatment at trigger points, which can be temporary using local anesthetics or permanent using alcohol, freezing, and heating. Surgical radiofrequency ablation involves destruction of the Gasserian ganglion by radiologic guidance of a device inserted into the cheek and through the foramen ovale into the Gasserian ganglion. The usage of glycerol injection called glycerol trigeminal rhizotomy is effective but has a high recurrence rate. Microvascular decompression is utilized to treat vascular loop compression of the trigeminal nerve by suboccipital retromastoid craniectomy. Other procedures utilized include gamma knife radiosurgery and botulinum toxin injections (1,17,18).

GLOSSOPHARYNGEAL NEURALGIA

Glossopharyngeal neuralgia is an uncommon disorder involving CN IX. This was first described in 1910 by Weisenburg described as repetitive, brief attacks or lancinating pain located in the soft palate, base of tongue, tonsillar fossa, and ear. Older men are most commonly affected between ages 50 and 60. Episodic attacks are triggered by pressure in the tonsillar fossa or hyothyroid membrane. Symptoms can be provoked by swallowing, yawning, and sneezing. Rarely this disorder can be associated with syncope when vascular compression of the nerve results in dysfunction of the glossopharyngeal-vagus reflex arc with bradycardia or asystole (19). Workup requires MRI evaluation to rule out oropharyngeal malignancy, infection, or vascular compression. Treatment is similar to trigeminal neuralgia. Surgical options are reserved for medical failures and include CN section or microvascular decompression of CN IX.

Eagle syndrome is a variant of glossopharyngeal neuralgia where the styloid process or a calcified stylohyoid ligament compresses CN IX causing symptoms of referred otalgia. Pain tends to be more persistent and dull in character (17–19)

OCCIPITAL NEURALGIA

Occipital neuralgia is defined by paroxysmal stabbing pain in the distribution of the greater and lesser occipital nerve. This is to be distinguished from a deep, aching pain in the occiput arising from diseases of the posterior cranial fossa and skull base. Associated symptoms can include visual disturbances, dizziness, nausea, tinnitus, and scalp paresthesias. Diagnosis is made by relief of pain by a nerve block. Treatment includes heat, physical therapy, transcutaneous electrical nerve stimulation (TENS) units, nonsteriodal medications, baclofen, and carbamazepine. Local blocks with bupivacaine, steroids, and alcohol can be performed. In protracted cases, nerve section has been performed.

SLUDER SYNDROME

Sluder syndrome was originally described in 1908 as unilateral, burning pain involving the lateral side of the nose, eye, forehead, and temporal or mastoid regions. Autonomic symptoms include lacrimation, rhinorrhea, and injected conjunctiva. This syndrome is now classified as a cluster headache but it is a form of sphenopalatine neuralgia. The term is now used loosely. Septal spurs impinging on the lateral nasal wall have been described as causing neuralgia. Diagnosis is aided by application of anesthesia in the region of the sphenopalatine ganglion. Treatment includes application of cocaine to the mucosa overlying the ganglion, removal of septal spur, or ablation of the sphenopalatine ganglion (18,20).

HEADACHE ASSOCIATED WITH VASCULAR DISORDERS

Headache in vascular conditions presents acutely and with associated neurologic signs and symptoms. Headache can be an initial warning symptom and it is crucial to recognize its association with vascular disorders. Warning signs include rapid onset of headache unrelieved by usual analgesics, persists or worsens, and becomes associated with other neurologic signs. Table 19.11 lists vascular causes of headache.

SUBDURAL HEMATOMA

Subdural hematoma is the most common cause of severe headache with abrupt onset. The patient who presents to the emergency room with a severe first or worst headache needs to be taken seriously. Subdural hematoma is life threatening with 50% mortality rate. Headache and third nerve palsy may be an early warning sign of impending aneurysmal rupture. Associated symptoms include nuchal rigidity, photophobia, fever, loss of consciousness, diplopia, or seizures. Workup includes a noncontrast CT scan, and if this is negative, a lumbar puncture (LP) is performed looking for elevated pressure and red blood cells. Patients should be hospitalized where there are appropriate neurosurgical services (18,21).

TABLE 19.11 VASCULAR CAUSES OF HEADACHE

Ischemic stroke
TIA
Subarachnoid hemorrhage
Cerebral aneurysm
Arteriovenous malformation (AVM)
Cerebral venous sinus thrombosis
Dural AV fistula
Giant cell arteritis
Carotid or vertebral artery dissection

TEMPORAL ARTERITIS

Temporal arteritis occurs most commonly in women greater than 50 years of age. Headaches are moderate to severe with a variable presentation. Pain can be burning, sharp or throbbing, bilateral or unilateral, intermittent or continuous. Jaw claudication is highly characteristic occurring in 40% with rare tongue claudication in 4% (21). Temporal or occipital artery thickening and tenderness occurs in two-thirds of patients. The most dreaded symptom includes blindness in 30% of untreated patients. Associated symptoms include scalp sensitivity, polymyalgia, fatigue, low-grade fever. Diagnosis is made by elevated erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP). Temporal artery biopsy reveals inflammation. Skip lesions can occur requiring long biopsy segments up to 5 cm to prevent false-negative results. Treatment includes high-dose prednisone 40 to 80 mg/day. Response is generally rapid in 24 to 48 hours but long-term steroids may be required to prevent visual loss (18).

CAROTIDYNIA AND CAROTID ARTERY DISSECTION

Classic findings of carotid artery dissection include sudden onset ipsilateral headache and/or neck pain with Horner syndrome. Head pain can refer to the ear or involve the ophthalmic division. Pain is often associated hours later with transient ischemic attack (TIA), stroke, or retinal ischemia. Arterial dissection can be seen on ultrasound, MRI/MRA, or angiography. Treatment involves early anticoagulation to avoid 15% mortality (18).

Carotidynia refers to radiating pain from inflammation of the carotid fascia to the jaw, face, ear, eye, or head. Pain is variable in its characteristic and duration. Pain is worsened by swallowing, sneezing, coughing, and neck motion. Other disorders should be ruled out including carotid dissection, aneurysm, and giant cell arteritis. Treatment includes NSAIDs (21).

HEADACHE ASSOCIATED WITH NONVASCULAR INTRACRANIAL DISORDERS

In this category of disorders, the otolaryngologist should be familiar with idiopathic intracranial hypertension otherwise known as pseudotumor cerebri or otitic hydrocephalus. Reduced CSF absorption is thought to cause a rise in intracranial pressure (ICP) and resultant symptoms. This entity is most common in obese females between the ages of 20 and 42. The headache is described as severe, daily, and pulsatile. Symptoms are made worst by cough, straining, or exertion. Papilledema is the hallmark of the disorder with elevated CSF pressure but otherwise normal

neurologic exam. Associated symptoms include tinnitus, visual changes, CN VI palsy, weight gain, endocrine abnormalities and predisposing mastoiditis or ear infection. Evaluation reveals normal MRI and contrast-enhanced CT scan with elevated CSF pressure on LP. The cornerstone of treatment includes weight loss, low salt diet, and diuretics including acetazolamide to reduce CSF production or furosemide. In chronic cases, surgical shunting or optic nerve sheath fenestration for decompression is performed.

HEADACHE OR FACIAL PAIN ASSOCIATED WITH CRANIOFACIAL OR CERVICAL DISORDERS

Cervicogenic headaches are relatively common secondary to cervical spine abnormalities. This term was first introduced in 1983 by Sjaostad et al. but is considered a controversial term. Women are more commonly affected than men and there is often a history of trauma. Headache is unilateral or bilateral localized to the occiput but can radiate to the frontal region. Pain is triggered by neck movement or palpation of trigger points. Pain is constant with episodes of throbbing. Associated symptoms include nausea, vomiting, photophobia, phonophobia, and blurred vision. On exam, tenderness over the suboccipital, C2, C3, or C4 regions with reduced range of motion is found. Cervical radiographs can reveal abnormalities on flexion–extension films, abnormal posture, and bone or joint pathology. Treatment includes physical therapy and NSAIDs. Nerve blocks can be diagnostic and therapeutic. Botulinum toxin injections have been used (23).

TEMPOROMANDIBULAR JOINT SYNDROME

TMJ syndrome is a collective term including intracapsular and myofascial pain disorders. Females between the ages of 20 and 40 are most commonly affected. The disorders are characterized by facial pain, otalgia, and headache. Organic causes are less common than myofacial pain disorder. Myofacial pain dysfunction is a muscular disorder that has a multifactorial origin including stress. Pain is diffuse and poorly localized. Early morning exacerbations are typical with dull, radiating pain. Pain is elicited on palpation of the joints. Treatment includes education of causes. A more comprehensive discussion of TMJ syndrome can be found in Chapter 54.

CONCLUSION

Headache and facial pain are commonly seen by the otolaryngologist. Primary headache disorders are much more common than headaches originating from the sinuses. History and physical exam are paramount to identifying underlying causes. MRI and CT scan are indicated based on identification of red flags including rapid onset, worsening headache, neurologic signs, associated fever, and history of trauma or headache awakening one from sleep. Secondary causes of headache including neuralgias, vascular disorders, cervical spine abnormalities, and TMJ syndrome should be recognized by the otolaryngologist. Many of these disorders are in the realm of treatment by the otolaryngologist.

HIGHLIGHTS

- Primary headache disorders are the most common cause of headache and facial pain.
- Pain sensitive intracranial structures include major venous sinuses, large cerebral vessels, upper cervical nerves, and CNs V, VII, IX, and X. The trigeminal nerve provides the majority of the innervation to the head and face region.
- Migraine headaches are the most common primary headache disorder lasting 4 to 72 hours. Diagnosis is made mainly by history. Associated symptoms include nausea, photophobia, and phonophobia. Most patients can identify at least one trigger. Auras are identified in 15% to 30% of migraine sufferers.
- Effective treatment for migraine includes acute headache resolution, avoidance of triggers, and preventions. Abortive treatments include analgesics, triptans, or ergotamine taken early in the course of the headache. Preventive treatment is indicated when headaches occur more than 4 per month, long acting greater than 12 hours, or interfere with daily activities.
- Secondary headache disorders are numerous. Red flags indicating further workup needed include rapid onset, rapid increasing frequency, history of trauma, systemic symptoms of fever, chills, change in mental status, age greater than 50, focal neurologic signs, headache upon awakening, or headache with signs of elevated ICP. MRI is the preferred study in most conditions.
- True sinus headaches are uncommon. Pain is usually deep, dull pain emanating from engorgement of the turbinates, sinus ostia, or nasofrontal ducts. Causes of sinogenic headache include rhinitis, acute rhinosinusitis, mucoceles, neoplasm, and contact points.
- The most common cause of neuropathic pain includes the trigeminal nerve and cervical roots 1, 2, and 3. Common disorders include trigeminal neuralgia, glossopharyngeal and occipital neuralgia. Trigeminal neuralgia is the most common cranial neuralgia involving most commonly women age 50 to 70.
- Vascular headaches present acutely and with associated neurologic signs. Subdural hematoma is the most common cause of severe, abrupt headache. Headache and third nerve palsy can be early signs of aneurysmal rupture.

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20 Complementary and Alternative Medicine

Li-Xing Man *Nicholas C. Sorrel*

A landmark survey by Eisenberg et al. (1) in 1993 surprised the medical community by revealing that over one-third of Americans used unconventional therapies for health and well-being. Three-quarters of these individuals did not inform their physicians of this practice. In a follow-up study, Eisenberg et al. (2) found that the prevalence of unconventional therapy use increased from 33.8% in 1990 to 42.1% in 1997. The most recent data from the 2007 National Health Interview Survey (NHIS) show that 38.3% of American adults and 11.3% of children had used a complementary and alternative medicine (CAM) in the past year (3). Estimated expenditures on CAM increased 25.6% between 1997 and 2007, with 22.0 billion dollars spent on CAM products and 11.9 billion dollars spent on 354.2 million CAM practitioner visits annually (4).

CAM usage is similarly common in other countries. In 2004, an estimated 52% of the Australian population had used a CAM therapy in the last year (5). A 2005 survey by the Canadian government found that 71% of Canadians had used a natural product in their lifetime, with 38% of this group using them on a daily basis (6). In Germany, approximately 60% of adults had used a natural or alternative healing method in the preceding year (7).

The use of CAM therapies has increased over the past several decades, and trends indicate that utilization will continue to increase (5,8). This burgeoning interest in CAM treatments can be monitored in the popular press, in bookstores, and on the internet. Formal courses on CAM have been introduced into the medical school curriculum (9), and a number of peer-reviewed journals are dedicated to CAM topics. The U.S. Congress established the National Center for Complementary and Alternative Medicine (NCCAM) in 1998 to support scientific research and disseminate evidence-based safety and effectiveness information on CAM practices.

The widespread popular interest in, and utilization of, alternative and complementary therapies has led to a corresponding movement in the mainstream medical and scientific communities to incorporate these modalities into existing realms of teaching, clinical practice, and research. Attempts at trying to develop a nomenclature for these modalities in the 1990s led to terms such as "unconventional," "nontraditional," "unorthodox," and "holistic." These terms had the characteristic of revealing cultural values and judgments regarding the appropriateness and legitimacy of these therapies and treatments (10). "Complementary medicine" refers to the use of modalities *in conjunction with* conventional medicine, such as the use of acupuncture in addition to the usual care to control and lessen pain. "Alternative medicine" refers to the use of treatments and therapies *in place of* conventional medicine. Over the past decade, the most widely accepted term has been "complementary and alternative medicine" (CAM). The NCCAM defines CAM as "a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine" (11). More recently, the term "integrative medicine" has become increasingly utilized. This designation reflects the attempt to assimilate legitimate CAM therapies into the continuum of mainstream health care. It refers to a practice that combines both conventional and CAM treatments for which there is evidence of safety and effectiveness. According to Snyderman and Weil (12), integrative medicine "has a far larger meaning and mission in that it calls for restoration of the focus of medicine on health and healing and emphasizes the centrality of the patient–physician relationship."

This chapter gives an overview of the most prevalent CAM modalities, reviews common CAM products and treatments that may have implications for the otolaryngology patient, and reviews CAM treatments for common otolaryngologic problems. Evidence on both the safety and efficacy of CAM modalities continues to evolve. Health care practitioners must be aware of the use of natural products

because of potential adverse effects and interactions with other medications. This chapter does not attempt to present every CAM product or therapy used for an otolaryngologic problem. Rather, it focuses on those modalities that have the most evidence, with an emphasis on randomized controlled trials (RCTs). In this chapter, the authors are in no way advocating the use of the therapies discussed. Knowledge of the clinical efficacy as well as adverse effects of these treatments is necessary so that otolaryngologist/head and neck surgeons can appropriately guide their patients, especially since most individuals using CAM therapies do not disclose their use to their physicians. Possessing an understanding of CAM practices and treatments improves physician–patient communication and enables the health care practitioner to better serve his or her patients.

TYPES OF CAM

The myriad and diverse products and practices that encompass CAM are often organized into broad categories, such as natural products, mind–body medicine, manipulative and body-based practices, whole medical systems, and other CAM practices. Natural products include herbal medicines, vitamins, and minerals. Mind–body medicine includes meditation, yoga, prayer, and biofeedback. Manipulative and body-based practices include spinal manipulation and massage therapy. Whole medical systems include Ayurveda, traditional Chinese medicine (TCM), homeopathy, and naturopathic medicine. Other CAM practices include a range of movement therapies as well as energy therapies. These categories are somewhat overlapping, and some CAM practices may fit into more than one domain. For example, acupuncture is often categorized within mind–body medicine, but has elements like TCM, manipulative and body-based practices, as well as energy medicine (11).

Natural Products

CAM natural products include the use of herbal or botanical medicines, vitamins, and minerals. This domain also includes probiotics, which are live organisms—usually bacteria—that may confer beneficial effects to their hosts. Probiotics are available in foods, such as yogurt, or as dietary supplements. Herbs or botanicals with medicinal qualities represent some of the earliest attempts to improve health and well-being. They are the foundation of most folk remedies and are the cornerstone for many medical systems. A number of modern drugs used in mainstream medical practice were derived from plant sources. For example, the malaria treatments quinine and artemisinin were isolated from the bark of the genus *Cinchona* (a tree native to South America) and the plant *Artemisa annua* (an herb described in "Traditional Chinese Medicine"), respectively.

Many natural products are sold over the counter as dietary supplements and represent the most popular form of CAM use among both adults and children in the United States. The 2007 NHIS found that 17.7% of American adults had used a nonvitamin/nonmineral natural product in the last year (3,11). The most commonly utilized product among adults was fish oil or omega-3, which was used by 37.4% of those who reported using natural products. Other prevalently used natural products included glucosamine (19.9%) and echinacea (19.8%). Over one in ten of those surveyed reported using ginkgo biloba.

Mind–Body Medicine

These approaches focus on the relationship of the mind and body, brain and behavior. Many ancient and indigenous medical systems emphasize this interconnection. Over time, the theory advanced by Descartes of a separation of mind and body became a dominant concept among Western physicians, psychiatrists, and psychologists. Scientific healing in the form of drug therapy and surgery evolved to become the primary Western form of treatment. Over the last several decades, there has been a reemphasis in exploring the mind's ability to affect the immune system as well as other organ systems. The fundamental tenets of mind–body medicine are the concept of treating the whole person and that individuals can be active participants in their own health care (13).

Mind–body techniques include psychotherapy, relaxation, meditation, hypnosis, biofeedback, and yoga. Psychotherapy refers to the treatment of emotional and mental health, which is interwoven with physical health. Relaxation techniques aim to manage and reduce stress. Meditation is a self-directed practice for the purposes of relaxing the mind and body. Some meditation techniques involve focusing attention on single thoughts or words, while others entail focusing on a physical experience such as a breath or a specific sound. All meditation techniques share a common goal of calming mental activity, incessant thoughts, and negative reactions to one's environment or circumstances. In hypnosis, an altered state of mind is induced in which the patient enters into a state of deep and focused concentration and is receptive to specific suggestions. Biofeedback involves the use of instruments that translate physiologic processes into audio or visual signals. Patients can adjust their mental processes to control brain wave activity and bodily processes previously thought to be involuntary by observing monitoring devices. The origins of yoga date back to about 1500 BC in present-day India and Pakistan. As the practice of yoga spread throughout the world, myriad schools of thought and styles of practice have developed. Many people now understand yoga to be a practice of postures, breathing exercises, and cleansing practices, but at its root yoga is the mental process and discipline through which the human consciousness is unified with the divine consciousness (14). The practice of yoga

attempts to achieve harmony between the individual and surrounding universe by bringing the physical body under the control of the mind.

Acupuncture may also be categorized within mind–body medicine. Derived from TCM techniques, acupuncture is a family of procedures involving the stimulation of specific points located along channels corresponding to the flow of energy through the body. Traditionally, these acupoints were stimulated using fine filiform needles (0.12 to 0.46 mm diameter) to penetrate the skin. Modern acupuncture has evolved to include the application of electric currents, pressure, and low-intensity lasers to stimulate the acupoints. Moxibustion is often utilized in combination therapy with acupuncture. Moxibustion involves using heat either on or close to the skin to affect the flow of energy in the channel (15).

Several mind–body techniques were among the most commonly used CAM therapies used by American adults in the 2007 NHIS. The survey found that 12.7% had used deep-breathing exercises, 9.4% had practiced meditation, and 6.1% had practiced yoga in the past 12 months (3). An estimated 3.1 million adults and 150,000 children had used acupuncture, a 48% increase compared to the 2002 NHIS.

Manipulative and Body-Based Practices

Manipulative and body-based techniques focus primarily on touching, massaging, and manipulating the physical body to provide healing (16). Common therapies in this domain are osteopathic or chiropractic spinal manipulation and massage therapy. The 2007 NHIS estimated that 8.6% of American adults and 2.8% of children used osteopathic or chiropractic manipulation, while 8.3% of adults and 1% of children had used massage (3,11). Movement-based therapies include Feldenkrais bodywork, Alexander technique, Trager Psychophysical Integration, Aston patterning, and Pilates.

Osteopathic Medicine

Osteopathic medicine was developed by the allopathic physician Andrew Taylor Still in 1874 when he became disenchanted with the crude techniques and harmful effects of the medicines used by doctors practicing along the 19th century American frontier. After the American Civil War, during which he practiced allopathic medicine while serving as a hospital steward in the Kansas Infantry, Still became disaffected with conventional medicine in 1864 after three of his children died in a meningitis epidemic. He quit medical practice and devoted time to investigate the relationship between structure and function in the body. By 1874, he had defined the principles and philosophy of practice of osteopathy. Still's primary tenet was that structural abnormality causes functional abnormality, leading to illness. Treatments were designed to use the body's own resources. Manipulation was used to promote appropriate blood delivery, lymphatic return, and transmission of neural impulses to restore health (17). Common forms of osteopathic manipulative treatment (OMT) used today include high-velocity low-amplitude thrust, muscle energy, counterstrain, and cranial osteopathy. Craniosacral therapy is a simpler variant of cranial osteopathy that is practiced by nonphysicians such as physical therapists and massage therapists.

Osteopathy has evolved differently in the United States and in other parts of the world. Internationally, osteopathic medicine has diverged into two branches, nonphysician manipulative medicine osteopaths and osteopathic physicians practicing the full scope of medical practice. In the United States, osteopaths always have been physicians and have the same practice rights as allopathic physicians. Current practitioners implement the osteopathic medical philosophy to varying degree along a continuum of medical care (17). Only a small percentage of osteopathic physicians limit their practice to OMT, many practice no manipulation at all, and some do not believe in the clinical efficacy of OMT at all.

Chiropractic Medicine

Daniel David Palmer, a self-taught healer in Davenport, Iowa, founded the chiropractic profession in 1895. Palmer believed that the body had "innate intelligence", or a natural healing ability (18). He theorized that "vertebral subluxation" (spinal misalignment causing abnormal nerve transmission) was the cause of disease, and that chiropractic adjustment (manual manipulation of misaligned vertebrae) was its cure (19). The American Chiropractic Association defines chiropractic as "a health care profession that focuses on disorders of the musculoskeletal system and nervous system, and the effects of these disorders on general health" (20). Chiropractors manually adjust the spine to reestablish motion in the vertebral column in order to restore the normal functioning of the nervous system, which serves as the foundation for health and well-being (21).

Chiropractic has engendered controversy from the outset. In the first chiropractic adjustment, Palmer restored the hearing of Harvey Lillard, a janitor in Palmer's office building who had been deaf for 17 years. Palmer touted chiropractic as a drugless system of healing and as a cure for almost all human ailments (19). Over time, philosophical differences have evolved within the chiropractic profession. A minority of chiropractors adhere to Palmer's conservative philosophy, relying on deductions from irrefutable doctrines and rejecting scientific reasoning. These practitioners believe that chiropractic adjustment should not be combined with other types of therapy. Most chiropractors, however, seek to combine chiropractic philosophy and scientific principles with a holistic paradigm of health. The mainstream chiropractor, therefore, may incorporate modalities such as nutrition and lifestyle counseling, stress management techniques, acupressure, soft tissue manipulation, and homeopathy.

Chiropractic has developed into the third largest independent health profession in the Western world, after allopathic medicine and dentistry. It is recognized as the largest, most regulated, and best recognized of the CAM professions (22). It is estimated that 30% of all CAM practitioner visits are to chiropractors (2). Many chiropractors, however, view themselves as practicing in the realm of integrated medicine or mainstream medicine and do not view themselves a CAM practitioners (23). Chiropractic training requires 4 years of study, with rigorous educational standards supervised by government-recognized accrediting agencies. In the United States, passage of the National Board of Chiropractic Examiners written examination is recognized or required in all 50 states. Most patients go to chiropractors for musculoskeletal problems, with 60% presenting with low back pain and the remainder with head, neck, and extremity symptoms (22).

Massage

Massage as a therapeutic technique dates back thousands of years, with references evident in the writings of ancient Greece (Hippocrates), Egypt, India, and China among other civilizations. Although there are many styles and techniques, massage therapy is based on the principle that the body functions best when arterial supply as well as venous and lymphatic return are unimpeded. Muscle tightness and pain may arise if this flow is hindered. The basic techniques of massage—effleurage, pétrissage, tapotement, friction, and vibration—are directed at the skin, fascia, and muscles and are designed to restore proper fluid dynamics (24). Effleurage is a gliding stroke applied with light to moderate pressure frequently used to start a session or to link between other techniques. Pétrissage massage movements are applied with deeper pressure to lift and compress the underlying fascia and muscle in a kneading motion. Tapotement involves a rhythmic percussion of rapid, repeated taps or blows administered with the edge of the hand, cupped hand, fist, or fingertips. Friction is a technique in which the tips of the fingers or thumbs are used in a circular motion. Vibration involves use of the hands in a light, quivering motion or a mechanical oscillator. Specific styles include Swedish massage, sports massage, acupressure, Shiatsu, trigger point massage, and reflexology.

Massage therapy is becoming increasingly popular in the United States. The 2007 NHIS showed a 66% increase in prevalence of use compared to 2002 estimates (3). There are approximately 1,500 massage therapy schools and training programs in the United States. As of 2010, 43 states had laws regulating massage therapy. Regulations are increasing with states are increasingly requiring that massage therapists meet minimum training requirements at an accredited institution, pass a national exam, complete continuing education requirements, and carry malpractice insurance (25).

Whole Medical Systems

Whole medical systems are complete systems of theory and practice that evolved over time outside of conventional allopathic medicine. Ancient whole medical systems include Ayurveda and TCM. More modern systems that developed over the last several centuries include homeopathy and naturopathy. In the 2007 NHIS, homeopathy ranked as the tenth most commonly used CAM therapy among adults (1.8%) and fifth among children (1.3%) (3).

Ayurveda

Ayurvedic medicine originated during the Vedic period (2000 BC) of ancient India. The word *Ayurveda* is a compound of two Sanskrit words: *Ayus*, which means "life" or "life span," and *Veda*, which means "knowledge" or "science." Ayurveda, translated as "the science or wisdom of long life," is a holistic system of health care that emphasizes wholeness (26). Treatment approaches cover the full range of a patient's life: mind, body, behavior, environment, and consciousness (27). In Ayurveda medicine, understanding the patient's mind and body type are essential to diagnosis and treatment. Therapeutic qualities of diet and techniques to balance emotions are emphasized. Ancient Ayurvedic texts contain both an extensive materia medica on the use of medicinal plants and writings on surgery and surgical instruments. One of the eight main disciplines of Ayurveda encompasses otolaryngology-head and neck surgery as well as ophthalmology. Sushruta, a surgeon who practiced and taught along the Ganges River between 800 BC and first century AD described skin flaps, rhinoplasty techniques, and pedicled cheek and forehead flaps for nasal reconstruction (28,29).

Ayurveda is grounded in the metaphysics of five great elements—earth, water, fire, air, and ether—that comprise the universe, including the human body. Three bodily humors, *doshas*, are derived from the elements and govern the functioning of the body. The doshas are *Vata*, which governs flow, motion, and homeostatic mechanisms; *Pitta*, which regulates bodily functions related to heat and metabolism; and *Kapha*, which controls structure, cohesion, and growth (27). It is believed that a harmony between the three doshas is necessary for optimum health and to maintain the body's natural state of balance. Ayurveda places great emphasis on strategies to prevent illness. Modalities for the treatment of disease involve rebalancing the patient's doshas.

Traditional Chinese Medicine

The history of TCM dates back thousands of years, with its origins linked to mythical emperors said to have lived around 2900 to 2600 BC. Shen Nong, or the Devine Farmer, is considered the originator of Chinese herbal medicine. The *Devine Farmer's Materia Medica* (*Shen Nong Ben Cao Jing*) was written around 220 AD and is the earliest known Chinese pharmacopeia with some 365 entries

of medications (30). Huang Di, the Yellow Emperor, is known as the originator of TCM. The *Yellow Emperor's Inner Classic* (*Huang Di Nei Jing*) was compiled around 200 to 100 BC and is considered the fundamental doctrinal source for Chinese medicine.

Chinese medicine is rooted in Taoist philosophy with the fundamental concepts of *yin*, *yang*, and *qi*. Yin and yang convey "the idea of opposing but complementary phenomena that exist in a state of dynamic equilibrium" (31). Yin represents dark, night, cold, female, water, and inside. Yang represents light, day, hot, male, fire, and outside. There is equilibrium between yin and yang in the body. The concept of qi is very broad and can be translated in many ways, but it fundamentally refers to the vital energy or life force throughout the body and the universe. TCM describes 12 bodily organs. These organs are divided into six solid organs (viscera) and six hollow organs (bowels), which are paired in a yin–yang or interior–exterior relationship. Each viscus and bowel has an associated channel that runs through the organ, its paired organ, across the body, and connects with the channel of its related organ. There are 12 regular channels as well as extra channels, divergent channels, and collaterals. Qi is understood to circulate in these channels and can be influenced by accessing 361 specific holes or points that lie along the path of 14 channels (12 regular, 2 extra). Disease can arise when there is an imbalance of yin and yang. Modulating the flow of qi can reestablish balance and restore health and well-being.

Therapeutic modalities in TCM include acupuncture, moxibustion, cupping, bleeding, massage (*tui na*), qigong, and herbal medicine. Acupuncture and moxibustion are described separately in this chapter. Cupping refers to the use of a heat to induce a vacuum in a small glass or bamboo cup, which is applied as a suction to the skin to bring blood and lymph to the skin surface. Bleeding is performed to drain a channel or to remove heat from the body. Chinese massage refers to manual stimulation of acupressure points. Qigong aims to manipulate qi through breathing, physical activity, and mind awareness. Qigong practices may range from meditative systems to martial arts (31). Contemporary herbal therapy in TCM is comprised of approximately 500 herbs, with about half used frequently in formulations combining 3 to 25 herbs.

Homeopathic Medicine

Homeopathy is a whole medical system that seeks to stimulate the body's ability to heal itself by giving very small doses of diluted substances. This therapeutic system was developed by the German physician Samuel Hahnemann at the end of the 18th century. Hahnemann articulated two main principles. First, the law of similars (*similia similbus curaentur*), or "let likes be cured by likes," states that a disease can be cured by a substance that produces similar symptoms in healthy people. The law of minimum dose states that the lower the dose of the medication, the greater the potency. In a process referred as potentiation, homeopathic remedies are diluted in a stepwise fashion and shaken vigorously between each dilution. Many homeopathic medicines are diluted beyond the molecular threshold of Avogadro's number with no molecules of the healing substance remaining. Homeopaths believe that the substance leaves its essence or imprint, stimulating the body to heal itself. Hahnemann developed his philosophy after a series of experiments in which he ingested therapeutic doses of chincona bark and experienced symptoms similar to the intermittent fever of malaria. He hypothesized that giving a remedy that mimicked a patient's symptoms reinforced the body's ability to heal.

In the United States, homeopathic remedies are prepared according to the guidelines of the *Homeopathic Pharmacopeia of the United States* and are regulated by the U.S. Food and Drug Administration. Most homeopathic remedies are regulated in the same manner as nonprescription drugs. Since homeopathic products contain minimal to no active ingredients, they do not undergo the same safety and efficacy testing as other over-the-counter drugs. According to the 2007 NHIS, an estimated 3.9 million adults and 900,000 children in the United States used homeopathy in the previous year (3). In many areas of Europe, homeopathy is the most popular form of CAM: 25% of all German physicians use homeopathy, 32% of primary care physicians use it in France, and up to 42% of physicians in the United Kingdom refer patients to homeopaths (32).

Naturopathic Medicine

The foundations of naturopathic medicine may be traced back to Hippocratic practitioners who first used the term *vix medicatrix naturae*, or "the healing power of nature," to describe the body's ability to heal itself. Other philosophical influences include the hydrotherapy movement (use of hot and cold water for health maintenance and disease treatment), nature cure (natural living, vegetarian diet, use of light and air to improve health), Christian Science (religious study, spirituality, and prayer in the treatment of disease), homeopathy, osteopathy, and chiropractic. These eclectic threads were woven into a comprehensive Western system of natural medicine with professional practitioners in the late 19th century by Benedict Lust, who himself had formal training in hydrotherapy, osteopathy, chiropractic, massage, and homeopathy.

Naturopathic medicine emphasizes health promotion, disease prevention, patient education, and patient self-responsibility (33). Naturopathy is not defined by any particular therapy but by the philosophical principles of the practitioner. The concepts of vitalism (life is more than the sum of its biochemical parts) and vix medicatrix naturae (the body has the innate intelligence to heal itself) are fundamental to the practice of naturopathic medicine. In 1989, the American Association of Naturopathic Physicians defined seven core principles of naturopathic medicine, including

1. The healing power of nature (*vis medicatrix naturae*)
2. First do no harm (*primum non nocere*)
3. Find the cause (*tolle causam*)
4. Treat the whole person
5. Preventive medicine
6. Wellness and health promotion
7. Doctor as teacher (*docere*)

Naturopathic doctors are trained as family physicians, but may also practice as specialists with additional training. The scope of practice, therefore, may include primary care, botanical medicine, homeopathy, nutritional medicine, acupuncture, Ayurvedic medicine, Chinese herbal medicine, spirituality, counseling, midwifery, and minor surgery.

Other CAM Practices

CAM also includes a wide range of movement therapies and energy techniques. The Feldenkrais method is a system of movement and manipulation aimed at enhancing awareness through movement and reestablishing proper balance and neuromotor patterning. The Trager Approach is a system of movement education in which gentle, rhythmic movement and touch is taught to enhance psychophysical integration and improve physical mobility and performance. Rolfing, also known as structural integration, is a system of soft tissue manipulation and movement education based on the interaction of the human body with earth's gravity. The Alexander Technique is a method that coordinates breath, posture, and movement. Energy work involves techniques to manipulate the life force or vital energy of the patient. Examples of energy work include qigong, Reiki, therapeutic touch, and healing touch.

CAM FOR THE OTOLARYNGOLOGIST

Prevalence of CAM Use in Otolaryngology Patients

Patients with otolaryngologic complaints commonly use complementary and alternative therapies. In a survey of 1,789 patients presenting to an academic otolaryngology practice in Scotland, 35% had used a CAM treatment in the last 12 months and 18% had used the therapy for an ear, nose, or throat condition (34,35). Less than half of the patients disclosed CAM use to their physicians. The same group found similar responses in their rhinology and head and neck oncology subspecialty clinics (36,37). A study performed at an academic rhinology practice in Canada found that 16% of patients diagnosed with chronic rhinosinusitis had used a CAM therapy for their condition (38). Another recent Canadian study of patients presenting with thyroid nodules to a head and neck oncology practice found that approximately one-half were on CAM oral supplements and one-third of the patients reported using supplements known to affect hemostasis (39). Other investigators in the United States and Europe have found lower prevalence of CAM use in head and neck oncology patients ranging from 6 to 23% (40,41).

Practice Implications

Patients may not inform their physicians regarding CAM use for a number of reasons. They may believe that products are "natural" and thus pose no potential for harm. They may be concerned that the physician might impose judgment for not using mainstream therapy, or they may doubt the physician's knowledge and ability to provide advice regarding CAM products. Although rare, the use of CAM products has the potential—both theoretic and documented—to negatively impact prescribed medical and surgical treatments. A recent survey of 844 patients presenting to an outpatient clinic revealed that 15% were using herbal medicines and 40% of these had potential herb–drug interactions (42).

Drug–Herb Interactions

Although a complete list of potential herb–drug interactions is beyond the scope of this chapter, some general guidelines and common interactions are discussed. The reader is referred to the resources listed in Table 20.1 to research specific effects and interactions. In the United States, the practitioner should report all suspected adverse events to the United States Food and Drug Administration's (FDA's) Medwatch Program (*http://www.fda.gov/medwatch*) and should encourage patients to inform use of supplements to their pharmacists. When reviewing the literature regarding herbal treatments, one must remember that the evidence is largely anecdotal and based on case reports (43). The preparation of supplements is not regulated by the FDA. There is heterogeneity in both potency and purity

TABLE 20.1 ONLINE RESOURCES ON HERBAL SUPPLEMENTS

Resource	Website
NCCAM	nccam.nih.gov/health/herbsataglance.htm
Office of Dietary Supplements	ods.od.nih.gov
Memorial Sloan Kettering Cancer Center Integrative Medicine	mskcc.org/aboutherbs
Cochrane Library	thecochranelibrary.com/details/browseReviews/1238803/Ear-nose-throat.html
Natural Medicine Comprehensive Database	naturaldatabase.com
Natural Standard	naturalstandard.com
ConsumerLabs.com	consumerlab.com
HerbMed	herbmed.org

depending on where the plant was grown, what part of the plant was used, how it was processed, and what active ingredients are in the preparation (44).

Drug–herb interaction is defined as a pharmacologic or clinical response to the coadministration of an allopathic medication and a herbal product (45). The interaction may magnify or reduce the effect of the pharmaceutical due to altered absorption, distribution, metabolism, or excretion (46). Interactions may lead to toxicity or lack of efficacy and complicate dosing of long-term medications. This is especially concerning for drugs with narrow therapeutic indices such as warfarin and digoxin in which improper dosing may be life threatening (46,47). Special care should be taken with warfarin, as it is the most common cardiovascular medication reported to have drug–herb interactions (43) even though there is no definitive evidence that warfarin metabolism is affected by herbal supplements and natural products other than vitamin K and, potentially, ginseng and St. John's wort (48).

Herbal and nutritional supplements alter drug metabolism by various means. Cytochrome P450 (CYP) is an important hepatic enzyme system that has been implicated in a number of drug–herb interactions. CAM therapies that induce CYP include St. John's wort, garlic, and flavonoids (49). These medications may decrease serum concentration and efficacy of a myriad medications metabolized by the liver (49). Other supplements such as grapefruit, goldenseal, echinacea, piperine, ginkgo, and licorice may inhibit CYP and thus potentiate drug effects (44,50,51). There are, however, a number of CYP isoforms, and the interaction of herbal supplements with this system is complex; each active ingredient may simultaneously activate some isoforms while inhibiting other isoforms.

The use of CAM natural products may alter the bioavailability of prescription drugs by modifying absorption via changes in gastrointestinal pH, motility, and enterocyte activity (46). Examples include fiber, bentonite clay, charcoal, and acacia (44,51). Garlic and St. John's wort may also affect drug bioavailability by interacting with P-glycoprotein, a drug transporter expressed by intestinal enterocytes (46). Potential interactions of some popular natural products are listed in Table 20.2.

Perioperative Management

The surgeon also must be cognizant of the potential for perioperative complications related to therapy with herbal supplements and natural products. Studies have reported that between 7% and 22% of adult presurgical patients use herbal medications (55). CAM treatments have the potential to alter anesthetic drug metabolism. Alterations in physiologic processes by herbal therapies with potent cardiovascular (e.g., ma huang), neurologic (e.g., kava), or other systemic effects may also pose risks for the patient under general anesthesia (56,57).

TABLE 20.2 POTENTIAL DRUG INTERACTIONS OF COMMON HERBAL SUPPLEMENTS AND NATURAL PRODUCTS

Supplement	Common Uses	Potential Interaction
Co Q-10	Cardiovascular	Structural similarity with vitamin K—may decrease effects of warfarin (52)
Echinacea	Upper respiratory tract infections	No specific interactions reported but recommended caution with autoimmune disease, immunosuppression (steroid therapy), tuberculosis, alcohol use (disulfiram reaction) (52–54)
Fish Oil	Cardiovascular protection	Anticoagulant and antiplatelet drugs (theoretical risk of bleeding with high doses) (53)
Garlic	Hyperlipidemia, prevention of atherosclerosis	Protease inhibitors (saquinavir), anticoagulant and antiplatelet drugs, hypoglycemics (51,52)
Ginkgo biloba	Erectile dysfunction, improvement of cognitive and physical function	Thiazides, nifedipine, anticoagulant and antiplatelet drugs, trazadone (increased sedative), caution with seizure disorder (51,52)
Ginseng	Energy, fertility	Anticoagulant and antiplatelet drugs, lithium and neuroleptics (irritability, sleeplessness, manic behavior), hypoglycemics, estrogenics, caution with autoimmune disease, immunosuppression, hypertension (52–54)
Glucosamine	Osteoarthritis	May increase international normalized ratio (INR) in patients taking warfarin (52)
Melatonin	Insomnia, reproductive function	May decrease nifedipine; nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, beta agonists and antagonists, scopolamine, and valproate may alter melatonin metabolism (52)
St John's wort	Depression	Serotonin syndrome with neurologic and psychiatric drugs, reduction of serum concentration of drugs metabolized by CYP (digoxin, birth control, cyclosporine, protease inhibitors, warfarin, theophylline, anticonvulsants, etc.), caution with immunosuppression (52,54)

One of the most pertinent issues related to herbal therapy for the surgeon is altered hemostasis. A recent review identified documented or theoretical alterations of platelet function by 42 herbal products, the coagulation cascade or warfarin metabolism by 60 herbal products, and coagulation effects by 20 nutritional supplements (55). This review and other reports are largely based on case reports, but the potential implications cannot be ignored and the American Society of Anesthesiology recommends that patients stop all herbal medications 2 to 3 weeks before an elective surgical procedure (55,57). Guidelines produced by the British Association of Day Surgery recommend stopping ginseng, garlic, ginkgo, and St. John's wort 1 week prior to surgery and stopping echinacea if immunosuppression is required (54). Commonly implicated supplements that may alter hemostasis include garlic, ginger, flax seed oil, ginkgo biloba, ginseng, vitamin E, and eicosapentaenoic acid (omega-3 fatty acid) or fish oil (56,58).

These studies and recommendations should be interpreted with caution as recent data suggest herbal therapies and nutritional supplements may not affect hemostasis to the extent as historically reported. One *in vivo* study found no effect on platelet function based on PFA-100 assay after 2-week administration of ginkgo biloba, garlic, Asian ginseng, St. John's wort, and saw palmetto at their recommended doses (59). Similarly, although garlic inhibits platelet aggregation *in vitro* (60), consuming garlic at dietary doses may have no effect on platelet activity in healthy individuals (61).

Another perioperative consideration is the effect of herbal and nutritional supplement therapy on wound healing. Echinacea may theoretically reduce wound healing by affecting the immune system, and some caution against its use in the perioperative period (50,54,56). Some report improved wound healing with certain herbal therapies and nutritional supplements such as bromelain, grape seed extract, and vitamins A, C, and E (50,58). One randomized, placebo-controlled crossover study found that consumption of an oral supplement containing proteolytic enzymes, bromelain, grape seed, rutin, vitamin C, calcium, and potassium accelerated skin wound healing time by 17% (62).

COMMONLY USED CAM THERAPIES FOR OTOLARYNGOLOGIC CONDITIONS

The following section reviews the evidence for some of the most commonly used CAM therapies for disorders of the ear, nose, and throat. When possible, we highlight treatments with the most robust data.

Tinnitus

Practitioners and patients have turned to a variety of alternative therapies for tinnitus due to its high prevalence and the limited effectiveness of allopathic strategies for treatment. Ginkgo biloba is thought to have a variety of beneficial effects on the central nervous system and has been commonly used for tinnitus. Although initial reports were promising, its efficacy has not been substantiated by RCTs and meta-analyses (63–65). Acupuncture continues to be used for tinnitus, with patients often reporting subjective improvement, but studies indicate this therapy is no better than placebo (66,67). Myriad multiherb and vitamin preparations are also widely advertised for the treatment of tinnitus. The majority purport to increase microcirculation of the inner ear, improving hearing and tinnitus. Lipoflavonoid is a commonly used preparation that is a combination of eriodictyol glycoside, bioflavonoids, vitamin B_6/B_{12} complex, vitamin C, niacin, riboflavin, thiamine, choline, inositol, and pantothenic acid. A brief review of the literature does not reveal any current evidence supporting its claims of efficacy.

Vertigo

Similar to tinnitus, the treatment of vertigo with CAM mainly has been through the use of herbal supplements that theoretically increase microcirculation of the inner ear. Betahistine, a histamine analog, has been proposed to increase vestibular blood flow and reduce the symptoms of vertigo compared to placebo (68–70). Vertigoheel is a popular remedy composed of four active ingredients—ambra grisea, cocculus indicus, conium maculatum, and petroleum (71). It is believed to improve microcirculation and activate vestibular regulatory systems within the brainstem (72). In 1998, an equivalence trial showed therapeutic equivalence between vertigoheel and betahistine in the reduction of frequency, duration, and intensity of vertigo over a 6-week treatment period (73). The significance of such a trial is unclear, as betahistine has not proven to be an effective agent and is thus a poor control (74). A more recent study comparing the use of vertigoheel to ginkgo biloba for the treatment of atherosclerosis-related vertigo found that both therapies improved tinnitus equivalently (75). Overall, the evidence for possible efficacy of vertigoheel is encouraging but limited, and more data is needed. Other CAM treatments for vertigo include ginger (antiemetic), hawthorne berry (increased cardiac output), and t'ai chi (increased balance) (72,76).

Otitis Media

In 2004, the American Academy of Pediatrics and American Academy of Family Practice jointly issued clinical practice guidelines for the management of acute otitis media (AOM), citing observation as an option for the management of nonsevere AOM in children above the age of 2 years (77). This recommendation is based on data showing high likelihood of uncomplicated spontaneous resolution of disease and concern regarding increasing antimicrobial resistance (78). Practitioners espouse these

principles when advocating CAM treatments for AOM (79). However, neither the clinical practice guidelines for AOM nor otitis media with effusion (OME) report any specific recommendations regarding CAM treatments due to insufficient and controversial data (77,80). The guidelines caution that almost any intervention can be shown to be beneficial unless judicious "parallel-group, randomized, controlled trials with valid diagnostic methods and adequate sample sizes" are used. Furthermore, CAM techniques should be used with caution as complications have been reported (77,80). Regardless, CAM therapies are frequently employed for the treatment of both AOM and OME.

Common botanicals employed for the treatment of otitis media include chamomile, echinacea, marshmallow, and mullein (79). Homeopathic practitioners use a variety of herbal preparations that are chosen and individualized based on the patient's clinical presentation and symptom profile. A pilot study on individualized homeopathy for AOM reported a statistically significant reduction of symptoms compared to placebo, but no difference in treatment failures between the groups (81). Naturopathic doctors also use a variety of different herbal preparations to treat AOM. A double-blind RCT compared the treatment of AOM with three therapies in various combinations: naturopathic herbal extract ear drops (NHED), a topical anesthetic, and oral antibiotics. The aim of this study was to explore means of symptom relief in the first 2 to 3 days of infection before antibiotics could affect the disease course. The authors found that NHED without antibiotics engendered improved pain control compared to NHED with antibiotics, but time was the greatest contributor to symptom reduction. They concluded that herbal preparations may be beneficial during the observational period of AOM, but the study was criticized for lacking an antibiotic-alone control group (82).

Xylitol is a sugar alcohol that has been found *in vitro* to inhibit pneumococcal growth and adhesion to nasopharyngeal walls (83,84). Xylitol in solution and as a chewing gum have been shown to reduce the number of AOM episodes and the need for antibiotics in blinded RCTs (84,85). Study subjects, however, took the medication five times a day for 2 to 3 months. Rare side effects included abdominal discomfort and osmotic diarrhea. More recent studies attempt to determine whether similar results can be achieved with more favorable dosing regimens. One study failed to show a difference between xylitol and placebo when given three times daily for 3 months during respiratory infection season (86). Another study showed that xylitol failed to prevent the development of AOM if started after the onset of an acute respiratory infection (87).

Zinc and cod liver oil also have been used to prevent otitis media. A recent Cochrane review reports there is no convincing evidence that zinc supplements reduce middle ear infection incidence (88). Trials have been published supporting the use of cod liver oil for the prevention of AOM but the data is limited (89).

Some osteopaths believe that restriction of the normal physiologic motion of the temporal bone may lead to eustachian tube dysfunction. They believe that normal temporal bone physiology can be restored by neurocranial restructuring, a technique in which a variety of balloons and manual maneuvers are used to rearrange cranial structure (90). One small study found that osteopathic manipulation in addition to pediatric primary care reduced antibiotic use and surgical procedure rates (91). A more recent RCT showed that neither osteopathic manipulation nor echinacea reduced the risk of recurrent AOM (92). Those who oppose neurocranial restructuring techniques cite case reports of complications (facial fractures, mortality) as well as the physiologic improbability of the technique (93).

Other CAM techniques for otitis media include lymph node drainage (manual milking of periauricular nodes), eliminating "mucus-producing" foods (wheat, dairy, eggs, corn, citrus, soy, refined sugar) from the diet, and testing for food allergies (79). Similar to many otolaryngologists, CAM practitioners commonly recommend certain lifestyle modifications such as encouragement of breastfeeding and avoidance of daycare, pacifiers, and smoking (79).

The natural history of otitis media is for spontaneous resolution without intervention in the majority of cases. Guidelines state that antibiotics should be started if there is no improvement after 48 to 72 hours of observation. Thus, the otolaryngologist who wishes to employ a CAM therapy must be convinced that, based on the current literature, there is no significant risk of harm with that particular technique. The standard of care, antibiotics, should be prescribed for persistent infection. Antibiotics should be used for all patients under the age of 2 years.

Head and Neck Oncology

Due to the often poor prognosis of head and neck cancer as well as the arduous treatment regimens of allopathic medicine, patients commonly seek CAM therapies both for the treatment of cancer itself and for side effect and symptom relief. A recent survey found that 22.7% of head and neck cancer patients in Europe utilized CAM and that their CAM use dramatically increased after cancer diagnosis (41). Most patients use CAM therapies in combination with conventional treatments rather than as an alternative to mainstream therapies (94).

Specific data on cancer treatment and prevention with CAM modalities are limited. One must remember, however, that a number of currently used chemotherapeutics were isolated from plants (e.g., etoposide, vinblastine, vincristine, taxol) and therefore research in this area remains very important. One example is recent studies on the effects of green tea as a promising supplement for cancer prevention and treatment (95). A Phase II RCT suggested possible suppression of oral premalignant lesions by green tea extract (96). Numerous oral and topical CAM therapies have also been suggested—despite very limited data—for

the prevention of skin cancer, including green tea, beta-carotene, vitamin C, vitamin E, and a low-fat diet (97).

A variety of techniques are used for cancer-related pain. A recent systematic review reported that there is a paucity of RCT data to sufficiently support the efficacy of these treatments, but that hypnosis, imagery, support groups, acupuncture, and healing touch seem promising (98). Several studies report the benefit of acupuncture to treat cancer-related pain, but a 2011 Cochrane review found that the evidence is insufficient (99). Also, in regard to radiation therapy, both topical aloe vera and honey have been shown to reduce cancer treatment-related mucositis in several RCTs (100,101). Mind–body treatments such as meditation, imagery, prayer, relaxation therapy, biofeedback, hypnosis, yoga, art and music therapy, and t'ai chi have also been used to treat the psychological and physical stress associated with cancer diagnosis and treatment (72,102).

Allergic Rhinitis and Rhinosinusitis

There are a myriad of CAM therapies for treating both allergic rhinitis (103) and chronic rhinosinusitis. Few are studied with rigorous double-blind RCTs for clinical efficacy. Often, the pharmacologic mechanisms and adverse effects are even less well understood. A few therapies for allergic rhinitis, including spirulina, butterbur, and phototherapy hold some promise.

Spirulina, the dried biomass of the blue-green algae *Arthospira platensis*, is considered safe for consumption by the FDA and is thought to inhibit histamine release from mast cells (71,104). RCTs have shown reductions in serum IL-4 levels and clinical nasal symptom scores in allergic rhinitis patients taking spirulina (105,106). Additional studies are needed to determine the efficacy and the active pharmacologic agent of spirulina.

The leaf and root extracts from the shrub butterbur (*Petasites hybridus*) have been shown to inhibit leukotriene and histamine synthesis (107) as well as mast cell degranulation *in vitro* (108). Alkaloids that are hepatotoxic and carcinogenic must be removed from raw butterbur extract before it can be used (109). In RCTs, butterbur was found to significantly improve nasal symptom scores compared to placebo (110) and to be comparable in efficacy to cetirizine (111) and fexofenadine (112,113). Another RCT, however, found no difference in symptom scores and peak nasal airflow compared to placebo (114). Moreover, butterbur did not inhibit skin-test reactivity in a study comparing butterbur to an antihistamine and placebo using skin-prick tests (115). Although preliminary data suggest butterbur may be effective in allergic rhinitis, additional studies are needed to elucidate its efficacy and safety.

Phototherapy with ultraviolet (UV) light is believed to have immunosuppressive effects, including the reduction of antigen presentation by dendritic cells, inhibition of proinflammatory cytokine synthesis and release, and induction of apoptosis in immune cells (116). A RCT investigating the use of a combination of low-dose UV-B, UV-A, and visible light in patients with ragweed-induced allergic rhinitis resulted in decreased nasal symptom scores and serum eosinophil levels (117). Phototherapy was found to be superior to fexofenadine in the reduction of rhinorrhea, nasal obstruction, and total nasal symptom scores (118). However, it has not been directed compared to intranasal corticosteroids. UV light induces DNA damage and, at high doses, is associated with carcinogenesis. The long-term effects of phototherapy on nasal mucosa are unknown.

There are fewer studies on various CAM therapies for rhinosinusitis compared to allergic rhinitis, and the existing literature is more difficult to interpret because investigators may use different definitions for acute and chronic rhinosinusitis. Two of the best-studied CAM treatments are sinupret and bromelain. Sinupret is an herbal preparation containing extracts of elder flower, primrose flower, common sorrel, vervain, and gentian root. Bioflavonoids in sinupret have been found to stimulate transepithelial chloride transport (119). For acute rhinosinusitis, one RCT comparing sinupret to placebo as an adjunct to antibiotics and a nasal decongestant showed significantly improved radiographic and patient-assessed outcomes (120) while another RCT found no difference between sinupret and placebo (121).

Bromelain is the crude extract from the stem and immature fruit of pineapple. It contains concentrates of closely-related proteinases and is thought to prevent and reduce edema, promote absorption of antibiotics, and induce production of cytokines (122). A meta-analysis of two RCTs found that bromelain decreased nasal mucosal inflammation, nasal discomfort, breathing difficulty, and overall symptom scores compared to placebo (123). A number of other herbal treatments have single studies showing positive effects for rhinosinusitis, but these results have not been replicated (123).

Honey made from the nectar obtained from manuka, a small tree native to New Zealand, is believed to have antibacterial and antifungal properties attributed to the active ingredient methylglyoxal (124). Recently, manuka honey has been shown to be effective against the biofilms of *Pseudomonas aeruginosa* and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (125). Treatment of honey solution in an animal nasal mucosal model did not show evidence of histologic epithelial injury (126). In an RCT assessing the use of a sprayed manuka honey solution in patients with allergic fungal rhinosinusitis, patient-assessed symptom scores improved in those treated with honey, but there were no differences in culture results or endoscopy scores (127). The authors of this chapter are currently conducting a RCT comparing topical nasal irrigations with manuka honey solution to culture-directed oral antibiotics for acute exacerbations of chronic rhinosinusitis.

CONCLUSION

This chapter reviewed some of the main types of CAM utilized by patients. Possible drug–herb interactions as well as perioperative issues are discussed. Finally, the existing evidence for CAM therapies used for ear, nose, and throat diseases are reviewed. Given that a large number of patients use CAM therapies, it is important that the practicing otolaryngologist should have some insight into the world of CAM.

HIGHLIGHTS

- According to national surveys, the prevalence of CAM use is approximately 40% for adults and 10% for children in the United States.
- Use of CAM therapies is increasing.
- About half of patients using CAM treatments do not inform their physicians of such use.
- Herbal medicines have the potential to alter the absorption and metabolism of conventional pharmaceutical drugs, especially those metabolized by the hepatic CYP system.
- Herbal medicines that may alter hemostasis should be held 1 to 2 weeks prior to surgery.
- A number of CAM therapies are commonly used for otolaryngologic disorders. Most of these have not been studied rigorously, and questions remain regarding their safety and efficacy.

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Tobacco Cessation: How-to Guidance and Resources for Practitioners

21

Henry R. Diggelmann *Grant S. Hamilton III*

BACKGROUND

Smoking tobacco is the single most preventable cause of death and disease in the United States (1). In 2005, smoking tobacco was responsible for 467,000 deaths, accounting for about 1 in 5 deaths in US adults (1). In the United States, an additional 8.6 million people have serious illnesses that are caused by smoking—chronic bronchitis and emphysema account for more than half of them. For every person who dies from tobacco use, another 20 suffer with at least 1 serious tobacco-related illness (2). Tobacco use also represents a huge economic burden. During the time period from 2000 to 2004, cigarette smoking was estimated to be responsible for $96 billion in direct medical costs and $97 billion in lost productivity (3).

Unfortunately, it is estimated that 46 million American adults currently smoke cigarettes (4). Even though the numbers remain high, there has been a significant decrease in cigarette smoking over the last 40 years (5). From 1965 to 2008, the percentage of the US population who smoke decreased from approximately 42% down to 20.6% (4,5). However, this decrease has leveled off over the last 5 years (4). Fortunately, of the estimated 94 million people who have ever smoked, 51.1% have now quit, and since 2002, the number of former smokers outnumbers the number of current smokers (4).

Smoking has historically been more common in men. Centers for Disease Control and Prevention data from 2008 suggest a prevalence of smoking in the United States of 23.1% among men and 18.3% among women. There is also some variability with regard to age. In general, the percentage of smokers 18 to 65 years of age does not vary significantly from the national average—however, there are significantly fewer adults over age 65 who smoke. This age group has a smoking prevalence of only 9.3%.

Tobacco use patterns also vary by socioeconomic status. The prevalence of smoking among adults with a graduate degree is only 5.7%, while the prevalence of smoking is highest among adults who had only earned a General Education Development certificate. This is consistent with data demonstrating that individuals with higher education also have a much higher awareness of the risks associated with smoking (6). Smoking is also much more common in adults living below the poverty level compared to those living above the poverty level, with a prevalence of 31.5% and 19.6%, respectively. Tobacco use is also not uniform between different ethnic groups. Asians have the lowest prevalence at 9.9%, followed by Hispanics at 15.8%, non-Hispanic blacks at 21.3%, non-Hispanic whites at 22.0%, and American Indians the highest at 32.4% (4).

The chemical primarily responsible for tobacco dependence is nicotine. Nicotine is a highly addicting drug. Its main targets in the central nervous system are neuronal nicotinic acetylcholine receptors. It also acts on the mesolimbic dopamine system, resulting in reward signaling and addiction. Its effects on the brain reduce anxiety and relieve stress, in addition to slight cognitive enhancement and increased ability to fight fatigue (7,8). Interestingly, there is a strong genetic component to nicotine dependence (9). The bioavailability of nicotine is around 12% in cigarette smoke, representing an uptake of about 1 mg of nicotine per cigarette. However, this uptake is variable depending on the method used to smoke the cigarette and can be increased to up to 40% bioavailability. It is generally considered that a dose of 5 mg of nicotine per day can result in addiction, but this is variable among individuals. Nicotine is metabolized in the liver and the principal metabolite is cotinine. Cotinine levels in blood, urine, hair, saliva, or nail can be measured and are directly proportional to the amount of nicotine the patient has recently been exposed to. Per cigarette, smokers produce 14 ng of cotinine per milliliter of blood. It is generally considered that a nonsmoker should have 3 ng/mL or less of cotinine in his or her bloodstream (10,11). The clinician can verify cessation of smoking using this test.

Tobacco cessation is a critical part of the patient encounter for the otolaryngologist. Smoking impacts patients in a multitude of ways, and efforts directed toward cessation provide the foundation of preventive medicine for all areas in the field of otolaryngology. In fact, tobacco abuse can lead to decreased olfaction, thyroid disease, rhytids, tooth discoloration, gum disease, cancer, decreased taste, voice changes, sore throat, hearing loss, and many of other conditions. Smoking also increases the rate of postoperative complications and impairs wound healing.

Head and neck cancer is directly caused by tobacco use. Smoking cessation efforts are fundamental to efforts to decrease the incidence of head and neck cancer. Multiple studies conclude that quitting smoking can lower the incidence of second malignant lesions in head and neck cancer patients from 40% down to 5% to 20%. However, this is controversial. Other data suggest that patients who have reached a critical level of damage due to prolonged tobacco exposure will not see this benefit. In this model, it is hypothesized that after a certain level of exposure, the damage caused by tobacco exposure is irreversible, even with cessation. This model also proposes that, for this reason, individuals who have the least amount of tobacco exposure will have the most benefit from cessation (12).

Secondhand smoke also poses a significant health risk. In fact, there is no level of secondhand smoke that is risk-free and the presence of any secondhand smoke carries risk of developing complications. Secondhand smoke has been proven to cause premature death and disease in both children and adults who are nonsmokers. In children, secondhand smoke results in increased risk for sudden infant death syndrome, acute respiratory infections, ear infections, and asthma. Children exposed to smoking by their parents also demonstrate slowed lung growth and suffer from respiratory symptoms. Adults exposed to secondhand smoke can develop coronary artery disease and lung cancer (13).

THE CLINICAL INTERVENTION

Smoking cessation is an integral part of today's medical practice and has received extensive investigation in the medical literature. Consequently, this area has been investigated on a scale rarely achieved in the field of otolaryngology.

In 2008, among current cigarette smokers, an estimated 45.3% of smokers tried to quit and managed to stop smoking for 1 or more days (4). Unfortunately, an unassisted attempt at smoking cessation only has a success rate of around 4%. Interventions that have been demonstrated to effectively decrease the use of tobacco include increasing price of tobacco products, instituting smoke-free policies, limiting advertisements and promotions, controlling access, and assisting and promoting users to quit (14). Herein lies the role of the physician, to assist and promote users to quit.

The physician occupies an important and unique position to intervene in smoking cessation. Unfortunately, physicians often do not take advantage of their authority, as only 37.2% of smokers reported they received advice to quit during a visit to a health care provider in the last year. This is significant as 70.2% of all smokers reported seeing a physician during the same time period (15). The responsibility of the physician is emphasized by Kreuter et al. (16), who found that smokers were 54% more likely to try to quit if a physician told them to quit. With this in mind, and with 70% of smokers reporting that they want to quit (17), a positive interaction in the physician's office is a key portion of the tobacco cessation process.

Therefore, all patients should receive guidance and advice concerning tobacco usage at every clinical visit, including current smokers, former smokers, or nonsmokers. For current smokers, it has been demonstrated that interventions that are as short as 3 minutes can significantly increase rates of tobacco cessation. This intervention should include a combination of counseling and the initiation of pharmacotherapy. It has been demonstrated that there are improved outcomes when counseling and pharmacotherapy are used in combination. While each is effective alone, cessation rates are significantly improved when used in combination (18).

BRIEF CLINICAL INTERVENTION

The Public Health Service has published extensive literature on smoking cessation and endorses the intervention commonly referred to as the "5As" (Table 21.1). This is a brief intervention to be performed in clinic that requires only 2 to 3 minutes and has demonstrated excellent results. It is composed of five parts: ask, advise, assess, assist, and arrange.

- Ask:
  - Every patient who walks into the clinic must be asked about tobacco usage. One simple way to implement this is to make tobacco use part of vital signs. Usage should also be documented in the chart. In fact, there is strong evidence that the use of "provider reminders" by health care providers improves tobacco cessation rates. These reminders could take the form of a chart sticker, vital sign stamp, medical record flow sheet, or checklist. These represent systems-based reminders to the provider to prompt the provider to discuss tobacco cessation (19).

TABLE 21.1 OVERVIEW OF BRIEF CLINICAL INTERVENTION

Ask
Advise
Assess
Assist
Arrange

- Advise:
  - Otolaryngologists should advise all patients on the risks of tobacco usage at every clinic visit. This includes nonsmokers, smokers, and former smokers. Doctors should also strongly urge all users of tobacco to quit, advise patients of the risk of continued use, and explain the benefits of quitting. All advice should be stated in a clear and strong statement. The advice should also be personalized. Discussion of personal benefits of successful cessation could include examples such as saving money, decreasing risks to others (kids), cutting personal risk, or living longer. Unfortunately, only 37.2% of smokers reported they received advice to quit during a visit to a health care provider in the last year. This is even more worrisome as 70.2% of all smokers reported seeing a physician during the same time period (15).
- Assess:
  - It is also important to ask all tobacco users "Are you willing to give quitting a try?" If the patient indicates that he or she is ready to quit now, then provide assistance to do so. At this time, either deliver or set up intensive intervention for the patient. Also initiate pharmacotherapy, and provide resources the patient can use to help. Just telling the patient to quit is not good enough. Intensive intervention has been shown to be far superior than simple advice (20).
  - For those patients who are not interested in quitting, consider motivational interviewing techniques, or any other intervention geared toward increasing the probability the patient will be ready to quit in the future. It has been demonstrated that these techniques appear to be effective in increasing the likelihood that the patient will make a future quit attempt. To perform these techniques, clinicians must proceed with four basic principles: express empathy, develop discrepancy, roll with resistance, and support self-efficacy. It is also advantageous to utilize the "5Rs," a concept that helps capture the content areas to be addressed. These include relevance, risks, rewards, roadblocks, and repetition. Under this umbrella, the otolaryngologist can begin to explore the patient's fears and begin to offer reasons and ideas that lessen the patient's resistance to change (21).
  - It is also imperative to assess the patient's readiness to change. A firm grasp of the transtheoretical model is important when dealing with any process of behavioral change. This model assesses the individual's readiness to change and is commonly referred to as the "Stages of Change." Familiarity with this model allows the clinician to more effectively communicate with patients and to tailor both the discussion and recommendations specifically to the individual patient's willingness to change.
    - The first stage of change is Precontemplation. This stage is characterized by the individual's lack of intent to take action in the foreseeable future. Patients may be in this stage because they are uninformed or underinformed, or they may have failed to quit smoking previously and now are demoralized about the prospects of succeeding. These patients will avoid thinking about or may not even be aware of their high-risk behaviors (22).
    - The second stage of change is the Contemplation stage. This stage is characterized by the individual who intends to change in the next 6 months but remains in a state of chronic contemplation as he or she weighs the pros and cons—with a majority of his or her focus on the cons. This individual may be more open to seeking out information but most likely shows ambivalence (22).
    - Preparation is the third stage and is defined by the individual who intends to take action in the immediate future, typically within 1 month. These patients have thought about a plan of action and are usually seeking information. These are excellent candidates for action-oriented programs in smoking cessation (22).
    - The Action stage is when the individual makes the modification to his or her lifestyle and continues it for 6 months. With smoking cessation, this stage represents the quit date, followed by abstinence. Unfortunately, of the six stages, this is the only stage that is actually observable to the outside individual (22).
    - After 6 months of abstinence, the patient moves into the fifth stage, Maintenance. This stage is characterized by the patient working to prevent relapse, but no longer actively changing. With smoking cessation, this stage can last years with a relapse rate at 12 months of 43%, decreasing to 7% after 5 years. This stage usually lasts as long as the change endures (22).
    - The final stage, Termination, is a theoretical goal, but not usually attained. It is defined by the individual achieving a state where there is no temptation to revert no matter his or her condition or the situation he or she is in. In this stage, it would be as if the patient had never initially acquired the habit. Unfortunately, this is rarely attained and in the setting of smoking cessation efforts has no practical use (22).
    - Some patients do relapse and restart smoking. Relapse is not a stage by itself but represents a form of regression with a return to an earlier stage. Luckily, only about 15% of patients return all the way to precontemplation. In the event of relapse, identify what stage the patient has returned to, and then immediately restart the motivational interviewing process (22).
- Assist
  - It is important to provide advice and support to those patients interested in quitting. Many steps should be taken to assist the patients in their difficult endeavor, including set a quit date, have the patient tell their family their plan, have the patient tell friends and coworkers so there are more people to provide support and encouragement, encourage the patient to remove all tobacco products, and help the patient change routines and develop a new lifestyle (Table 21.2).

TABLE 21.2 EXAMPLES OF PRACTICAL TOPICS FOR COUNSELING

- Activities that can increase the risk of relapse include stress, being around other tobacco users, or drinking alcohol.
- The patient should be warned to anticipate experiencing urges and should learn behaviors to cope with them, including distracting attention and changing routines.
- Patients should be aware of their smoking cues and the availability of cigarettes.
- Patients should learn to avoid trigger situations.
- Reduce negative moods by developing cognitive strategies.
- Change lifestyle to reduce stress and reduce exposure to smoking cues.
- Any smoking increases the chance of a full relapse.
- Withdrawal symptoms peak within 1–2 wk and include problems with concentration, mood, or urges. These can last for many months.
- Reinforce the idea that smoking is an addiction.
- Assure the patient effective treatments are available.
- Reinforce the reasons the patient wants to quit.
- Note that half of all people who have ever smoked have now quit.
- Encourage the patient to talk about the quitting process.
- Communicate your concern for the patient. Encourage the patient and build confidence in the patient.

Adapted from Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons, and Staff. A Clinical Practice Guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. *Am J Prev Med* 2008;35(2):158–176.

- When offering practical advice, it should be done with specific consideration to problem-solving skills. Have the patient commit to total abstinence. Review past attempts and why they did not work, what could be done differently, and use any positives from those experiences to bolster the patient's resolve. Anticipate triggers and challenges and develop strategies about how to overcome them. Encourage the patient to limit or abstain from alcohol, as the use of alcohol is associated with higher incidence of relapse. Diminish exposure to secondhand smoke, including identifying other smokers with whom the patient may have contact. Encourage other individuals at home to quit at the same time to provide both a smoke-free environment and a support system.
- One of the most important steps in assisting the patient is to set them up with counseling, specifically intensive intervention. Also, if possible, use pharmacotherapy in conjunction with the counseling. Multimodality treatment has been proven to have a higher success rate than single modality treatment. Provide supplementary materials to patients with additional information on resources and smoking cessation. Also provide support to the patient by offering your office and time as available to assist with any problems. Telephone support as a component of the intervention is strongly recommended and has been demonstrated to increase success rates for tobacco cessation (19). This could include follow-up telephone calls or informational messages left for the patient.
- Every state in the United States has a tobacco quitline. These lines offer free counseling and are able to get patients in contact with other local programs. These services can be accessed by calling either 1-800-QUIT-NOW or 1-877-2NO-FUME. The National Cancer Institute of the National Institute of Health also sponsors a quitline, 1-800-44U-QUIT. In a meta-analysis, these quitlines have been found to be effective methods of treating tobacco dependence (21).

- Arrange:
  - Follow-up appointments are crucial and should be supplemented with telephone calls. Schedule the first follow-up right after the quit date to ensure compliance and address any immediate problems. A second follow-up visit should occur shortly after. At these visits, congratulate success, identify problems, anticipate problems, encourage further intervention, and assess pharmacotherapy use and compliance. Also, remind patients of the resources available to them, and go over and reinforce the reasons why they quit. For those patients who have relapsed, review the circumstances, and make new plans to quit again.

MULTIMODALITY TREATMENT

Multimodality treatment plans are the cornerstone of tobacco cessation. These plans should consist of intensive counseling, pharmacotherapy using multiple medications if possible, access to support and counseling networks including quitlines and Web-based resources, and close follow-up.

Intensive Counseling

The first modality required to achieve success is intensive counseling. A recent Cochrane review assessed preoperative smoking interventions, specifically evaluating smoking cessation and the incidence of postoperative complications. In the analysis, the patients who had undergone brief interventions were separated from those who had undergone intensive interventions—which consisted of weekly counseling sessions over a period of 4 to 8 weeks. Surprisingly, the results were that only with intensive counseling was there a significant reduction in overall complications, wound complications, and continued smoking cessation 12 months after surgery. Brief counseling, defined as counseling during the routine preoperative assessments, did not achieve any of these results (20). These data form the foundation for the current recommendations that all patients must undergo intensive counseling sessions when considering smoking cessation. Otolaryngologists simply telling their patients they should quit, while important, is of minimal long-term value.

Pharmacotherapy

Pharmacotherapy should be used together with counseling whenever possible. Multimodality treatment has been proven to have a higher success rate than single modality treatment. However, there are certain populations where pharmacotherapy is contraindicated or there is a lack of sufficient evidence to support use. These populations include pregnant women, light smokers, adolescents, and smokeless tobacco users.

The otolaryngologist's primary pharmacologic armamentarium for smoking cessation is comprised of three medications in seven forms: bupropion, nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, nicotine patch, and varenicline. There are also a number of second-line pharmacotherapies including clonidine and nortriptyline. However, the food and drug administration (FDA) has not approved these for smoking cessation (Table 21.3).

Nicotine Replacement Therapy

Nicotine replacement therapy (NRT) is one of the cornerstones of smoking cessation. It helps control cravings, reduces withdrawal symptoms, and improves cessation success rates. There are many forms to choose from, including a patch, gum, an inhaler, a lozenge, and a nasal spray. Of these, the patch has established itself as the primary form of delivery.

The nicotine patch offers a constant level of nicotine delivery, ease of use, and a record of high levels of compliance. Dosage is one 21-mg patch every 24 hours for 4 weeks and then one 14-mg patch every 24 hours for 2 weeks, followed by one 7-mg patch every 24 hours for 2 weeks. There are also 16-hour release forms available, but they may be more difficult to use due to potential for severe morning cravings. The effectiveness of a high-dose patch is excellent with regard to abstinence rates, with an odds ratio of 1.9 compared to placebo. Adverse effects include a local skin reaction, allergic reactions, and insomnia. The potential for skin irritation can be avoided by rotating patch sites, but if it does develop, it can be treated with topical corticosteroids. The ability to titrate the dose of nicotine can also be an issue in patients who are heavy users or continue to have cravings. Because of this, combination NRT is a good practice for all patients, to provide a baseline nicotine level with the patch and actively titrate levels using another source of nicotine replacement (18,23).

One option for a secondary source of nicotine is nicotine gum. This modality has the major advantage of satisfying oral cravings. The dosage for patients smoking fewer than 25 cigarettes per day is the 2-mg gum, and patients may chew up to 24 pieces per day. For patients smoking 25 or more cigarettes per day, the 4-mg gum is used, and patients may chew up to 24 pieces daily. Recommended duration of treatment is up to 12 weeks. Adverse effects include mouth soreness and dyspepsia. Also, it is important to remember that gum may not be socially acceptable in certain situations (18,23).

Nicotine lozenges can also satisfy oral cravings and are more socially discreet compared to gum. Dosage is based on the amount of time after patients wake up in the morning that they need their first cigarette. If patients smoke their first cigarette within 30 minutes of waking up in the morning, they should use the 4-mg nicotine lozenges. If they smoke their first cigarette more than 30 minutes after waking up, they should use the 2-mg lozenge. Patients can use between 4 and 20 lozenges per day, for up to 12 weeks. Adverse effects include hiccups, nausea, dyspepsia, and flatulence (18,23).

Nicotine inhalers, like lozenges, deliver nicotine to the bloodstream via the buccal mucosa. It also provides the user with a mechanism of delivery, with regard to hand and respiratory use, similar to that of smoking a cigarette. The inhaler comes with cartridges, each containing 10 mg of nicotine, of which 4 mg can be delivered and 2 mg is absorbed. Dosages range from 6 to 16 cartridges per day, and the patient can use the inhaler up to 6 months, with a gradual reduction in dosage. Adverse effects include irritation to the throat and mouth, and possible cough (18,23).

Nicotine nasal spray is the fastest method of delivery of nicotine into the blood system. The spray delivers 0.5 mg of nicotine in each 50-mL squirt. One dose consists of two squirts, one in each nostril. Patients can use anywhere from 8 to 40 doses per day and can use the spray for up to 6 months. Adverse effects include nasal irritation (18,23).

Varenicline

Varenicline (Chantix) is a powerful choice for treatment of smoking cessation. Varenicline is a nicotine receptor partial agonist. Acting as an agonist, it maintains moderate levels of dopamine, which help relieve withdrawal symptoms. However, acting as an antagonist, it successfully reduces the satisfaction patients feel from smoking (24). At a dose of 2 mg/day, varenicline produces the highest abstinence rate compared to any other single pharmacologic agent, with an estimated odds ratio of 3.1 compared to placebo. Dosage is 0.5 mg daily for 3 days, then 0.5 mg twice daily for 4 days, and then 1.0 mg twice daily. Treatment should be initiated 1 week before the anticipated quit date. Duration of therapy is 12 to 24 months. Side effects include nausea, vomiting, flatulence, constipation, sleep disturbance, severe angioedema, serious skin reactions, visual impairment, accidental injury, depressed mood or other psychiatric symptoms, and vivid/strange dreams. Drinking large amounts of water may ameliorate some of the side effects. Coadministration of varenicline with NRT increases the risk of adverse drug events. To prevent premature discontinuation of treatment, NRT should not be used in conjunction with

TABLE 21.3 PHARMACOTHERAPY OPTIONS FOR TOBACCO CESSATION

Pharmacotherapy	Precautions/ Contraindications	Adverse Effects	Black Box	Dosage	Duration	Availability
First-line agents						
Varenicline	Pregnancy, kidney disease, patients on dialysis, previous allergic reaction	Nausea, vomiting, flatulence, constipation, sleep disturbance, severe angioedema, serious skin reactions, visual impairment, accidental injury, depressed mood or other psychiatric symptoms, suicidal ideation, and vivid/strange dreams	■	0.5 mg/d for 3 d, then 0.5 mg twice/d for 4 d, then 1 mg twice/d. Begin treatment 1 wk before quit date	3–6 mo	Prescription only
Bupropion	Hx of seizure, hx of eating disorders, diabetics using insulin or other glycemic medication	Insomnia, dry mouth, nausea, seizures	■	150 mg every morning for 3 d, then 150 mg twice daily Begin treatment 1–2 wk prior to quit date	7–12 wk, with	Prescription only
Nicotine patch		Local skin reaction, insomnia, allergic reaction		21 mg/24 h 14 mg/24 h 7 mg/24 h or 15 mg/16 h	4 wk, then 2 wk, then 2 wk 8 wk	Prescription and over-the-counter (OTC)
Nicotine gum		Mouth soreness, dyspepsia		1–24 cigarettes/d: 2-mg gum, up to 24 pieces/d >25 cigarettes/d: 4-mg gum, up to 24 pieces/d	Up to 12 wk	OTC only
Nicotine lozenge		Hiccups, nausea, dyspepsia, flatulence		Time to 1st cigarette >30 min use 2-mg lozenge Time to 1st cigarette ≤30 min use 4-mg lozenge May use 4–20 lozenges/d	Up to 12 wk	OTC only
Nicotine inhaler		Irritation of mouth and throat, cough		6-16 cartridges per/d	6 mo	Prescription only
Nicotine nasal spray		Nasal irritation		8-40 doses/d	6 mo	Prescription only
Second-line agents						
Nortriptyline	Recent MI, concurrent or recent use of MAOI	Dry mouth, sedation, constipation, nausea	■	Start 25 mg per day, titrate up to goal of 75-100 mg/day Begin treatment 10–28 d prior to quit date	12 wk	Prescription only
Clonidine	Rebound hypertension	Dry mouth, drowsiness, dizziness, sedation, constipation, allergic reaction, bradycardia, high or low blood pressures		Transdermal: Start 0.10 mg/d, titrate up to 0.15–0.75 mg/d Oral: Start 0.10 mg twice/d, titrate up to 0.15–0.75 mg/d	3–10 wk	Prescription only

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varenicline. Contraindications to use include pregnancy or breast-feeding, previous hypersensitivity or skin reactions to varenicline, and patients with significant kidney disease or those who are on dialysis. There has been widespread concern regarding the increased risk of both suicidal ideation and suicide in patients on varenicline, resulting in a black box warning being placed on the medication in 2009. However, causality of these reports of self-harm and suicide are difficult to prove, as smokers have an increased baseline risk of suicide (25). Current data do not demonstrate a significantly increased risk of suicide in patients on varenicline but remain concerning due to extremely wide confidence intervals reported (26). For this reason, it is recommended to routinely observe patients for changes in behavior—including depression, suicidal ideation, or agitation—while on the medication (18,27).

Antidepressants

Sustained release bupropion is an antidepressant with dopaminergic and adrenergic actions. It also noncompetitively inhibits nicotinic acetylcholine receptors (28). In a Cochrane review examining the role of antidepressants in smoking cessation, it has been demonstrated that bupropion increases the number of successful quit attempts compared to placebo, with demonstrated quit rates around 24% (18,29). The method of action of the medication is unclear. It has been postulated that nicotine withdrawal may produce depression-like symptoms, that nicotine itself is an antidepressant and the medication simply takes the place of the action of the nicotine, or that the neural pathways and receptors modulated by the drug help break the addiction. Interestingly, the use of antidepressant medications for smoking cessation is not limited to smokers who have a previous history of depression-like symptoms. It appears that the medication works in the entire population, in those with depressive symptoms and those without (29). Recommended dosage is 150 mg every morning for 3 days and then increasing to 150 mg twice daily. The duration of therapy should last from 7 to 12 weeks and may be maintained up to 6 months. The treatment should begin 1 to 2 weeks before the anticipated quit date (18). Side effects include insomnia, dry mouth, and nausea. Rarely, it can cause seizures (29). Contraindications to use of bupropion include a history of seizures, diabetics using insulin or other glycemic medication, or a history of eating disorders (27). It is also imperative to remember that all antidepressants carry a black box warning for increased risk of suicide. When using bupropion for smoking cessation, the patient should be closely monitored for the development of behavior changes, agitation, hostility, suicidal ideation, or attempts of suicide (26).

Nortriptyline, a second-generation tricyclic antidepressant, has also been shown to increase quit rates (29). The abstinence rate of the medication compared to placebo is significantly higher, with an odds ratio of 1.9 (18). It has been proposed that the medication acts by inhibition of the reuptake of serotonin and noradrenalin. Recommended dosage is initially 25 mg/day, gradually increasing to a goal of 75 to 100 mg/day for a treatment period of 12 weeks. The treatment should also be initiated 10 to 28 days before the target quit date. Side effects include dry mouth, sedation, constipation, and nausea. Contraindications for use include a recent myocardial infarction (MI), or the concurrent or recent use of monoamine oxidase inhibitors (MAOIs). There is also a potentiating effect when combined with alcohol, and overdose can lead to numerous dangers (29,30). Of note, the FDA has not yet approved this medication for smoking cessation.

Not all antidepressants help with smoking cessation. Selective serotonin reuptake inhibitors (SSRIs) and MAOIs are not effective medications in smoking cessation. In a Cochrane review, SSRIs demonstrated the same effectiveness in smoking cessation as a placebo (18,29).

Other Medications

Clonidine, an alpha-2-noradrenergic agonist, has also been shown to increase the rate of smoking cessation, with an odds ratio of 2.1 compared to placebo (18). Dosage starts at 0.10 mg twice per day orally or at 0.10 mg/day using a transdermal patch. Dosing is then increased if needed by 0.10 mg/day to a final dosage of 0.15 to 0.75 mg/day. Duration of treatment is 3 to 10 weeks. Adverse effects include dry mouth, drowsiness, dizziness, sedation, and constipation. Contraindications include rebound hypertension. It is also critical to be aware of the potential for allergic reactions, bradycardia, or extremely high or low blood pressures (30). The FDA has not approved this medication for smoking cessation.

Naltrexone, an opioid receptor antagonist, does not have a role in smoking cessation. In fact, when compared to a placebo, it was found to be less effective (18).

Pharmacotherapy Conclusions

There are many viable options for pharmacotherapy (Table 21.4). At a dose of 2 mg/day, varenicline produces the highest abstinence rate compared to any other single pharmacologic agent. However, single modality pharmacotherapy is not the rule. Combination therapies can also offer excellent abstinence rates. Combining the nicotine patch with a second medication can achieve slightly higher rates of abstinence compared to using the patch alone. The patch can be combined with another form of ad lib nicotine replacement (gum, inhaler, lozenge, or spray), and/or it could be added to bupropion, nortriptyline, or clonidine. In all these combinations, it has been demonstrated there is likely a slight increase in abstinence rates compared to the use of a single medication alone. However, it is important to remember that varenicline should not be combined

TABLE 21.4 EFFECTIVENESS AND ABSTINENCE RATES OF PHARMACOTHERAPY FOR SMOKING CESSATION COMPARED TO PLACEBO

Medication	Estimated OR (95% CI)	Estimated Abstinence Rate (95% CI)
Nicotine patch + ad lib NRT (gum or spray)	3.6 (2.5, 5.2)	36.5 (28.6, 45.3)
Varenicline (2 mg/d)	3.1 (2.5, 3.8)	33.2 (28.9, 37.8)
Nicotine patch + bupropion SR	2.5 (1.9, 3.4)	28.9 (23.5, 35.1)
Nicotine nasal spray	2.3 (1.7, 3.0)	26.7 (21.5, 32.7)
Long-term nicotine gum (<14 wk)	2.2 (1.5, 3.2)	26.1 (19.7, 33.6)
Nicotine inhaler	2.1 (1.5, 2.9)	24.8 (19.1, 31.6)
Clonidine	2.1 (1.2, 3.7)	25.0 (15.7, 37.3)
Bupropion SR	2.0 (1.8, 2.2)	24.2 (22.2, 26.4)
Nicotine patch	1.9 (1.7, 2.2)	23.4 (21.3, 25.8)
Nortriptyline	1.8 (1.6, 2.6)	22.5 (16.8, 29.4)
Nicotine gum (6–14 wk)	1.5 (1.2, 1.7)	19.0 (16.5, 21.9)
Placebo	1	13.8
Selective serotonin reuptake inhibitors	1.0 (0.7, 1.4)	13.7 (10.2, 18.0)
Naltrexone	0.5 (0.2, 1.2)	7.3 (3.1, 16.2)

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with nicotine replacement due to the pharmacodynamics of the drug (18).

CESSATION PROGRAMS AND RESOURCES

Quitlines

Telephone quitlines exist in every state. In fact, these quitlines have been found to be effective methods of treating nicotine dependence. In a recent meta-analysis, not only were quitlines found to produce significantly higher cessation rates compared to individuals who had not undergone counseling, but when combined with medications, they were also found to offer significantly better results compared to patients using pharmacotherapy alone (21). These data suggest that quitlines represent another form of intervention that can be utilized in multimodality therapy. These services can be accessed by calling either 1-800-QUIT-NOW or 1-877-2NO-FUME. The National Cancer Institute of the National Institute of Health also sponsors a quitline, 1-800-44U-Quit. These lines offer free counseling and are able to get patients in contact with other local programs.

Online Resources

The World Wide Web is another excellent supplemental resource as there are many online tools available for both patients and health care professionals.

- For health professionals
  - US Department of Health and Human Services Cessation Guidelines site contains the most definitive literature on tobacco cessation. http://www.surgeongeneral.gov/tobacco/default.htm
  - The National Center for Chronic Disease Prevention and Health Promotion of the Centers for Disease Control and Prevention. www.cdc.gov/tobacco
  - American Cancer Society data site: http://www.cancer.org/Healthy/StayAwayfromTobacco/index
  - The World Health Organization http://www.who.int/topics/tobacco/en/
  - National Cancer Institute http://www.cancer.gov/cancertopics/smoking
- For smokers
  - CDC tobacco Web site http://www.cdc.gov/tobacco/quit_smoking/index.htm
  - The National Cancer Institute http://www.cancer.gov/cancertopics/smoking
  - Smoke-free Web site, the Tobacco Control Research Branch of the National Cancer Institute http://www.smokefree.gov/
  - American Heart Association: http://www.americanheart.org
  - NIH http://www.nlm.nih.gov/medlineplus/smokingcessation.html
  - American Lung Association Freedom From Smoking http://www.ffsonline.org

SMOKING CESSATION FOR THE SURGEON—PERIOPERATIVE CONSIDERATIONS

The effects of smoking are important to consider in the perioperative period as smokers have an increased risk of intraoperative and postoperative complications. These risks are due to the added stress placed on the cardiac and pulmonary systems as well as complications with wound healing.

Perioperative myocardial infarctions are caused by either acute coronary thrombosis or supply–demand mismatches in the setting of critical coronary stenosis (31). Unfortunately, both the cardiac and circulatory systems are damaged by smoking—specifically by the development of atherosclerosis. Also, in the smoker who has recently smoked, nicotine and carbon monoxide are present and work to cause a mismatch in the amount of oxygen availability compared to the rate of consumption. The presence of nicotine stimulates the cardiovascular system, increasing oxygen demand (20). However, carbon monoxide reduces the availability of oxygen to tissues by reconfiguring the structure of hemoglobin resulting in a decreased affinity for binding oxygen and also by acting as a competitive inhibitor to oxygen (32).

The pulmonary system is also negatively impacted by smoking. This is in part due to the fact that smoking leads to lung disease such as chronic obstructive pulmonary disease. It also leads to an increased risk of complications in the perioperative period. In fact, smokers have approximately six times the risk of developing postoperative complications compared to nonsmokers (33). Increased mucus production in combination with decreased ciliary movement leaves the airway at increased risk. Also, smoking impairs pulmonary immune function (20,34).

Smoking also is associated with complications with surgical wound healing, primarily due to hypoxia related to reduction of blood flow, decreased oxygen carrying capacity, and peripheral vasoconstriction. Hypoxia also limits the ability of tissue to repair itself and also leads to increased susceptibility to infection. Also, smoking may inhibit fibroblasts, interfere with angiogenesis, and significantly reduce peripheral microcirculation (35–37).

Smoking cessation in the perioperative period can help prevent these postoperative complications. Optimal risk control is obtained by helping the patient quit smoking 1 to 2 months before surgery, incorporating the cessation methods outlined previously in this chapter. This results in significantly lower complication rates and also obtains the highest short-term and long-term quit rates (20,38). However, if this is not possible due to time constraints, it has also been demonstrated that simply stopping 4 weeks before surgery does decrease overall complication rates (39). In fact, in patients undergoing cancer resection with free flap reconstruction, it was determined that preoperative smoking cessation longer than 3 weeks prior to surgery significantly reduced the wound healing complications (40). With this in mind, every attempt should be made to achieve smoking cessation in the preoperative period. While it is not clear exactly what is the shortest duration of preoperative abstinence from smoking needed to reduce perioperative complications, it is clear that a longer duration is better—specifically 1 to 2 months—and that long-term quit rates are best achieved with the addition of intensive counseling and pharmacotherapy.

The optimal timing for smoking cessation in the perioperative period specifically with respect to pulmonary complications remains perplexing. Investigations have revealed mixed results, with some noting that patients are at a decreased risk by stopping smoking before surgery, while others have noted a higher risk of pulmonary complications by stopping smoking in the immediate preoperative period. In fact, some publications found that stopping smoking before an operation can result in a rate of pulmonary complications up to seven times the normal rate (33). However, it does seem clear that the closer to surgery the patient ceases smoking, the higher the risk that the patient has of pulmonary complications. One thought is that the increased mucus production that occurs after cessation plays a role in this process. In any case, the overall rate of complications is decreased with smoking cessation no matter how close to surgery it is initiated, so this should not be a reason to continue smoking (34).

NRT is one of the cornerstones of pharmacotherapy for smoking cessation. With this in mind, it is important to consider the effects of NRT on the surgical patient. Smoking has been found to reduce tissue blood flow to tissues, reduce oxygen levels, and significantly negatively impact aerobic metabolism. It was previously assumed that these effects were due to nicotine. Though nicotine can cause vasoconstriction and has been shown to decrease surgical flap survival in animal experiments, these effects occurred at much higher doses than seen with smoking or NRT (41).

Recent work found that administration of IV nicotine resulted in a significant increase in tissue oxygen levels, with only a limited vasoactive effect and no change in the aerobic metabolism of the tissue (35). This is in sharp contrast to the effects of smoking. It has also been suggested that nicotine stimulates dermal cells and promotes angiogenesis (42). In another study, when administered at therapeutic levels, transdermal nicotine had no effect on digital perfusion compared to individuals who had just stopped smoking. Also, microvascular responses were similar to that of the control group of nonsmokers (43). In another population, the use of NRT starting 6 to 8 weeks before surgery has demonstrated dramatic reductions in both the overall complication rates and wound complication rates in patients undergoing hip or knee replacement (44). Also, NRT does not increase the perioperative cardiac risk (41).

With these studies in mind, nicotine replacement may not result in the complications that we have historically attributed it to. At this point, nicotine use in the perioperative period has not been fully investigated, although current evidence suggests it does not significantly impair wound healing after surgery.

CONCLUSIONS

Tobacco abuse represents a chronic disease that is regularly encountered by the otolaryngologist. It impacts our practice in a variety of ways, contributing to the development of many disease processes, and impedes our ability to deliver excellent surgical outcomes. With this in mind,

it is imperative that every otolaryngologist includes a systems-based tobacco cessation program that allows for the identification of tobacco users and facilitates the initiation of a multimodality approach to cessation. This approach should include intensive counseling, pharmacotherapy using multiple medications, access to support and counseling networks—including quitlines and Web-based resources, and close follow-up. Comprehensive smoking cessation programs have been shown to have a significant impact on patients' long-term success rates and should be offered to every tobacco-dependent patient.

HIGHLIGHTS

- Tobacco dependence is a chronic disease, and it is extremely difficult to overcome addiction to nicotine.
- There are effective treatments for tobacco cessation.
- Clinicians must consistently identify and document tobacco use and perform the brief clinical intervention—the 5As—on every tobacco user.
- Multimodality treatment includes counseling, pharmacotherapy using multiple medications, access to support and counseling networks including quitlines and Web-based resources, and close follow-up.
- Intensive weekly counseling sessions should be conducted for a period of 4 to 8 weeks.
- Pharmacotherapy should consist of either varenicline or a long-acting nicotine patch in combination with an additional source for acute nicotine replacement and, optionally, the addition of an antidepressant.
- For patients not ready to quit, motivational interview techniques should be employed.
- Efforts directed toward tobacco cessation are among the most important things we can do for our patients.
- NRT does not result in tissue hypoxia and should be offered to patients in the weeks before surgery.

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22 Palliative Care and Pain Management

Robert M. Taylor *Amit Agrawal*

Palliative care (PC) is a holistic approach to medical care for patients with serious illness that focuses on optimizing comfort and quality of life (QOL) for patients and their families. The Report of the National Consensus Project (NCP) Clinical Practice Guidelines for Quality Palliative Care states: "The goal of PC is to prevent and relieve suffering and to support the best possible QOL for patients and their families, regardless of the stage of the disease or the need for other therapies. PC is both a philosophy of care and an organized, highly structured system for delivering care. PC expands traditional disease-model medical treatments to include the goals of enhancing QOL for patient and family, optimizing function, helping with decision making, and providing opportunities for personal growth. As such, it can be delivered concurrently with life-prolonging care or as the main focus of care" (1). As such, PC is appropriate for many patients with head and neck cancer (HNC), even those who may be cured of their cancer, but suffer significant symptoms and/or functional impairments, as well as the risk of recurrence.

Indeed, patients with HNC represent an important and challenging population for modern medicine. Although new therapies have significantly improved life expectancy and survival for patients with HNC, many patients who benefit from these treatments are left with significant problems as a result of their cancer and therapy, including pain, dysphagia, dysarthria, disfigurement, and psychological sequelae. Family and social problems may be significant. Because addiction to alcohol is a risk factor for HNC, and because many alcoholics abuse other substances, addiction and substance abuse may further complicate the patient's struggles and the medical system's ability to provide care.

Ideally, treatment of patients with HNC should include a collaboration of surgery, medical oncology, radiation oncology, speech therapy, nutrition, and a PC team. PC teams often include professionals from medicine, nursing, social work, chaplaincy, pharmacy, and other professional disciplines. Among the other disciplines that may provide additional important support for HNC patients are psychology and addictionology.

One of the priorities of those working in the field of PC is to encourage incorporation of PC into the earlier phases of cancer treatment, often referred to as moving PC "upstream." This priority is based on the reality that PC is much more than end-of-life (EOL) care and provides important benefits for patients with cancer during the earlier phases of their illness. PC must be distinguished from hospice care, which is appropriate for, and limited to, patients who are estimated to have 6 months or less to live (assuming their disease runs its expected course). Although hospice is an important component of PC, PC is a much broader enterprise that is appropriate for patients at any stage in a serious illness, such as cancer. Furthermore, although comprehensive PC is best provided by an interdisciplinary PC team, the principles of PC can often be integrated into the care of cancer patients by non-PC clinicians.

PRESENTING SYMPTOMS AND ASSESSMENT OF PATIENTS WITH HNC

While presenting symptoms and level of dysfunction caused by early stages of HNC are typically less severe, it is extremely common in patients presenting with advanced-stage primary or recurrent disease to experience significant and often debilitating symptoms caused either directly or indirectly by their tumor. Although variable according to tumor type and location, progressive pain is an extremely common symptom particularly in patients presenting with advanced and/or recurrent disease (2–4). Pain in patients with advanced disease may be due to one or multiple factors (5,6) including extensive soft tissue and/or bony

infiltration, direct perineural involvement by tumor, and/or disease affecting substantial portions of exposed mucosal surfaces resulting in local ulceration/irritation. As such, pain caused by cancer or its treatment is felt to be mediated by neuropathic and/or local inflammatory mechanisms (7) and may be associated with systemic inflammation as well (8). Pain causes not only physical distress and dysfunction, but significant psychological effects with negative impact upon overall QOL (3). Unfortunately, underassessment of severity of pain as well as factors involving physician discomfort, lack of understanding pain mechanisms and thus strategies necessary to achieve sufficient symptom relief, lack of recognition of important coexisting psychological factors such as depression, as well as concerns regarding potential for addiction or substance abuse often lead to undertreatment of pain in patients affected by this disease. It is thus important for physicians and healthcare providers to both become knowledgeable in basic tenets involved in oncology pain management as well as to regularly involve healthcare providers with specific expertise in pain and PC in order to maximally benefit patients and minimize suffering due to such symptoms.

Progressive disease bulk due to disease location in the upper aerodigestive tract and/or neck can also result in severe functional compromise by interfering with vital functions including eating, swallowing, and respiration which may require more urgent intervention independent of disease status. Assessment by the head and neck surgeon and/or oncologist is necessary to determine both oncologic course as well as to guide management of existing or potential tumor and/or treatment-related complications (airway compromise, dysphagia, bleeding, infection) including consideration of whether patients may benefit from adjunctive interventions such as tracheostomy or feeding tube placement. Such interventions must be discussed with patients as to their impact which although may extend longevity are not likely to be temporary measures in patients with recurrent and often incurable disease.

Not uncommonly, particularly in cases of advanced disease, troublesome bleeding occurs due to friability and vascularity of exposed tumor surfaces which can be a source of significant distress to both patients and caregivers. In mild cases, it is reasonable to employ local measures such as application of direct pressure, use of topical hemostatic agents, coagulation, and wound care (e.g., measures to maintain moisture and reduce bacterial load). In recalcitrant cases, interventional radiologic procedures such as endovascular tumor embolization can be considered to control recurrent bleeding (9,10). In the dire situation of threatened, impending, or actual severe sudden bleeding resulting from exposure, erosion, or compromise of major vascular structures (e.g., carotid blowout), depending upon the acuity and stability of the patient, consideration can be given to intervention such as endovascular carotid stenting, occlusion, or open carotid artery ligation which often achieves immediate stabilization and control of bleeding (11,12). It must be realized, however, that such measures are considered extreme and although potentially lifesaving in the short term are associated with high morbidity (e.g., stroke) with dubious impact upon QOL and overall survival. As such, in patients recognized to be at risk of such events (previously treated patient with recurrent neck disease in setting of open neck and/or pharyngeal wound), this potential event should be discussed with patients and families and the patient's wishes ascertained including the use of aggressive resuscitation measures, which may not be desired particularly when the goals of care remain primarily palliative.

Due to the significant and variable presentation of advanced head and neck malignancy, whether primary or recurrent, patients require assessment often in multidisciplinary fashion in order to address the oncologic as well as functional, and symptomatic aspects of their disease. Although there may be some overlap, involvement of caregivers in the areas of oncology, pain and PC, speech/swallowing, nutrition, mental health, and nursing play crucial roles in the management of patients with HNC.

PALLIATIVE ANTINEOPLASTIC THERAPIES

In the setting of advanced head and neck malignancy in which standard curative intent therapy is not felt feasible, it is still not unreasonable to consider antineoplastic strategies in an effort to achieve reduction in tumor burden as this has been shown to achieve meaningful palliation of debilitating symptoms such as pain, swelling, and dysphagia (13,14). Although more difficult to measure, additional factors potentially improved by such efforts also include reduction in tumor-related complications such as bleeding or impingement upon local vital functions such as airway. Such strategies include palliative use of chemotherapy/systemic therapy, radiotherapy, and surgery. The use and selection of such modalities alone or in combination often depend upon factors such as patient functional status, prior therapy, as well as practical feasibility and expected functional morbidity associated with such measures.

Chemotherapy

It has been shown that systemic therapy can be expected to achieve meaningful response and thus reduction in tumor burden ranging from 10% to 30% of cases of advanced recurrent disease when patients have undergone significant prior therapy although the effect of therapy is temporary (median time to progression 6 months, survival <12 months) (15–17). Higher rates of disease response can be achieved with combination of more than one systemic agent compared to monotherapy, although such response typically occurs at the expense of higher toxicity and morbidity either without substantial improvement or only modest improvement in overall survival (15,16).

Such impact may not be desirable when the intent of therapy is symptom palliation particularly in situations where declining patient functional status may preclude aggressive measures. As such, it is not unreasonable to utilize systemic monotherapy in such situations, although multiagent therapy should be considered particularly when patients possess good performance status as there is some evidence that multiagent therapy can achieve improvement in specific parameters such as pain and swallowing without negatively impacting overall global QOL measures (14). Commonly utilized systemic agents used either as monotherapy or in combination include methotrexate, platinum compounds (cisplatinum, carboplatinum), 5-fluorouracil, taxanes (paclitaxel, docetaxel), as well as in recent years targeted therapy strategies using agents such as cetuximab which target the epidermal growth factor receptor pathway. Although symptomatic benefit is more likely in patients who achieve measurable disease response to therapy, interestingly, symptomatic improvement can also be observed despite absence of overt response to treatment albeit in a smaller proportion of patients (13).

Radiation Therapy

In the setting of advanced recurrent locoregional disease, the use of radiotherapy in palliative format can be considered, although in most cases of advanced recurrent disease, prior radiotherapy in affected regions may preclude its use. The use of reirradiation has been utilized in situations in an effort to reduce tumor burden and achieve disease response with variable success using varying methodology involving standard fractionated, altered fractionated, stereotactic/conformal delivery, or brachytherapy delivery methods (18–22). It must be understood that even with altered delivery methods reirradiation alone is associated with low overall response rates and disease control in previously treated regions. Furthermore, despite demonstrated feasibility, the rate of severe treatment-related toxicity (i.e., grade 3 or greater) of reirradiation is significant (21,22). As such, in light of the low rate of observed disease response and significant treatment toxicity, the role of palliative reirradiation in achieving meaningful symptom relief in patients with otherwise incurable recurrent HNC remains unclear (21).

The use of reirradiation in combination with systemic chemotherapy (with or without surgery) has also been utilized in patients with advanced locoregional recurrence with sustained disease response documented in a small but significant proportion of patients (23–25). It must be understood, however, that long-term survival in this patient group remains low, and the morbidity and mortality associated with such measures are not small (23–25). Furthermore, the intent of such treatment should be considered definitive in nature, and as such, it would be difficult to categorize such treatment as palliative in intent. In situations of distant disease such as bony or central nervous system (CNS) metastases, it is reasonable to consider palliative radiotherapy to these sites in situations of severe symptoms or high potential for debility from disease (e.g., bone pain, impingement upon spinal cord/CNS) (26).

Surgery

The use of surgery to reduce tumor burden in palliative fashion when meaningful chance of cure does not exist is controversial. In the situation of advanced recurrent head and neck malignancy, surgery is often not feasible or practical due to disease extent (i.e., unresectable) or patient factors (medical debility, poor nutritional/performance status). Even if feasible, surgery often carries substantial morbidity with high risk of postsurgical wound complications and substantial potential for negative impact upon functions including speech, swallowing, and respiration and as such is frequently associated with need for adjunctive devices such as tracheostomy and/or feeding tube which may be either at least temporary or may be long term or permanent in a significant proportion of patients (27). Furthermore, in patients previously treated for advanced disease, surgery for recurrent disease is associated with low chance of long-term disease control (27,28). As such, the benefit of surgical measures must always be carefully weighed against the potential substantial negative impact upon function and QOL particularly when odds of meaningful disease control are low and treatment intent is palliative. It is not unreasonable however to consider surgical efforts—even aggressive efforts—in situations where symptoms, QOL, and longevity are primarily impacted by locoregional disease provided that disease is felt to be reasonably addressed using surgery (with or without further adjuvant measures) and potential for recovery of function is substantial (i.e., via reconstruction and/or rehabilitative methods). It is also reasonable to consider palliative surgical measures in situations where distant disease may exist yet have indolent behavior provided that locoregional disease can be controlled where other methods such as chemotherapy and/or radiotherapy carry poor odds of reducing locoregional disease burden (e.g., adenoid cystic carcinoma, well-differentiated thyroid cancer). Such considerations must be taken in concert with careful surgeon assessment of the feasibility and functional impact of surgical treatment and honest discussion with patients and families regarding realistic expectations of any such proposed measures particularly with regard to symptom control and QOL.

PALLIATIVE CARE CLINICAL PRACTICE GUIDELINES

The number of hospital-based PC programs more than doubled between 2000 and 2009, according to study done by the Center to Advance Palliative Care (29). In 2009, the NCP published updated Practice Guidelines (1)

"to promote quality and reduce variation in new and existing programs, develop and encourage continuity of care across settings, and facilitate collaborative partnerships among PC programs, community hospices, and a wide range of other health care delivery settings." In their effort to promote a holistic view of PC as well as to encourage appropriate clinical standards, they identified eight essential domains of PC:

1. **Structure and processes of care**: This domain emphasizes the importance of ensuring that adequate resources and personnel are available to provide holistic care for patients with serious illness. Ideally a well-resourced and staffed PC team should be available to assist with the care of patients with significant PC needs, and their families. Most patients will be receiving significant assistance and support from their family (broadly defined) and want their family involved in any important decisions. Some patients will be very selective as to which family members they want involved. Rarely, patients will not want anyone else involved in their care; while their wishes should be respected, treatment options will likely be limited by a lack of support from others. Treatment options will, of course, also be limited for patients who have no family assistance. Eliciting patient—and, if appropriate, family—values and goals is a necessary step in providing optimal care. Likewise, coordinating care among the many providers is essential. Furthermore, understanding and accessing available resources in the hospital and community, such as mental health services, cancer-specific resources, support for children, home health services, and hospices, is critical to ensure that patients and families receive the care they need.
2. **Physical aspects of care**: All patients with cancer should be provided with the best available management of pain and other physical symptoms. All physicians who treat cancer should understand and apply the basic principles of managing pain and other physical symptoms to minimize unnecessary suffering by their patients. They should be skillful at eliciting and recognizing sources of physical distress and know the limits of their own ability to manage such problems. They should be aware of options for patient referral for pain and symptom management and be prepared to advocate for and support the development of PC services within their own institutions to ensure that their patients' physical distress is addressed appropriately.
3. **Psychosocial and psychiatric aspects of care**: Patients with cancer typically suffer significant psychological distress. This may include depression and anxiety related to their disease and associated physical symptoms and debilitation, losses resulting from the disease—such as loss of employment, income, or relationships, concerns about one's ability to fulfill one's responsibilities, etc. If the patient has a preexisting mental illness, addiction, or cognitive impairment, their ability to cope with cancer may be significantly diminished. All cancer patients should be assessed for such problems, ideally by a trained professional, such as a social worker or psychologist. Resources and personnel to evaluate and manage such common problems should be available to all those who treat cancer patients. Some patients may require referral for specialized care, such as a psychiatrist or a substance-abuse program. Finally, families of patients who die should have access to grief and bereavement services and clinicians should be capable of assessing the need for such services.
4. **Social aspects of care**: Patients with cancer live and struggle within families and communities. Although families provide critical support for many cancer patients, all families suffer along with the patient and, for some patients, families may be an additional source of stress—due to complexity of family structure, dysfunctional relationships, or inability to fulfill one's historical responsibilities within the family. Other concerns include the family's ability to fulfill caregiver needs for the patient; when families are unable, other resources may or may not be available, depending on a variety of factors. A patient's and family's access to resources in the community may vary considerably, based on their socioeconomic and insurance status, as well as integration into their community, for example through work, friendships, or church. Inadequate social support may interfere with a patient's ability to comply with treatment recommendations and have a negative impact on outcomes. Identifying and addressing the social needs of patients and families is best accomplished with the help of an interdisciplinary team, including social workers experienced in the care of patients with cancer.
5. **Spiritual, religious, and existential aspects of care**: Patients with serious illness inevitably confront spiritual and existential issues. Spirituality is usually conceptualized as encompassing the patient's sense of meaning and purpose, his or her connectedness to self, family, friends, and community, the significance of suffering, and a possible connection to a higher power. Existential issues are the result of one's encounter with one's own mortality and the reality of nonexistence in this world. As such, all patients, on some level, struggle with spiritual and existential concerns, whether they identify them as spiritual or not. For many patients, religious beliefs, communities, and traditions will influence how they understand and cope with their illness. Other related spiritual issues include life review, assessment of hopes and fears, a sense of guilt and forgiveness, and life-completion tasks. All patients with cancer should be assessed for spiritual, existential, and religious concerns. Spiritual and religious concerns may take on added significance for patients approaching the

EOL. Often, spiritual assessment and care is provided through pastoral care, although other members of the health care team, including physicians, may be able to perform a spiritual assessment. Resources for providing spiritual care include the hospital chaplain, other members of a PC team, and community resources, especially—if a patient has one—the patient's own faith community. A useful spiritual screening tool is the acronym FICA, where each letter stands for a word which prompts certain questions:

a. **Faith**—Do you consider yourself spiritual or religious? Do you have spiritual beliefs that help you cope with stress? What gives your life meaning?
b. **Importance or Influence**—What importance does your faith or belief have in your life? Have your beliefs influenced how you take care of yourself in this illness? What role do your beliefs play in regaining your health?
c. **Community**—Are you a part of a spiritual or religious community? Is this of support to you and how? Is there a group of people you really love or who are important to you?
d. **Address or Apply**—How would you like me, your health care provider, to address these issues in your health care?

6. **Cultural aspects of care**: Many patients are influenced by the beliefs and traditions of their community, ethnicity, or religion. For example, one's culture may affect patterns of communication and decision making within the family, as well as the significance of illness in the patient's worldview, or even one's understandings of the mechanisms of disease. Communication may be hindered by language differences. Simple considerations such as diet and activity may be influenced by cultural concerns. Preferences related to EOL care, including especially the ritual aspect of care, as well as the handling of the body after death, may be influenced by cultural considerations. However, because a patient's and family's sense of cultural identity is complex and unpredictable, it is important to elicit their perspective and its significance in a culturally sensitive manner. Social workers and pastoral care are often the most skilled in eliciting cultural perspectives and concerns.
7. **Care of the imminently dying patient**: A patient who is imminently dying is in a specific and unique condition that is fundamentally different from the condition of other seriously ill patients. Properly caring for an imminently dying patient requires appreciation of this reality and specific knowledge and skills, which, unfortunately, have not been widely taught to medical trainees in the past. Medical care is ordinarily provided for patients based on the assumption that the goal is to help them survive and, ideally, be restored to health. As such, many "routine" and "standard" treatments, such as respiratory support or artificial hydration and nutrition (AHN), serve to maintain survival while more specific treatments are applied to treat an illness or injury. However these "routine" treatments may provide no benefit, or even cause harm, to a patient who is actively dying. For example, dying patients, whose organs are progressively and irreversibly failing, are unable to effectively process and utilize AHN and often develop respiratory distress due to pulmonary edema if AHN is continued during the dying phase. Understanding and explaining this effectively and compassionately to families is critical to providing optimal care to imminently dying patients. Although it is not always easy to determine when a patient has entered the dying process, it usually becomes evident to experienced clinicians sometime before the patient dies. Furthermore, recognition that the patient's death is probable, or even inevitable, is often apparent well before he or she is imminently dying. When a patient is recognized to be imminently dying, two goals should become primary: to strive to ensure the comfort of the patient (based on best medical evidence, within ethical and legal guidelines) and to provide support for the family and significant others. Ideally, a hospice or a PC program should provide such care, as those programs are best able to achieve both goals. Delaying referral to hospice or PC until the patient is imminently dying may result in suboptimal care for the patient and family. EOL care for patients with HNC is discussed in more detail below.
8. **Ethical and legal aspects of care**: Physicians should ensure that patients are adequately informed about their treatment options and elicit their goals and preferences. Patients should be encouraged to complete advance directives, so that they have the opportunity to appoint a surrogate decision maker and inform the physician and surrogate of their preferences regarding EOL care. Advance care planning should be presented to patients as an opportunity to ensure that their preferences are honored if they ever lose the capacity to make their own decisions. If a patient does lose the capacity to make decisions, ethical and legal guidelines should be followed to ensure that the decisions regarding the patient's care are made appropriately. Most conflicts or uncertainties in EOL care can be resolved through compassionate communication. It is often helpful to have such conversations facilitated by experienced PC physicians. However, in cases where conflict persists, an ethics consult may be helpful.

PAIN IN HEAD AND NECK CANCER

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (30). Pain is always subjective, and consists of a physiologic and a psychological component, both of which can alter the perceived severity and the level of distress resulting from pain.

Acute pain in HNC is often associated with therapeutic interventions, for example acute postoperative pain. Such pain is typically managed with short-term intravenous opioid therapy in the acute-care setting. Although management of acute pain can certainly be challenging and problematic, the predominant challenge in managing cancer-related pain relates to the management of chronic pain. Therefore, the focus of this discussion is on chronic pain in HNC.

In cancer pain, the etiology and mechanism of the physiologic component of the pain is often apparent, or can be inferred, based on the history, exam, and imaging studies. However, the distress caused by pain may be greatly influenced by a multitude of other factors, including psychological, social, and spiritual factors. Furthermore, cancer pain is often perceived as indicating persistent, progressive, or recurrent disease; whether it turns out to be correct or incorrect, this perception frequently further increases distress. Indeed, reassurance that the pain does not reflect active cancer may be very therapeutic (31).

Pain in HNC can occur as a result of the disease itself or therapy. HNC may cause somatic pain by invasion and destruction of soft tissues and bone, it may cause neuropathic pain (NP) by invasion or destruction of nerves of the head and neck, or it may cause mixed pain (a combination of somatic pain and NP). Similarly, treatment may cause pain by similar mechanisms as well as additional mechanisms. Radiation therapy (RT) may cause mucositis, xerostomia, fibrosis, and radionecrosis. Pain related to HNC, or its treatment, most often involves the head, neck, shoulder, and arm. However, certain chemotherapy regimens may be neurotoxic and cause painful polyneuropathies unrelated to the specific cancer site. Pain may resolve with treatment or subsequently, or may be persistent. Persistent pain may or may not reflect persistent disease. Recurrent pain or progressive pain frequently reflects recurrent or progressive disease (32). The impact of pain on psychological distress, sense of well-being, and QOL is complex and is discussed below.

There are few studies documenting the incidence and prevalence of pain in HNC and many of these were performed several years ago. Although subsequent changes in treatment regimens create uncertainty as to the applicability of these studies to current patients, the data they provide remain among the best available at this time.

One recent prospective study, published in 2009, assessed pain over a 3-month period, in HNC patients undergoing RT who reported pain on initial evaluation (33). Seventeen percent were treated with only RT, 57% were treated with surgery and RT, 14% with chemotherapy and RT, and 11% with all three modalities. On a "0-5 verbal pain descriptor scale," worst pain was 3.03 at first visit, 3.18 at second visit, and decreased at subsequent time points. Continuous pain was reported by 57%, and combined continuous and intermittent pain by 79%. Although they did not report the percentages of patients reporting neuropathic, nociceptive, or mixed pain, the most common NP descriptors endorsed were burning (27%) and aching (20%); nociceptive descriptors were tender (35%), sore (32%), throbbing (23%), and dull (22%); and affective/evaluative descriptors were annoying (41%) and tiring (25%). Overall, 29% were not satisfied with their level of pain.

A 2-year, prospective, longitudinal study published in 1999, assessed pain, life satisfaction, and psychological distress, in 93 of 201 patients treated for HNC who remained disease free at the end of the study (34). Head and neck pain (HNP) were reported by 48% of patients at presentation and by 25% and 26% at 1 and 2 years, respectively. Moderate to severe HNP was reported by 27% at presentation, and 10% and 15% at 1 and 2 years, respectively. Shoulder and arm pain (SAP) were reported by 14% at presentation, and 37% and 26% at 1 and 2 years, respectively. Moderate to severe SAP was reported by 3% at presentation, and 18% and 14% at 1 and 2 years, respectively. There was no significant difference in pain experienced by those treated with surgery, radiation, or both. However, neck dissection was significantly associated with SAP at 2 years. Life satisfaction was adversely affected by any pain at 1 and 2 years, whereas psychological distress was only associated with pain at 3 months.

Despite the quality of this study, there are several reasons that it may be of limited applicability to current HNC patients. First, treatment regimens for HNC have changed; for example, none of the patients in the study were treated with chemotherapy. Second, as it was an observational study; pain management was neither provided nor assessed. Nevertheless, the authors report that "it became clear … that their pain was generally unreported to their doctor and was self-medicated." Finally, because they included only patients who remained disease free at 2 years, their results are of limited applicability to patients with residual, recurrent, or advanced disease.

A prospective study of pain in 167 patients with HNC, published in 1993, may be more widely applicable to patients with HNC, as they included patients with all stages of disease and included information about treatment (35). They found that 83% had pain related to cancer and 28% related to treatment. Systemic analgesics were administered to 97% of patients and adjuvants to 100%; 5% of patients reported severe pain despite treatment. The most common side effects of pain treatment were insomnia, dysphagia, anorexia, constipation, and nausea; serious side effects were rare.

A prospective study of 2,266 cancer patients referred to a pain service, published in 1996 provided a different perspective on pain in HNC (36). All patients had pain; 17% had HNC. Pain in HNC patients was most common in head, face, and mouth (78%) and cervical region (45%); 9% had pain in the shoulder or upper limb and 7% in the thoracic region. 81% had disease-related pain, whereas 31% had treatment-related pain. NP was diagnosed in 25% of the former and 45% of the latter.

The combined results of these studies suggest a few conclusions:

1. The majority of patients with HNC will have pain, which may be difficult to treat. Pain may be somatic, neuropathic, or mixed.
2. Up to a quarter of patients who remain disease free at 2 years may have persistent pain, which may be moderate to severe in up to 15%.
3. Persistent SAP is associated with neck dissection.
4. Of the HNC patients who seek treatment for pain, the most common sites of pain are the head, face, mouth, and neck.

Principles of Pain Assessment and Management

The principles of pain management for cancer patients are well described in multiple sources. For example, The National Cancer Institute's Physician Data Query Web site provides a brief overview of the principles of cancer pain management (37), *The Oxford textbook of palliative medicine* devotes several chapters to this topic (38), and Portenoy (39) recently provided a concise review of this topic. This discussion attempts to apply those principles to the HNC population. Although pain management may be a significant consideration for head and neck patients with nonmalignant syndromes involving the head and neck, it is especially important for patients with HNC. Furthermore, although the principles of pain management for HNC are generally applicable to patients with nonmalignant syndromes, the ethical and legal considerations are more complex for the latter group of patients. Specifically, although concerns about misuse or abuse of medications, addiction, and diversion are always important in every patient population, with nonmalignant disease, there is a stronger legal and ethical requirement to monitor for and manage these problems. In addition, as in any nonmalignant pain syndrome, there must always be a strong focus on monitoring and improving functional status, as a decline in functional status may often indicate misuse, abuse, or addiction. In contrast, this may not be as relevant to the care of patients with malignant disease, who may have a decline in functional status due to disease progression, even while receiving optimal pain management. Nevertheless, decline in functional status of HNC patients that is not associated with disease progression should raise concern about medication misuse, abuse, or addiction.

Portenoy (39) offers a summary of "Key messages" that should inform the management of cancer pain; these are reproduced in Table 22.1.

The first step in treating pain is to determine the etiology of the pain and the mechanism of the pain. In patients with HNC, the mechanism of the pain is often easily

TABLE 22.1 KEY MESSAGES

- The assessment and management of pain in populations with cancer are best considered as an essential component of the broad therapeutic approach known as Palliative Care
- Pain assessment should characterize the pain complaint, take into account the status of the underlying disease, clarify the pain in terms of its cause, syndrome, and pathophysiology, and obtain details about other factors that contribute to illness burden
- Pain can be addressed with primary disease-modifying treatment, most often radiotherapy, if this approach is available, feasible, and consistent with the goals of care
- The mainstay symptomatic treatment for cancer pain is opioid-based pharmacotherapy, and all clinicians who provide care to patients with cancer should aim to optimize the positive outcomes from these drugs and minimize the risks associated with both side effects and outcomes related to chemical dependency (misuse, addiction, and diversion)
- Effective opioid treatment depends on appropriate selection of a drug and route, individualization of the dose, consideration of so-called rescue dosing for breakthrough pain, and treatment of common opioid side effects
- The addition of a NSAID to opioid treatment can be helpful, especially in some painful conditions, but the gastrointestinal, cardiovascular, and renal risks of these drugs should be weighed against their benefits on a case-by-case basis
- Adjuvant analgesic drugs, such as glucocorticoids, antidepressants, and anticonvulsants, have many uses when opioid treatment is not sufficient; clinicians should familiarize themselves with the common indications and agents
- Many nonpharmacologic treatments can be used to improve pain control, coping, adaptation, and self-efficacy; mind–body strategies have established benefit and can be used in a restricted but potentially useful manner by nonspecialists
- Interventions, including neural blockade and implanted therapies, play a small but important part in the management of refractory pain

From Portenoy RK. Treatment of cancer pain. *Lancet* 2011;377:2236–2247.

determined, based on the history and examination, and imaging studies. If it is not clear, appropriate investigations should be made to determine the etiology. However, for HNC patients, treatment of moderate or severe pain generally should be initiated while such investigation is undertaken, rather than waiting for a definitive explanation of the pain. Furthermore, the mechanism of the pain (e.g., somatic, neuropathic, or mixed) will be an important consideration in the comprehensive management of the pain. However, as discussed below, opioids are typically indicated for moderate to severe pain, regardless of the mechanism (39,40).

It is important to remember that determinations of the etiology and mechanism of a cancer pain syndrome is rarely definitive—most often it is a reasonable inference based on the information at hand and, therefore, always subject to revision. Furthermore, the response to specific treatments (or lack of response) may provide additional information about the etiology and mechanism—the so-called therapeutic trial. Finally, in any patient with active cancer or undergoing treatment, the pain syndrome may evolve and change over time, so that the clinician should always be alert to new information that may require a change in the treatment plan.

The patient's description of the characteristics of the pain is an important element of the pain history. A useful mnemonic for this purpose is "PQRST," which stands for Provokes or Palliates, Quality, Radiation, Severity, and Temporal course. Specific questions to ask, may include For P: Does anything make the pain better? What makes it worse? For Q: What does the pain feel like (sharp, dull, stabbing, burning, etc.)? For R: Where is the pain? Does it radiate? For S: How severe is the pain? For T: When did the pain start? Has it changed over time?

There are several severity scales available (3). Most widely used is the "Ten-point scale" (actually 11 points, including 0), where 0 = no pain and 10 = "the worst pain you can imagine." For patients who have difficulty with the numeric scale, a descriptive scale of "none, mild, moderate, and severe" often works well. It is useful to ask the patient to rate the pain at its best, its worst, and the usual level of pain. Although, not standardized, it is common to define mild pain as a worst pain score of 1 to 3, moderate pain as a worst pain score of 4 to 6, and severe pain as a worst pain score of 7 to 10.

There are a variety of validated tools to assist the clinician in assessing pain. One widely used tool is the Brief Pain Inventory, which is available online (41).

This information, combined with other clinical information related to the cancer and its treatment, usually will enable the physician to determine the etiology and mechanism of the pain.

Other important aspects of the pain history include the impact of the pain on the patient's function and relationships, any current or past problems with depression, anxiety or other mental illness, current or past personal of alcohol or drug abuse, or family history of alcohol or drug abuse.

In general, there are four major categories of therapies for managing cancer pain: (a) analgesics, including nonopioids and opioids, (b) adjuvant analgesics, including agents targeted to NP, (c) nonpharmacologic therapies, and (d) interventional therapies. The focus of this discussion is the first two categories. Nonpharmacologic therapies are only briefly discussed; interventional therapies are beyond the scope of this chapter and are not discussed.

The WHO Pain Ladder provides guidelines for managing cancer pain, based on the severity and mechanism of the pain (40).

Mild pain—Step 1: Simple analgesics (nonopioid, e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs]); consider adding an adjuvant (e.g., tricyclic antidepressants [TCAs], anticonvulsants) for NP.

Moderate pain—Step 2: Weak opioid (e.g., tramadol, codeine, or hydrocodone); consider adding an adjuvant for NP.

Severe pain—Step 3: Strong opioid (e.g., morphine, oxycodone); consider adding an adjuvant for NP.

For patients with HNC who have moderate to severe pain, most will require treatment with opioids.

A Pharmacologic Approach to Cancer Pain Management

The management of pain in patients with cancer is based on the principle that every patient deserves to have his or her pain assessed and managed in accordance with the best available medical evidence. Specific treatments for specific syndromes, such as mucositis, are discussed elsewhere in this text and are not discussed here. It is well established that opioids are the mainstay of pharmacologic treatment of cancer pain. It is also well established that opioids are associated with certain risks, most notably from side effects, abuse, misuse, and diversion. Misuse behaviors in the medical setting are most-commonly referred to as aberrant drug-related behaviors or, more simply, aberrant behaviors (39). Aberrant behaviors do not necessarily indicate addiction or diversion, but rather raise concern for some form of medication abuse or misuse and therefore warrant careful assessment and monitoring.

Thus every patient who is treated with opioids should be assessed for risk of abuse and addiction and his or her treatment and monitoring should be guided by this assessment. Evidence of aberrant behaviors occurring after treatment has been initiated should lead to reassessment and may require an adjustment of the treatment plan (39,42).

Cancer pain that is severe will typically require opioid therapy. Many patients with moderate pain will require opioid therapy. Opioids are relatively safe if titrated carefully, based on their pharmacologic properties. See Table 22.2 (39) for a summary of basic pharmacologic information about selected opioids.

There are a few general principles that should guide outpatient opioid management of chronic, moderate to severe pain (39,40):

1. Opioid therapy should usually be initiated with the use of short-acting medications, taken on an as-needed (prn) basis, to determine the effective and safe dose. The frequency of dosing should generally be roughly equivalent to the duration of action of the drug.
   a. For opioid-naive patients, the usual starting dose is the equivalent of 5 to 10 mg of oral morphine given every 3 to 4 hours as needed. For opioid-tolerant patients, the dose should be adjusted accordingly.
2. Initial titration should be with a single opioid.
3. The dose may be escalated by 25% to 50% every 24 to 48 hours in the absence of side effects, but slower escalation is acceptable if pain is not severe.
4. Once an effective and tolerated dose is determined, the total 24-hour dose of opioid required to control the pain is calculated.
5. The equivalent of approximately 50% to 75% of the total 24-hour requirement should be provided as scheduled opioids, usually in sustained-release form.
   a. If the opioid used for the scheduled dosing is different than the opioid used in the titration, the dose should be reduced an additional 25% to allow for cross-tolerance.
6. The patient should continue to use a prn dose of a short-acting opioid for breakthrough pain. This dose should be roughly 15% (range 10% to 20%) of the total 24-hour dose and the frequency should be roughly equivalent to the duration of action of the drug.
7. Both the sustained-release and the short-acting opioid should be adjusted as needed for pain control
   a. Sustained release medications should be increased only after reaching steady state (Table 22.2).
8. Methadone should only be used by those who understand its pharmacokinetics and by or under the guidance of those who are familiar with it.
9. All patients taking scheduled opioids should be treated preventatively for constipation and monitored for other side effects.

Special Considerations in HNC

A major distinction in HNC versus the general cancer population is that dysphagia and the frequent dependence on a percutaneous gastrostomy (PEG) tube will limit the options for opioid therapy. Most sustained-release opioids must be taken whole or they become short acting which can result in overdose and even death. Oral sustained-release tablets, such as morphine, oxycodone, hydromorphone, and oxymorphone, should never be crushed or broken for this reason. Therefore, they cannot be used in patients who cannot safely swallow whole pills. They should never be given to be taken per PEG tube or other feeding tube. The exceptions are Kadian and Avinza, sustained-release morphine capsules that can be opened and the contents put into a feeding tube, although this may occasionally clog the feeding tube.

For patients dependent on a feeding tube for their oral medications, there are several options. Liquid medications or crushed short-acting tablets can be administered through the feeding tube. These can be used for both prn and for scheduled dosing. For scheduled dosing, they should usually be given every 4 hours. A fentanyl patch may be used as a sustained-release medication for patients with dysphagia, but dosing conversions can be challenging (39,43). It is recommended that those unfamiliar with fentanyl patches seek guidance from a PC specialist or a pharmacist familiar with opioid therapy.

Methadone is intrinsically long acting and available as a tablet and a liquid and can be given by feeding tube. Methadone's duration of action is quite variable, as is its potency relative to other opioids (44). Converting from other opioids to methadone is challenging. Again, for those unfamiliar with the medication, guidance should be sought from a PC specialist or a pharmacist familiar with opioid therapy (39,40). In addition, methadone may prolong the QTc interval and therefore should be used with caution in patients with cardiac disease or who have other risk factors for QTc prolongation. All patients treated with methadone should have a baseline and follow-up electrocardiograms according to recent published guidelines (45).

Physicians who treat patients with HNC should learn the basic principles of opioid therapy. They should understand the pharmacology of the commonly used medications, as well as the risks and how to mitigate them. They should develop relationships with PC or pain specialists and learn when and how to refer to them.

Neuropathic Pain in HNC

The IASP defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system" (30). NP in HNC may result from tumor compression or infiltration of the peripheral nerves of the head and neck, trauma or injury to those same nerves as a consequence of surgery or radiation, or the neurotoxic effects of chemotherapy, which may cause local nerve damage or may produce painful neuropathies distant from the primary tumor (e.g., painful polyneuropathy). Secondary illnesses, such as herpes zoster virus, which result from immunosuppressive effects of the cancer or treatments, may also cause NP, either locally or remotely.

The IASP further notes that "NP is a clinical description (and not a diagnosis) which requires a demonstrable lesion or a disease that satisfies established neurologic diagnostic criteria." Despite this caveat, most clinicians and the literature commonly refer to "NP" as a diagnosis. The typical clinical features of NP include the following: it develops in association with a known or presumed injury to the relevant somatosensory nervous system, it may be

TABLE 22.2 SELECTED OPIOID ANALGESIC DRUGS

Drug (and Formulation)	Equianalgesic Doses	Half-life	Duration of Analgesia	Comments
Codeine	200 mg PO	2–4 h	4–6 h	Sometimes used for moderate pain
Hydrocodone	30 mg PO	3–4 h	4–8 h	Used for moderate pain in a combination product containing acetaminophen, ibuprofen, or aspirin.
Morphine	10 mg IM/IV/SQ; 30 mg PO	2–3 h 2–3 h	3–4 h 3–6 h	Standard for comparison for opioids; several routes available
Controlled-release morphine (MS Contin)	30 mg PO	NA	8–12 h	
Extended-release morphine (Kadian, Avinza)	30 mg PO	NA	12–24 h	
Hydromorphone	1.5 mg IM/IV/SQ; 7.5 mg PO	2–3 h; 2–3 h	3–4 h; 3–6 h	Potency and high solubility can be beneficial for patients needing high opioid doses and for subcutaneous administration
Extended-release hydromorphone	7.5 mg PO	NA	24 h	
Oxycodone	20–30 mg PO	2–3 h	3–6 h	Available as a single entity or combined with acetaminophen, ibuprofen, or aspirin
Controlled-release oxycodone	20–30 mg PO	NA	8–12 h	
Oxymorphone	1 mg IM/IV/SQ; 10 mg PO		3–6 h; 4–6 h	
Extended-release oxymorphone (Opana ER)	10 mg PO	NA	12 h	
Methadone	3 mg IM/IV/SQ, 6 mg PO	12–150 h	6–12 h	Dose conversion must be individualized for each patient based on drug, dose, and patient tolerance; these numbers apply to patients taking <100 mg OME per 24 h (44). Can be far more potent than indicated here, presumably because potency of available racemate attributable in part to the D-isomer, an NMDA antagonist that can reverse tolerance and augment analgesia; with highly variable half-life, patients need increased vigilance for weeks, until steady state has definitely occurred; can prolong the QTc interval, so ECG should be monitored according to consensus guidelines (45).
Fentanyl	50–100 µg IV/SQ	7–12 h	1–2 h	
Fentanyl transdermal patch		NA	48–72 h per patch	Not usually recommended for opioid-naive patients in currently available doses; not recommended for acute pain. Because the fentanyl patch is a continuous delivery system, dose to dose conversions are not applicable; the recommended conversion is based on 24-h use of oral or parenteral opioids: 60 mg OME/24 h = 25 mcg/h fentanyl patch (43).
Transmucosal fentanyl citrate formulations		7–12 h	1–2 h	New formulations indicated for the treatment of breakthrough pain; available in various forms, including buccal lozenge, buccal tablet, buccal patch, sublingual, and intranasal formulations; not recommended for opioid-naive patients; starting dose for breakthrough pain should always be one of the lowest doses available, even if the patient is receiving a high dose of a scheduled opioid

PO, by mouth; IM, intramuscular; IV, intravenous; SQ, subcutaneous; NA, not applicable; PR, by rectum; OME, oral morphine equivalents; NMDA, *N*-methyl-D-aspartate. ECG, electrocardiogram.
From Portenoy RK. Treatment of cancer pain. *Lancet* 2011;377:2236–2247 (slightly revised).

associated with altered sensory function, it is commonly described as burning, pricking, sharp, stabbing, hot, cold, squeezing, or electric-shock-like, and may be characterized by typical neuropathic features, such as allodynia (non-painful stimuli producing pain) or hyperalgesia (mildly painful stimulation producing severe pain).

Several sources provide excellent information about treating NP in patients with cancer (46,47). A recent authoritative review of the pharmacologic management of NP, published in the journal *Pain* (47), is available online and provides detailed evidence-based recommendations for the treatment of NP associated with cancer. A brief summary of their recommendations includes

Step 1

A. Establish the diagnosis of NP; if uncertain, refer to a pain specialist or neurologist
B. Establish and treat the cause, if possible
C. Identify relevant comorbidities or associated symptoms that might influence treatment decisions or require dosage adjustments (e.g., cardiac, renal, or hepatic disease, depression, ataxia)
D. Explain the diagnosis and treatment to the patient and establish realistic expectations.

Step 2

A. Initiate treatment with one or more of the following first-line medications:
   a. nortriptyline or desipramine—secondary amine TCAs or duloxetine or venlafaxine—selective serotonin and norepinephrine reuptake inhibitors (SNRIs)
   b. gabapentin or pregabalin (sometimes referred to as gabapentinoids)
   c. topical lidocaine, if pain is localized
   d. opioid analgesics or tramadol for prompt relief of moderate to severe pain

Recommendations are included regarding starting and maximum dosages, as well as titration schedules, for each of the above medications.

Step 3 involves reassessment and additional trials of first-line medications, either alone or in combination. Step 4 recommends that if trials of first-line medications fail, the clinician should consider trials of second- and third-line medications or referral to a pain specialist. Discussion of second- and third-line medications is beyond the scope of this chapter.

The choice of specific agents will depend primarily on comorbidities and associated symptoms and side effects (46,47). For example, TCAs may cause dry mouth and urinary retention, and should be used with caution in patients with significant cardiac disease, seizures, suicide risk, or in combination with tramadol (due to increased risk of serotonin syndrome), but may improve depression and insomnia. SNRIs may cause nausea and should be used with caution in patients with hepatic or renal dysfunction, cardiac disease, or in combination with tramadol, but may improve depression. Gabapentin and pregabalin may cause sedation, dizziness, and peripheral edema, and should be used with caution in renal insufficiency, but have no clinically relevant drug interactions and may improve sleep. Topical lidocaine may cause local skin irritation, but has no systemic side effects at standard doses. Opioids and tramadol may cause constipation, nausea and vomiting, drowsiness, and dizziness (most side effects, except for constipation are usually transient) and should be used with caution in patients with a history of, or at risk for, substance abuse, but have a rapid onset of analgesia. Tramadol also may increase seizure risk and should be used with caution in combination with TCAs or SNRIs.

A pragmatic approach to the treatment of NP in HNC based on the above recommendations would be

1. For patients who are depressed or have insomnia, who have no contraindications, to initiate treatment with a TCA or SNRI.
2. For patients who are not depressed, do not have insomnia, or have a contraindication to a TCA or SNRI, to initiate treatment with a gabapentinoid.
3. For patients with relatively localized pain, consider combining topical lidocaine with any of the above.
4. For patients with moderate to severe pain or those who have mixed pain, opioid therapy should usually be combined with any of the above; however, use caution for patients with a history of, or at high risk for, substance abuse (see above discussion).

END-OF-LIFE CARE FOR PATIENTS WITH HNC

Physicians should attempt to provide the most appropriate—that is, most beneficial, least harmful—treatment for each patient, based on the medical situation. Extensive research over the last several years supports the assertion that involvement of PC and hospice is essential to providing optimal care for patients whose death is anticipated. Indeed, late referral for PC or hospice can result in increased and unnecessary suffering for both the patient and family (48).

Many of the issues that patients dying of HNC must face are similar to those faced by any patient dying of cancer or any other progressive disease. As with most cancers, patients who die of HNC typically deteriorate fairly gradually and their death rarely comes completely without warning. Nevertheless, because physicians are often reluctant to discuss patients' prognoses with them and their families, many patients and families are unaware that death is approaching until death is very near (49). For HNC patients, as for other cancer patients, as death approaches, appropriate care must include attention to psychosocial and spiritual aspects of care—attending to the needs not

only of the patient, but also the family. Many issues that arise, including psychosocial, spiritual, and existential, may be beyond the capacity of the physician to address adequately. This is another reason to involve PC and hospice, which typically include mental health professionals, pastoral care, and other specialties; together such teams can provide the holistic interdisciplinary care necessary to address the complex challenges faced by dying patients and their families. Patients and families often struggle with the realization that the patient has reached a point that anticancer treatment will no longer benefit the patient. The perception that "there is nothing else we can do" is both disheartening and false. Indeed, the unofficial motto of PC is: "Actually, there is more we can do." For patients who are dying, PC and hospice are not about doing less, they are about doing those things that are most appropriate for dying patients, that is, most likely to benefit and least likely to harm them. Because presenting the option of PC and hospice as a positive good for dying patients is often a challenge for those who have little experience with such care, it is often beneficial to encourage patients and families to at least meet with PC or hospice representatives who can present the most accurate explanation of the benefits (50).

An important consideration for patients who are recognized to be dying is to address resuscitation status. It is important to understand that, for patients dying of advanced cancer, cardiorespiratory arrest is the mechanism of death, not the cause of death (51). This is an important difference between dying patients and other seriously ill patients, including many HNC patients who are not imminently dying, for whom a cardiorespiratory arrest may be the cause of death—that is, but for the cardiorespiratory arrest, the patient is not imminently dying. Whereas it makes sense to attempt resuscitation when the arrest is the potential cause of death, it does not make sense to attempt to treat an arrest that is merely the mechanism of death. With this in mind, when discussing resuscitation status with imminently dying patients and their families, rather than simply asking their preferences, it is appropriate to *recommend* that resuscitation *not* be attempted at the time of death. An example of a "script" to be used for such patients is "Unfortunately, because we cannot treat your underlying disease, it will soon cause your death. When that happens, your heart will stop beating and your breathing will stop. Therefore, I would recommend that, when that happens, we focus on assuring that you die peacefully and comfortably, rather than using shocks and machines to try to restart your heart or breathing. Does that make sense to you?" This approach is discussed in greater detail in a recent article (51).

Another medical issue that is often of critical importance for patients with HNC is correctly understanding—and explaining to the patient and family—when the provision of artificial hydration and nutrition is appropriate and beneficial and when it is inappropriate and harmful. Although this is an issue that is relevant to all dying patients, it is of particular importance for patients with HNC as many will have feeding tubes in place and would have been receiving AHN for some time prior to entering the dying process. As with any treatment, it is important to understand it in the medical context, considering the benefits and risks specific to that context. It is also important to consider the symbolic meaning of providing AHN—that is, feeding symbolizes sustenance and nurturing—and to distinguish that from the actual medical consequences.

The key point is that (for patients without feeding tubes) it is the natural course of the final stages of the dying process that essentially all patients lose their appetite and, eventually, their ability to swallow. Dying patients stop eating because they are dying; they do not die because they stop eating. As their gastrointestinal system begins to shut down, along with all other organ systems, they can no longer process and absorb hydration and nutrition. Furthermore, as their kidneys and heart fail, any excess fluid in their system tends to accumulate in their lungs causing pulmonary edema and respiratory distress. Indeed, this is one of the most common causes of distress in dying patients. In patients without feeding tubes, the discontinuation of feeding tends to occur naturally and is often recognized as a natural part of the dying process. However, in patients who have feeding tubes, the decision to discontinue AHN must be made deliberately and should be done according to the medical condition of the patient, for example, when gastrointestinal symptoms or evidence of fluid overload begin to develop—preferably earlier rather than later. Often, AHN can be gradually weaned as the patient declines, to minimize the risk of adverse symptoms. It is optimal to discuss this eventuality with patients and families ahead of time, so they can ask questions and prepare themselves psychologically for the terminal phase of the dying process. Once again, this discussion is often best accomplished with the help of PC and hospice personnel who are familiar with the natural dying process—another reason why early referral to PC or hospice is beneficial to patients and families.

Defining a Good Death

One important question, which can be addressed both philosophically and empirically, is what constitutes a "good death?" Steinhauser et al., used focus groups and in-depth interviews of a wide range "of persons involved with EOL care—physicians, nurses, social workers, chaplains, hospice volunteers, patients, and recently bereaved family members," in an attempt to provide an empirically based description of a good death (52). They found six components that were widely endorsed as essential components of a good death

- Pain and symptom management
- Clear decision making
- Preparation for death

- Completion
- Contributing to others
- Affirmation of the whole person

Not surprisingly, the importance of managing pain and other symptoms remained a paramount consideration for all groups. This reiterates the importance of providing excellent and appropriate medical care to dying patients. However, the main message of this study is that providing excellent medical care, although necessary, is not sufficient to ensure a good death.

Among the needs expressed by providers and families was the need for improved communication and clearer decision making, to improve the chances that a patient's preferences were known before a medical crisis occurs. The "lack of opportunity to plan ahead, arrange personal affairs, decrease family burden, or say good-bye" was identified as contributing to a bad death. The authors comment that "for dying patients and their families, preparation does not preclude hope; it merely frames it." The concept of "completion" is related and helps explain the importance of providing honest, compassionate prognostic information. Completion involves spending "meaningful time with family and close friends and attention to religious or spiritual beliefs." They note that terminally ill patients often frame the experience of dying within the larger trajectory of their life, thereby identifying and responding to opportunities for healing of relationships and personal growth. This may be part of the reason that terminally ill patients often rate their own QOL higher than observers.

The authors were somewhat surprised that a common theme was the desire of patients to contribute to others, but noted that "social psychologists describe this need for 'generativity' as one of the great emotional tasks of human development, particularly during later life." The focus groups also emphasized the importance of recognizing and appreciating dying patients as "whole persons," rather than primarily as persons with an illness or disease.

Specific Considerations in EOL Care for Patients with HNC

Due to the anatomical features of their disease, many patients with HNC have problems that are more or less specific to HNC. Among the problems that are common in patients with HNC are problems related to communication, swallowing, breathing, and the risk of catastrophic bleeding. A few studies have investigated this specific population and provide some insight into these and other problems and some guidance on how to best manage them.

A retrospective study from Taiwan addressed symptom patterns in HNC patients cared for on an inpatient palliative care unit (PCU) by a multidisciplinary team consisting of physicians, nurses, psychologists, social workers, pastors, and volunteers (53). Patients were typically referred late in their disease and had an average survival of about 22 days after admission to the PCU. Overall, the most common symptom was weight loss, followed by pain, cough, dysphagia, feeding difficulties, and communication difficulties. The only symptom that significantly correlated with the presence of a tracheostomy was communication difficulties. They found that pain was poorly controlled on admission and that opioid doses were typically increased after admission. Among their most interesting findings was a correlation between higher levels of education and higher doses of opioids. Most intriguing was their observation that the change (increase) of opioid dosage after PCU admission correlated with longer survival ($p < 0.001$). This supports the contention, often expressed by those experienced in EOL care, that optimizing pain control tends to prolong survival, presumably by diminishing distress and allowing better function, including better nutrition and increased activity. At the very least, this observation contradicts the widely believed myth that increasing opioid dosages at the EOL hasten death.

Another retrospective study, from Germany, presents a rather grim picture of the final days of patients with advanced HNC (54), describing the challenges encountered by an inpatient hospice team caring for 16 patients dying of HNC. The authors of this study note that Germany is about "25 years behind" Britain and the United States in the development of PC and hospice care, which may explain some of the findings of this study. Average survival after admission in this study was 19.5 days. In this group, pain was reported to be well managed on admission and aggressive opioid protocols generally maintained good pain control. One of the most common and challenging problems encountered was communication, largely related to tracheostomy and also impaired mental status. Several patients (it is not clear exactly how many) had large, exophytic tumors with skin breakdown, infection, and even maggot infestation in three patients. This was the most distressing problem encountered by staff and was also distressing to patients and families. Five patients had ongoing alcohol addiction and were permitted to continue their usual alcohol intake, either orally or per feeding tube. Fourteen of the 16 patients were visited fairly regularly by family members. None of the patients died alone; nine died in the presence of at least one family member and seven deaths were attended by a nurse. This emphasizes the relative predictability of death in advanced HNC. None of the patients suffered a catastrophic bleed.

In an American study, Shuman et al performed a survey of 58 surviving relatives of patients who died of HNC, using a variation of a validated survey instrument, the Family Assessment of Treatment at the End of Life (FATE), which consists of an overall score and nine domain scores (higher scores indicate greater satisfaction) (55). In their study, they evaluated the overall score and two domain scores, Management of Symptoms (MOS) and Care at the Time of Death (CTD). Approximately, one-third of the patients died in the hospital, the remainder died at home or in inpatient hospice (the exact numbers in each

of the latter two categories is unclear). Sixty-nine percent of patients had a PC consult, 90% had advance directives. There was no difference in overall FATE scores between patients with metastatic (45% of patients) versus locoregional disease (55%). Patients who died in the hospital had significantly lower overall FATE scores, as well as lower MOS and CTD scores, than those who died in hospice or at home. PC consult correlated with higher CTD scores, but not overall FATE or MOS scores. A history of palliative chemotherapy or radiotherapy correlated with higher MOS and CTD scores, but not overall FATE score.

One final consideration specific to HNC is the risk of terminal hemorrhage. Terminal hemorrhage—in HNC usually resulting from tumor eroding into the carotid artery—is typically an extremely distressing event for the patient and family and health care providers. Mercifully, such hemorrhages invariably result in rapid loss of consciousness, followed rapidly by death. The primary approach to management includes recognizing the risk and assuring that a sufficient quantity of dark towels are readily available to absorb the large quantity of blood and provide coverage of the wound. An additional option is to attempt to rapidly provide sedative or opioid medication to alleviate the patient's suffering. However, a recent study evaluating the use of anticipatory crisis anxiolytic or opioid medications for terminal hemorrhage through retrospective structured interviews of PC and head and neck oncology nurses, concluded that "anticipatory prescribing of crisis medication rarely benefits the patient and may unintentionally detract from nursing care" (56). The authors recommend focusing instead on providing nonpharmacologic management for patients with terminal hemorrhage.

These studies illustrate some of the challenges specific to the management of patients dying of HNC, as well as the value of an interdisciplinary team in providing EOL care. Experience with the dying process in general, and with the dying process of patients with HNC, is an important benefit provided by PC and hospice.

CONCLUSION

Patients with advanced, recurrent, or progressive HNC present a variety of challenges to the clinicians caring for them. Many of the challenges are common to all cancer patients with advanced disease, but many of the challenges are specific to patients with HNC.

Managing pain is a common challenge and all clinicians who care for patients with HNC should attempt to develop competence in the basics of cancer pain management. Patients with complex pain and other physical symptoms are likely to benefit from referral to a PC team. PC not only provides expert management of pain and other physical symptoms, it provides interdisciplinary care to address the multitude of complex problems experienced by patients with HNC, including psychosocial, spiritual, and existential problems.

Antineoplastic strategies (chemotherapy, radiation, surgery) can be considered in patients with incurable HNC carefully weighing factors such as expected symptomatic benefit, potential morbidity, patient performance status, and realistic patient and family expectations. Most common palliative antineoplastic strategies involve chemotherapy/systemic therapy. Symptomatic benefit occurs more often in patients who experience reduction in tumor burden, although symptomatic improvement can also occur in the absence of overt disease response.

It is important to recognize when patients are nearing the end of their lives, in order to ensure that they receive optimal care at that critical time. The most important considerations when patients are dying are to ensure comfort for the patient and support for the patient and family. This is best provided through PC or hospice referral. Learning to present PC and hospice as a positive option for patients with advanced disease is essential. Patients only die once. Although it is always tragic when patients die, it is doubly tragic when patients and families do not receive the support and care available to mitigate their suffering.

HIGHLIGHTS

- The goal of Palliative Care is to prevent and relieve suffering and to support the best possible quality of life for patients and their families, regardless of the stage of their disease or the need for other therapies.
- The Report of the National Consensus Project Clinical Practice Guidelines for Quality Palliative Care describes the eight essential domains that must be addressed by all clinical PC programs:
  - Structure and Processes of Care
  - Physical Aspects of Care
  - Psychological and Psychiatric Aspects of Care
  - Social Aspects of Careo
  - Spiritual, Religious, and Existential Aspects of Care
  - Cultural Aspects of Care
  - Care of the Imminently Dying Patient
  - Ethical and Legal Aspects of Care
- Antineoplastic strategies (chemotherapy, radiation, surgery) can be considered in patients with incurable head and neck cancer (HNC) carefully weighing factors such as expected symptomatic benefit, potential morbidity, patient performance status, and realistic patient and family expectations. Most common palliative antineoplastic strategies involve chemotherapy/systemic therapy. Symptomatic benefit occurs more often in patients who experience reduction in tumor burden, although symptomatic improvement can also occur in the absence of overt disease response.
- Pain in HNC can occur as a result of the disease itself or therapy. The evidence suggests that

  - The majority of patients with HNC will have pain, which may be difficult to treat. Pain may be somatic, neuropathic, or mixed.
  - Up to a quarter of patients who remain disease free at 2 years may have persistent pain, which may be moderate to severe in up to 15%.
  - Persistent shoulder and arm pain is associated with neck dissection.
  - Of the HNC patients who seek treatment for pain, the most common sites of pain are the head, face, mouth, and neck.
- The management of pain in patients with cancer is based on the principle that every patient deserves to have his or her pain assessed and managed in accordance with the best available medical evidence.
- Opioids are the mainstay of pharmacologic treatment of cancer pain; however, they are associated with certain risks, most notably side effects, abuse, misuse, and diversion. Misuse behaviors in the medical setting are most-commonly referred to as aberrant behaviors.
- Every patient who is treated with opioids should be assessed for risk of aberrant behaviors and his or her treatment and monitoring should be guided by this assessment. Evidence of aberrant behaviors occurring during treatment should lead to reassessment and may require an adjustment of the treatment plan.
- Physicians who treat patients with HNC should learn the basic principles of opioid therapy. Because neuropathic pain is common in HNC, they should also learn the basic principles of treating NP. They should understand the pharmacology of commonly used medications, as well as the risks and how to mitigate them. They should develop relationships with PC or pain specialists and learn when and how to refer to them.
- Extensive research over the last several years supports the assertion that involvement of PC and hospice is essential to providing optimal care for patients whose death is anticipated.
- For HNC patients, as for other cancer patients, as death approaches, appropriate care must include attention to psychosocial and spiritual aspects of care—attending to the needs not only of the patient, but also the family.
- Whereas it makes sense to attempt resuscitation when an arrest is the potential cause of death, it does not make sense to attempt to treat the mechanism of death. With this in mind, when discussing resuscitation status with imminently dying patients and their families, it is appropriate to *recommend* that resuscitation *not* be attempted at the time of death.
- One study suggested that the essential components of a good death are
  - Pain and symptom management
  - Clear decision making
  - Preparation for death
  - Completion
  - Contributing to others
  - Affirmation of the whole person
- Patients only die once. Although it is always tragic when patients die, it is doubly tragic when patients and families do not receive the support and care available to mitigate their suffering.

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II

Rhinology and Allergy

Berrylin J. Ferguson *Matthew W. Ryan*

Sinonasal Anatomy and Physiology

23

Randy M. Leung *William E. Walsh* *Robert C. Kern*

EMBRYOLOGY

Embryologic development of the nasal cavity and sinuses leads to the intricate features of sinonasal anatomy and can be divided into two ongoing processes. First, the embryo's head develops into a structure with two distinct nasal cavities; second, the lateral nasal walls then invaginate to create complex folds, known as turbinates, and spaces, known as sinuses. During the fourth to eighth gestational weeks, the embryo develops separate nasal cavities as the frontonasal and maxillary processes join. The frontonasal process grows over the developing forebrain, contributing to the formation of the nasal olfactory placodes. Medial and lateral nasal prominences develop on either side of the placode eventually becoming the nares. The nasal placode invaginates to form the nasal pit and eventually the nasal sac. Fusion of the medial nasal prominence with the maxillary process forms the upper maxilla and the philtrum of the upper lip (Fig. 23.1). The septum arises from the posterior midline growth of the frontonasal process and midline extensions of mesoderm from the maxillary processes. The primary and secondary palatal shelves join in an axial plane to separate the nasal cavity and nasopharynx from the oral cavity and oropharynx. The descending septum merges with the fused palate to create two distinct nasal cavities (Fig. 23.1). Fusion failure of the medial nasal prominence with the maxillary process or fusion failure of the palatal shelves results in a cleft lip or palate deformity. Because clefting can extend into the nose, rhinoplasty to correct an associated nasal deformity is often technically difficult.

During the sixth gestational week, mesenchyme forms a simple lateral nasal wall. During the seventh week, three axial furrows form, giving rise to the three turbinates (Fig. 23.1). During the 10th week, development of the maxillary sinus begins with the invagination of the middle meatus. At the same time, the uncinate process and the bulla ethmoidalis form a narrow groove known as the hiatus semilunaris. During the 14th week, the anterior ethmoidal cells appear as several invaginations from the upper middle meatus and the posterior ethmoidal cells from the floor of the superior meatus. Finally, by the 36th week the lateral nasal wall is well developed and the turbinates are at adult proportions. All paranasal sinuses are present to varying degrees in the newborn, but sinuses have specific periods of significant growth. The ethmoid sinuses are the first to fully develop, followed in order by maxillary, sphenoid, and frontal sinuses.

ANATOMY

Refer to Figure 23.2 for illustrations of sinus anatomy discussed in the text.

Ethmoidal Sinuses and Lateral Nasal Wall

The ethmoid sinuses are the central structures of the nose with complex anatomy; they are best visualized as a box-like structure with open anterior and inferior faces. The lateral portions form the medial walls of the orbits, the sphenoid establishes the posterior face, the superior surface is formed by the skull base of the anterior cranial fossa, and many of the key structures of the lateral nasal wall, derived from basal lamellas, extend posteroinferiorly from the skull base.

The lateral wall of the ethmoid sinus, or lamina papyracea, forms the paper-thin medial wall of the orbit. The midline vertical plate of the ethmoid bone is composed of a superior portion in the anterior cranial fossa called the crista galli and an inferior portion in the nasal cavity called the perpendicular plate of the ethmoid bone that contributes to the nasal septum. The anterior cranial fossa is separated from the ethmoid air cells superiorly by the horizontal plate of the ethmoid bone, which is composed of the thin medial cribriform plate and the thicker, more

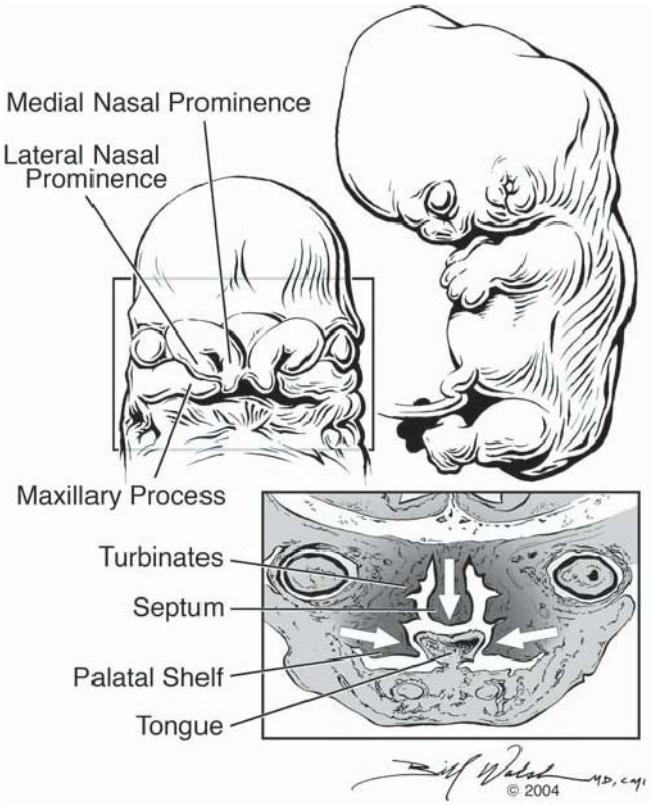


Figure 23.1 A 7-week gestational age embryo. Cross-section in **bottom right** shows the formation of turbinates and the separation of the nasal cavities by fusion of the nasal septum with the palatal shelves. Illustration by William E. Walsh, MD, CMI ©2004, used with permission.

lateral ethmoid roof. The ethmoid roof articulates with the cribriform plate at the lateral lamella of the cribriform plate, which is the thinnest bone in the entire skull base. The length of the lateral lamella depends on the position of the cribriform plate with respect to the ethmoid roof. In a Keros type 1 skull base, the plate is located 1 to 3 mm below the roof of the ethmoid, making the lateral lamella short or nonexistent (Fig. 23.2B). In Keros type 2, the distance is 4 to 7 mm. In Keros type 3, it is 8 to 16 mm, thus giving rise to a long vertical lateral lamella (Fig. 23.2C). Patients with a low cribriform plate, *Keros III in particular*, are believed to be at greatest risk for cerebrospinal fluid leak during endoscopic sinus surgery.

The ethmoid sinuses are separated by a series of recesses demarcated by five bony partitions or lamellae. These lamellae are named from the most anterior to posterior: first (uncinate process), second (bulla ethmoidalis), third (basal lamella), fourth (superior turbinate), and fifth (supreme turbinate). These partitions aerate during development forming the ethmoid air cells. If the aeration projects anterior to the attachment of the middle turbinate, the air cells are termed agger nasi cells. Continuing posteriorly, the uncinate process is an L-shaped bone that runs in an anterosuperior to posteroinferior direction. The posterosuperior margin of the uncinate runs parallel to the anterior border of the bulla ethmoidalis and the posterior end attaches to the palatine bone and the inferior turbinate. The superior portion of the uncinate most commonly attaches to the lamina papyracea but can also attach to the posteromedial wall of the agger nasi cell, the skull base, or the middle turbinate. The bulla ethmoidalis, or second lamella, gives rise to the most constant and usually largest anterior ethmoid air cell. It attaches laterally to the lamina papyracea and to a varying degree posteriorly to the ground lamella. Superiorly, the bulla may reach the roof of the ethmoid and form the posterior wall of the frontal recess. Minimal or absent pneumatization of the ethmoid bulla occurs in 8% of individuals (1). The basal lamella marks the dividing line between the anterior and posterior ethmoid sinuses. The inferior portion of the basal lamella connects the middle turbinate to the lateral nasal wall obliquely transitioning from a coronal plane anteriorly to an axial plane posteriorly. Preservation of the lower portion of the basal lamella during endoscopic sinus surgery provides stability to the middle turbinate. Posterior ethmoidal cells are generally larger and can pneumatize laterally and superiorly to the sphenoid sinus. This developmental variant is known as an Onodi cell, a risk factor for dehiscence and potential injury to the optic nerve during surgery.

The lamellae of the ethmoid sinuses are separated by a series of four recesses: the frontal recess, the infundibulum, the sinus lateralis, and the sphenoethmoidal recess. The frontal recess drains the frontal sinus; the anatomy is highly variable depending on the pneumatization patterns of the bulla ethmoidalis and agger nasi air cells (2). The ethmoidal infundibulum is a three-dimensional space lateral to the uncinate process. Between the free concave posterior margin of the uncinate process and the convex anterior face of the bulla ethmoidalis is a two-dimensional cleft called the hiatus semilunaris that serves as the door that leads anteriorly into the infundibulum. The ostium of the maxillary sinus lies deep within the ethmoidal infundibulum lateral to the uncinate process. The ethmoid sinuses anterior to the basal lamella, the maxillary sinus, and the frontal sinus all drain directly into or near the infundibulum. The ostiomeatal complex (OMC) refers to the area bounded by the middle turbinate medially, the lamina papyracea laterally, the basal lamella posteriorly, and the ethmoid roof superiorly (1). A sinus lateralis or retrobullar recess exists if the posterior wall of the bulla ethmoidalis aerates to become distinct from the basal lamella. The sphenoethmoidal recess is located at the posterior end of the superior meatus draining the posterior ethmoid and sphenoid sinuses separately, outside of the OMC.

The anterior ethmoid artery originates from the ophthalmic artery in the orbit and passes through the anterior ethmoidal foramen to enter the anterior ethmoidal cells. The artery typically crosses the ethmoids very near the skull base at the junction of the ethmoid roof and marks the posterior border of the frontal recess; the artery travels within a bony canal that may be partially or completely dehiscent in 40% of cases (1). The area where the anterior ethmoid

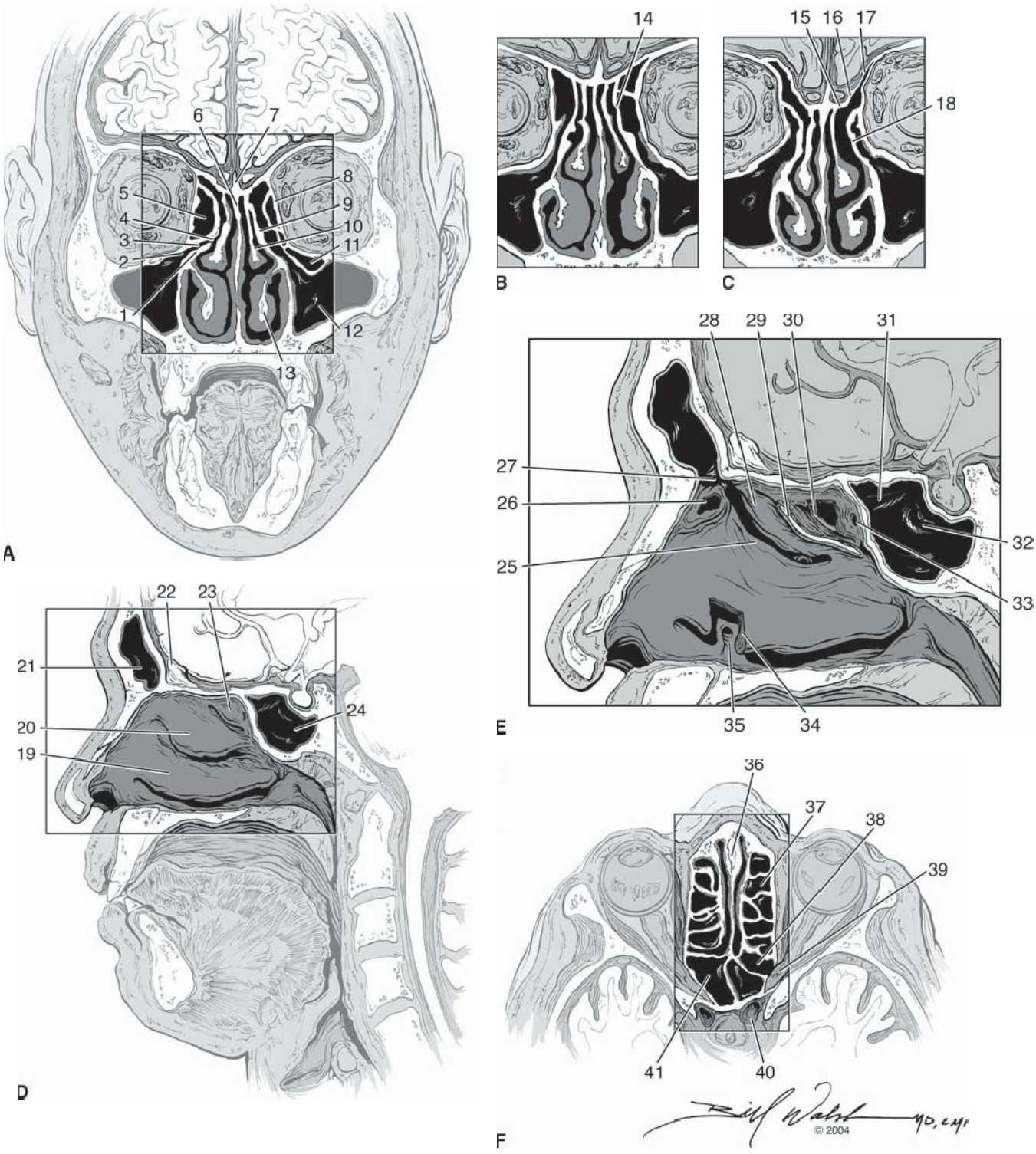


Figure 23.2 Sinus anatomy. **A**: Coronal section through the ostiomeatal complex with the left uncinate attaching medially to the septum. *1*, right uncinate process; *2*, maxillary sinus ostium; *3*, ethmoidal infundibulum; *4*, hiatus semilunaris; *5*, bulla ethmoidalis; *6*, perpendicular plate of the ethmoid bone; *7*, crista galli; *8*, lamina papyracea; *9*, left uncinate process attaching medially to the septum; *10*, middle turbinate; *11*, Haller cell; *12*, maxillary sinus; *13*, inferior turbinate. **B**: Keros 1 skull base with the uncinate processes attaching superiorly to the skull base. *14*, left uncinate process attaching superiorly to the skull base. **C**: Keros 3 skull base with uncinate processes attaching laterally to the lamina papyracea. *15*, cribriform plate; *16*, lateral lamella; *17*, ethmoid roof; *18*, left uncinate process attaching laterally to the lamina papyracea. **D**: Sagittal view of the lateral nasal wall. *19*, inferior turbinate; *20*, middle turbinate; *21*, frontal sinus; *22*, crista galli; *23*, superior turbinate; *24*, sphenoid sinus. **E**: Close-up sagittal view of the lateral nasal wall with the middle turbinate removed. *25*, uncinate process; *26*, agger nasi cell; *27*, frontal ostium; *28*, bulla ethmoidalis; *29*, middle turbinate cut edge; *30*, superior turbinate cut edge; *31*, optic nerve prominence in the sphenoid sinus; *32*, carotid artery prominence in the sphenoid sinus; *33*, sphenoid sinus ostium; *34*, inferior turbinate cut edge; *35*, nasolacrimal duct. **F**: Axial view. *36*, septum; *37*, ethmoid cell; *38*, Onodi cell; *39*, optic nerve; *40*, carotid artery; *41*, sphenoid sinus. Illustration by William E. Walsh, MD, CMI ©2004, used with permission.

artery enters the anterior cranial fossa through the lateral lamella is the weakest portion of the skull base, being only one-tenth as strong as the roof of the ethmoid (1).

Maxillary Sinus

The maxillary sinus is the pneumatized space within the maxillary bone and is the largest of the paranasal sinuses. The anterior wall derives from the facial surface of the maxilla, the posterior wall borders the pterygopalatine fossa, the medial wall constitutes the lateral wall of the nasal cavity, the floor of the sinus is the alveolar process, and the superior wall serves as the orbital floor. The infraorbital nerve crosses the orbital floor to exit the anterior portion of the maxilla via the infraorbital foramen. The canal for the infraorbital nerve is dehiscent into the maxillary sinus in 14% of cases and may be at risk during endoscopic sinus surgery. The first and second molar tooth roots are dehiscent into the maxillary sinus occurring in 2% of cases. These patients are at risk for development of an oroantral fistula following dental extraction at these sites.

The natural ostium of the maxillary sinus opens into the superior aspect of the medial wall to drain into the ethmoidal infundibulum. Accessory maxillary sinus ostia are found in 15% to 40% of subjects, most commonly superior and posterior to the uncinate process above the insertion of the inferior turbinate. Occasionally a Haller cell, or ethmoidal cell that pneumatizes laterally between the maxillary sinus and the floor of the orbit, may be present. The presence of Haller cells can potentially narrow the maxillary infundibulum and impair sinus drainage (3).

Frontal Sinus

The size of the frontal sinus varies depending on the degree of pneumatization, may be completely absent (5%), and is usually divided by an intersinus septum. The anterior table of the frontal sinus is twice as thick as the posterior table, which separates the sinus from the anterior cranial fossa. The floor of the sinus also functions as the supraorbital roof, and the drainage pathway is located in the posteromedial portion of the sinus floor. Drainage of the frontal sinus is complex with its outflow tract resembling an hourglass-shaped structure in the sagittal plane (1,2). The superior portion widens into the frontal sinus and the inferior portion expands into the frontal recess. The variability of the frontal sinus outflow tract drainage pattern depends on the pneumatization of the surrounding ethmoid air cells and the position of the uncinate process. A markedly pneumatized agger nasi cell or ethmoidal bulla can obstruct frontal sinus drainage by narrowing the frontal recess. Drainage of the frontal sinus also depends on the attachment of the superior portion of the uncinate process (4). In the most common variation, the anterosuperior portion of the uncinate process inserts onto the lamina papyracea so that the uncinate process separates the ethmoidal infundibulum from the frontal recess. In this setting, the frontal recess opens into the middle meatus medial to the ethmoidal infundibulum, between the uncinate process and the middle turbinate (Fig. 23.2C). When the uncinate process inserts onto the ethmoid roof (Fig. 23.2B) or inserts onto the middle turbinate (Fig. 23.2A), the frontal recess opens directly into the ethmoidal infundibulum, and is thought to be subject to obstruction in the presence of ethmoid inflammation. During endoscopic sinus surgery, the opening of the frontal sinus is often more medial than anticipated. The frontal sinus opens into the middle meatus medial to the uncinate process in 88% of patients and lateral to the uncinate in the remaining 12% of patients.

Sphenoid Sinus

The sphenoid sinus has many important neurovascular relationships. The internal carotid artery is lateral to the sphenoid sinus as it courses through the cavernous sinus producing a prominence in the lateral sphenoid sinus wall in 65% of individuals (3). Approximately 25% of bony capsules separating the internal carotid artery from the sphenoid sinus are partially dehiscent. An optic nerve prominence is present in 40% of individuals with dehiscence in 6% (3). The visibility of all structures related to the walls of the sphenoid sinus depends on the degree of pneumatization of the sinus. The degree of pneumatization is classified into three types: sellar type (86%), presellar (11%), and conchal type (3%) (3). Presellar and conchal types are more common in children due to the normal development of the sphenoid sinus reaching completion at 20 years of age. In a sellar type sphenoid sinus, the superior wall pneumatizes inferiorly to the sella turcica and the pituitary gland. The posterior wall of the sphenoid sinus is the clival wall and is the thickest wall of the sphenoid sinus.

The sphenoid sinus ostium opens into the sphenoethmoidal recess. An anatomic study of the sphenoid sinus ostium identified the posteroinferior end of the superior turbinate as the best landmark for identifying the natural ostium of the sphenoid sinus (5). In most cases, the posteroinferior end of the superior turbinate was located in the same horizontal plane as the floor of the sphenoid sinus. The ostium was located medial to the superior turbinate in 83% of cases and lateral to it in 17%. The sphenoid septum usually deviates posteriorly from the midline dividing the sinus into two asymmetric parts and can insert onto the bony prominences overlying the optic nerve or carotid artery.

Inferior Turbinate

The inferior turbinates are bilateral outgrowths from the lateral wall of the nasal cavity composed of a central bony skeleton covered by a mucosal layer. Each inferior turbinate articulates with the perpendicular plate of the palatine bone and the nasal surface of the maxilla. The inferior turbinate swells and shrinks to regulate nasal temperature and humidification via a rich vascular arcade.

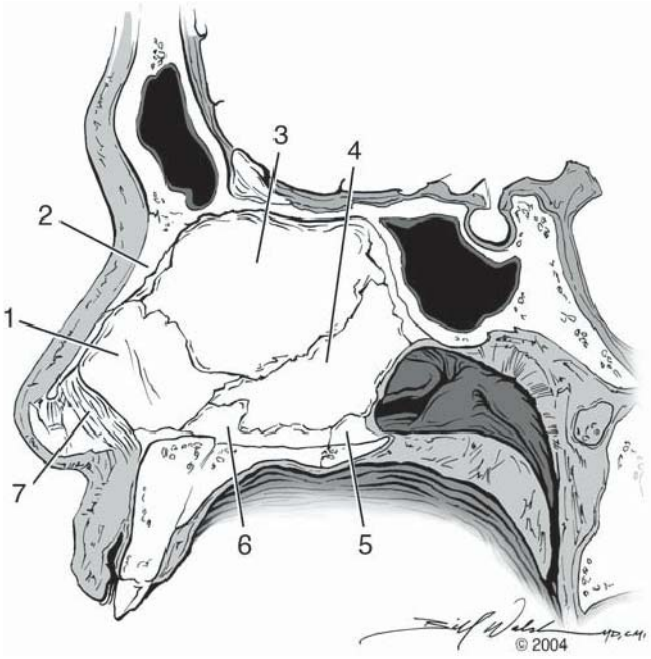


Figure 23.3 Nasal septum. *1*, quadrangular cartilage; *2*, nasal bone; *3*, perpendicular plate of ethmoid bone; *4*, vomer; *5*, nasal crest of palatine bone; *6*, nasal crest of maxilla; *7*, membranous septum. Illustration by William E. Walsh, MD, CMI ©2004, used with permission.

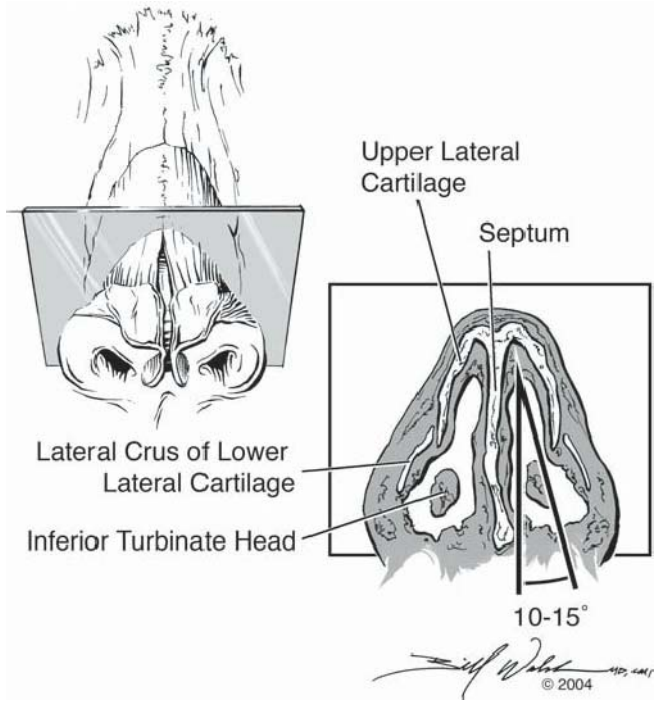


Figure 23.4 Nasal valve. Illustration by William E. Walsh, MD, CMI ©2004, used with permission.

Nasal Septum

The septum separates the two nasal cavities, provides structural support for the nose, and influences airflow in the nasal cavity. The septum is made of a sagittal plate of cartilage and bone covered by respiratory mucosa. The membranous septum connects the columella to the quadrangular cartilage. The quadrangular cartilage comprises the majority of the anterior septum. The perpendicular plate of the ethmoid bone forms the bony upper one-third of the nasal septum and the vomer makes up its bony posteroinferior portion. Finally, the nasal, frontal, maxilla, and palatine bones each contribute nasal crests to the periphery of the septum (Fig. 23.3).

Nasal Valve

The nasal valve is the mobile, airflow-regulating part of the nose that serves as the bridge between the bony skeleton and the nasal tip. This valve is the narrowest part of the nasal airway and poses the greatest resistance to nasal airflow. The nasal valve includes the area between the caudal end of the upper lateral cartilages and the superior septum. These segments usually form an angle of 10 to 15 degrees (Fig. 23.4). A decreased angle can induce airflow turbulence and nasal obstruction. The nasal valve region is bordered superolaterally by the caudal edge of the upper lateral cartilage. The lateral border includes the bony piriform aperture and the fibrofatty tissue of the ala. The nasal valve ends inferiorly at the nasal floor. Finally, the head of the inferior turbinate forms the posterior limit of the nasal valve (Fig. 23.4).

ANATOMIC CAUSES OF NASAL OBSTRUCTION

The trigeminal nerve endings in the nasal cavity provide the sensation of nasal airflow, and blockage of these receptors results in the sensation of nasal obstruction (6). A variety of intranasal deformities cause nasal obstruction and evaluation of each of the anatomic causes allows the surgeon to select the best procedure to correct the obstruction. This evaluation begins with a careful history and physical examination. Patients may report nasal congestion, stuffiness, or blockage; they may also report poor quality sleep or difficulty breathing during sleep. In addition to a fixed, anatomic obstruction, the physician must carefully seek other causes of nasal obstruction such as allergic rhinitis (AR), acute or chronic sinusitis, or medication-induced rhinitis. The physical examination includes external and internal nasal examination by anterior rhinoscopy and nasal endoscopy followed by a repeat examination after nasal decongestion. Obstruction that resolves with decongestion is caused by mucosal abnormality.

Septal Deviation

Patients with a symptomatic septal deviation complain of chronic obstruction that is frequently unilateral, possibly with a distant history of nasal trauma. They are often

keenly aware of the nasal cycle. Anterior rhinoscopy and nasal endoscopy documents the presence and degree of septal deviation. In addition, assessment of the columella from below helps evaluate caudal septal deflections, which can be underestimated on standard rhinoscopy. Palpation of the external nose and septum tests the support of the dorsum and the tip.

The treatment for nasal obstruction from septal deviation is septoplasty. Patients with septal deformity who undergo septoplasty generally report significant improvement in nasal obstruction at 3 and 6 months and use fewer medications (7). Unfortunately, no single test reliably predicts successful outcome preoperatively. Rhinomanometry has been used as an adjunctive research tool to document obstruction and degree of improvement postsurgery, but these tests are not widely used in the clinical setting. The location of the septal deformity strongly correlates with the surgical outcome and the postoperative airway resistance. Even minor septal deviations in the anterior part of the nose in the region of the nasal valve often result in significant nasal obstruction because the nasal valve is the critical resistive area of the nasal cavity; posterior deviations must be of great size to result in noticeable nasal obstruction.

Nasal Valve Collapse

The nasal valve is the narrowest part of the nasal airway accounting for most of the resistance to airflow; abnormalities in this region readily cause nasal obstruction. Two types of nasal valve dysfunction can occur: one involves dysfunction in the region of the nasal valve and the other involves collapse of the structures itself. Obstruction in the region of the nasal valve is most commonly from turbinate hypertrophy or septal deviation. The second type of nasal valve dysfunction results from collapse of the structure itself. Most cases are iatrogenic and nasal valve collapse must be considered in any patient who reports long-term obstruction postrhinoplasty. However, a small percentage of cases are congenital. Physical findings typically include an hourglass or pinched appearance of the middle segment of the nose, medial collapse of the alar cartilage on deep inspiration, or deep alar grooves. In the performance of rhinoplasty, nasal valve dysfunction results from aggressive narrowing of the nasal tip, over resection of the lateral crus, displacement of weak alar cartilages, excessive narrowing of the dorsum, over resection of upper lateral cartilages, or displacement of short nasal bones. A variety of surgical techniques have been developed to correct nasal valve dysfunction including spreader grafts, alar batten grafts, flaring sutures, overlay grafts, and lateral suture suspensions. Spreader grafts can be sutured along the length of the upper lateral cartilage to increase the cross-sectional area of the internal nasal valve and to augment the nasal structure preventing collapse. Alar batten grafts support flaccid lower lateral cartilages. Flaring sutures dilate the caudal margin of the upper lateral cartilages. Although these techniques correct nasal valve obstruction, each of these procedures may have aesthetic consequences.

The Cottle maneuver is the traditional method to diagnose nasal valve collapse. This maneuver widens the alae by placing lateral traction on the cheek. Some believe that the Cottle maneuver is a nonspecific test that improves breathing even when nasal obstruction is secondary to septal deviation or turbinate hypertrophy. To address this objection, a modified Cottle maneuver has been proposed to more specifically diagnose nasal valve collapse (8). In this modified maneuver, an ear curette separately supports the lower and upper lateral cartilages to see if nasal patency is increased.

Turbinate Hypertrophy

The inferior turbinate also affects airflow at the nasal valve depending on the degree of anterior turbinate engorgement. During inspiration, the anterior tip of the inferior turbinate in the region of the nasal valve generates up to two-thirds of upper airway resistance (9). Inferior turbinate enlargement leads to symptoms of nasal obstruction by increasing resistance. AR, nonallergic rhinitis, and rhinitis medicamentosa cause turbinate inflammation. If the inflammation persists, mucous glands grow in size and collagen accumulates beneath the nasal mucosa basement membrane resulting in irreversible hypertrophy.

Medical treatment for inferior turbinate hypertrophy includes *antihistamine nasal sprays*, decongestants, intranasal corticosteroids, mast cell stabilizers, and immunotherapy. A variety of surgical techniques also treat the nasal obstruction arising from turbinate hypertrophy and each methodology attempts to minimize complications such as bleeding, discomfort, and atrophic rhinitis while restoring normal turbinate size and function.

Concha Bullosa

A pneumatized middle turbinate, known as a concha bullosa, is one of the most common anatomic variations of the middle meatus with a reported incidence greater than 25%. The interior of a concha bullosa contains a lining of respiratory epithelium and drains through an ostium into the frontal recess, sinus lateralis, or hiatus semilunaris (1). The middle turbinate may grow to such an extent that it fills the space between the lateral nasal wall and the septum resulting in nasal obstruction and predisposing to sinus infection by blocking the OMC. Concha bullosa is suspected when an enlarged middle turbinate is observed during nasal endoscopy. A computed tomography (CT) scan demonstrating pneumatization of that turbinate confirms the diagnosis. Endoscopic excision of the lateral wall of the pneumatized turbinate can address this type of obstruction.

Choanal Atresia

Choanal atresia is a rare cause of nasal obstruction resulting from failure of the posterior choanae to develop properly. This condition occurs in 1 per 5,000 births with a female-to-male preponderance of 2:1. The extent of the atresia determines the severity of obstruction. Because newborns are obligate nose breathers, bilateral choanal atresia results in severe nasal obstruction and immediate airway distress relieved by crying. The diagnosis is suspected by the inability to pass a catheter or nasogastric tube on either side. Unilateral choanal atresia does not immediately threaten the child's life and usually presents in late childhood or young adulthood with unilateral nasal obstruction, rhinorrhea, or obstructive sleep apnea. Endoscopic assessment and CT scanning of choanal atresia can establish the diagnosis, characterize the lateral wall component of the atresia, evaluate the bony or membranous composition, and monitor the extent of surgical correction (10). The diagnosis of choanal atresia suggests the presence of other medical conditions and should prompt an evaluation for otitis media with effusion, upper and lower airway diseases, cardiac anomalies, and gastrointestinal (GI) tract disorders. Bilateral choanal atresia can coexist with cardiac disorders, CHARGE syndrome (colobomas, heart defects, choanal atresia, retarded growth, genitourinary hypoplasia, and ear anomalies), obstructive sleep apnea, hematologic problems, and failure to thrive (10).

In a large series of children treated for choanal atresia, the majority of children underwent transnasal repair with or without stenting. Other procedures performed less frequently include posterior septal window or dilation for unilateral choanal atresia, and transpalatal repair with stenting for bilateral choanal atresia. The repair of bilateral choanal atresia with dilation and removal of stents, on average, requires more procedures than unilateral choanal atresia to achieve a patent nasal airway without respiratory distress (10). The use of fibroblast-inhibiting topical mitomycin at the time of surgery may lead to improved patency.

Nasal Polyposis

Nasal polyposis (NP) is believed to be a multifactorial disorder characterized by the presence of edematous masses in the nasal cavity and sinuses triggering drainage, smell loss, and obstruction. The specific causes of NP remain unclear, but allergy, asthma, chronic rhinosinusitis (CRS), aspirin intolerance, and cystic fibrosis have been implicated in various studies. The majority of nasal polyps (80% to 90%) exhibit tissue eosinophilia and factors that could potentially trigger mucosal eosinophilia have been suggested as etiologic agents. Sinonasal inflammation from any etiology is believed to cause polyps to increase in size and number, with resultant nasal obstruction and sinus ostial blockage often triggering infectious sinusitis.

Intranasal and systemic steroids are the most common treatments for the management of nasal polyps. If evidence of purulence is seen on endoscopy, antibiotics are added to the treatment regimen. Endoscopic surgery is reserved for severe nasal obstruction resistant to maximal medical therapy. Nasal polyps tend to be more severe and refractory to medical and surgical treatment, especially in the subset of aspirin-sensitive asthmatics (11).

PHYSIOLOGY

The three major functions of the nose are olfaction, respiration, and protection. These functions are aided by the convoluted anatomy of the nasal cavity, which creates a large surface area. This mucosal lined, moist, ciliated surface of the nasal cavity increases contact with inspired air, thus maximizing olfaction, and resulting in efficient heating, humidifying, and filtering of inspired air before reaching the lower airways.

Respiration

The extensive vascular and secretory systems of the nasal cavity and paranasal sinuses serve to warm and humidify ambient air in preparation for access to the lower airways. The nose warms inspired air to 37°C facilitating alveolar gas exchange. This warming capacity is not overburdened even at 7 L per minute of inspired airflow (12). Independent of the environmental humidity, the sinonasal system can raise the humidity of inspired air to approximately 85%, thus decreasing the drying effect of inspired air and significantly benefiting gas exchange in the lower airways (12). This moisture comes from the water content of the mucus that is directly transudated from nasal blood vessels and supplied by nasal glands.

Turbulent nasal airflow is central to the physiology of the nose. Turbulent airflow occurs even at low air velocities in most parts of the nasal cavity and increases with higher air velocities (9). Turbulence increases contact between inspired air and the nasal mucosa enhancing not only the respiratory functions but also olfaction and protection. The main airflow passes over the head of the middle turbinate through the middle meatus with only minor changes in flow pattern as velocity increases. The percentage of air passing through the middle meatus increases with increased nasal congestion (9).

Nasal airway resistance can be divided into three parts: the nasal vestibule, the nasal valve, and the turbinated nasal cavity. The nasal vestibule contributes approximately one-third of nasal resistance. The compliant walls of the nasal vestibule are susceptible to collapse from the negative pressure created during inspiration; however, the facial muscles attached to the nasal vestibule contract during inspiration to splint the vestibule and prevent collapse. As previously mentioned, the nasal valve is the narrowest part of the nasal passage with the highest resistance. Venous sinusoids

control nasal airflow; thus, venous sinusoids of the anterior portion of the inferior turbinate and the nasal septum in the region of the nasal valve most significantly contribute to total nasal airflow resistance. The turbinated cavity of the nasal passage with its larger cross-sectional area contributes only minimally to nasal airway resistance (6).

The nasal submucosa is rich in vasculature including arterioles, capillaries, and venules. The mucosa of the inferior turbinate uniquely contains many small veins, called venous sinusoids. To cause expansion of this erectile tissue that brings congestion, these high capacitance sinusoids relax to fill with blood; in contrast, decongestion of the nose results from contraction of the sinusoids emptying them of blood. Sympathetic vasoconstrictor stimulation exerts the major control over venous sinusoid filling by decreasing the volume of blood held in the mucosa causing decongestion. Parasympathetic vasodilator fibers exert only minor control of nasal blood volume but cause more potent control of nasal secretions by stimulating a watery discharge. In general, sympathetic innervation controls nasal airflow and parasympathetic innervation controls nasal secretions (6).

In addition to autonomic regulation of nasal vasculature, nasal airflow is also influenced by the nasal cycle, head and body position, exercise, and nitric oxide (NO). The nasal cycle refers to spontaneous congestion and decongestion alternating between the two nasal passages. This cycle occurs in approximately 80% of the population and repeats every 0.5 to 3.0 hours. The nasal cycle results in airway resistance and nasal width changes that affect airflow turbulence. Although the resistance and airflow alternates between the two nasal cavities, the nasal cycle does not significantly change the combined nasal resistance and total airflow. Postural change can alter nasal airflow through changes in relative venous pressure. Exercise results in epinephrine release causing nasal decongestion. Sex hormones influence nasal airflow; thus, pregnancy, puberty, and menstruation can lead to increased nasal obstruction (6). Lastly, the neurotransmitter NO contributes to nasal blood flow regulation and mucus production. Nasal NO concentrations depend on nasal airflow but not on changes in the nasal cavities induced by the nasal cycle or posture. Increased nasal airflow from nasal decongestion removes NO from the nasal cavity and transports it to the lung where NO serves as a vasodilator gas. Conversely, decreased nasal airflow during congestion results in an elevated nasal NO concentration. While in the nasal passages, NO influences nasal cilia; higher concentrations stimulate nasal ciliary beat frequency, whereas low NO concentrations depress this frequency. Higher nasal ciliary beat frequency may help protect the nasal airway during congested states like acute sinusitis.

Nasal resistance can be measured using *rhinomanometry*. Rhinomanometry measures the airflow at a fixed pressure differential during the respiratory cycle. Airflow is measured directly with a mask. Transnasal pressure is simultaneously measured with pressure detectors at different locations depending on the technique. Anterior rhinomanometry measures transnasal pressure one nostril at a time at the nasal orifice; posterior rhinomanometry measures nasal resistance of both nostrils simultaneously with a pressure detector placed in the mouth. The information is recorded and displayed on a pressure-flow curve. Because nasal resistance is the ratio of pressure to airflow, the pressure-flow curve will show that at a given transnasal pressure, the more obstructed nose will achieve less airflow and thus display a higher resistance.

Nasal cross-sectional area can be measured using *acoustic rhinometry*. Acoustic rhinometry is a noninvasive way to measure cross-sectional area of the nasal cavity by analyzing reflected sound waves within the nasal cavity. Acoustic pulses enter the nasal passage through a nose piece, impact nasal structures, and are reflected back to a microphone. The reflected pulse is presented as an area-distance plot. The area of maximal narrowing corresponding to the nasal valve usually lies within the first 2 cm of the nasal vestibule. The next downward deflection in the acoustic rhinometry curve usually corresponds to the narrowing caused by the head of the inferior turbinate at the piriform aperture. According to Poiseuille's law, nasal airflow is directly proportional to the radius to the fourth power. Thus, any narrowing in the nasal airway significantly decreases flow. Acoustic rhinometry characterizes the geometry of the nasal cavities, quantifies nasal obstructions, and monitors results of medical or surgical treatment. Results have been validated with imaging studies. Acoustic rhinometry area measurements are most accurate for the anterior part of the nose, especially the nasal valve region (13).

The techniques of rhinomanometry and acoustic rhinometry give complementary information: rhinomanometry determines resistance or how hard it is to breathe, whereas acoustic rhinometry allows localization of abnormalities. Both techniques have been used extensively in the scientific study of the nose, although they have not entered into the everyday practice of rhinology. Some authors believe that these techniques are impractical in everyday office practice and the findings often do not correlate with patients' perception of nasal obstruction (8).

Olfaction

Olfaction is discussed in detail in *Chapter 24*. Briefly, the olfactory centers are housed within the sinonasal tract. Anatomically, the olfactory neuroepithelium is scattered through the superior portions of the nasal cavity, located between the septum and medial surface of the superior turbinate bilaterally. The olfactory neuroepithelium may extend anteriorly onto the middle turbinate, and inferiorly below the cribriform plate. This area is known as the olfactory cleft. Odorants reaching the olfactory cleft may be nasal or retronasal. Nasal stimulation results in the

conventional sense of olfaction, while retronasal stimulation plays a role in the sensation of flavor during the ingestion of food.

Histology of the olfactory neuroepithelium consists of various cell types. Primarily, the mucosa consists of pseudostratified columnar epithelium. Basal cells in the deeper layers give rise to the differentiated neural and nonneural cellular elements. Microvillar sustentacular cells reside at the epithelial surface and provide metabolic support to the neurons. Bowman glands extend ducts from the basement membrane to the epithelial surface. Olfactory neuron cell bodies reside superficial to the basal cells. Dendrites terminate in knobs at the epithelial surface, containing olfactory receptors. Axons extend through the lamina propria and converge with other axons to form nerve bundles, or fila olfactoria. These fila then proceed through the cribriform plate and form first-order synapses at the olfactory bulb, part of cranial nerve I. These neurons are unique in their capacity to communicate directly between the external environment and the central nervous system, as well as their ability to regenerate.

Each olfactory receptor represents a different receptor type. Work by Buck and Axel identified genes encoding nearly 1,000 different transmembrane G-protein receptors. Groups of receptor types are organized into zones, although the distribution within these zones is seemingly random. Axons will converge with similar receptor types on approach to the glomeruli within the olfactory bulb. Each odorant activates a different set of receptors and glomeruli, resulting in unique patterns of activation.

Protection

Normal sinonasal mucosa is made of an epithelial layer, lamina propria, submucosa, and periosteum. The nasal epithelial cells are ciliated, pseudo-stratified, columnar cells with a variable number of goblet cells. A thin layer of acellular basement membrane separates the epithelial layer from the thick lamina propria. Beneath the epithelium reside lymphocytes, plasma cells, and macrophages as well as vascular arcades and glands. Nasal airflow interfaces with the mucosa exposing it to a constant load of particulate matter. Turbulent airflow forces all inspired air to contact mucosal surfaces before passing to the lower airways. Coarse nasal hairs, vibrissae, located at the nasal orifice filter out large particles entering the nose. Smaller particles impact the mucosa as a result of turbulent flow and stick to the nasal mucus. Particles smaller than 0.5 μm pass through the nasal filter to the lower airways. Mucociliary clearance serves to transport trapped particles including pathogens out of the sinuses and nose. The mucous blanket is divided into the inner sol layer and outer gel layer. Goblet cell–produced glycoproteins give the gel layer of nasal mucus its viscosity and elasticity. The gel layer lies on top of the nasal cilia, whereas the sol layer surrounds the cilia. The sol layer of mucus is considerably less viscous so that ciliary movement can propel the overlying layer of mucus and any trapped particles.

In all the sinuses, mucus moves toward the natural ostia. Maxillary sinus mucociliary clearance begins at the floor and flows against gravity toward the maxillary infundibulum. The anterior ethmoids drain into the middle meatus and the posterior ethmoid cells drain into the superior meatus. Mucus in the frontal sinus drains toward the ostium only from the lateral side. Mucus medial to the ostium must course superiorly to join the lateral flow toward the ostium. Like the maxillary sinus, the sphenoid sinus flows against gravity toward its ostium that drains into the sphenoethmoidal recess. Once mucus has drained from the sinuses into the nasal cavity, mucus flow is toward the nasopharynx. Mucus from the anterior sinuses passes over the inferior turbinate and then anterior to the eustachian tube orifice, whereas posterior sinus secretions pass posterior to the eustachian tube.

The mucous blanket is cleared toward the nasopharynx every 10 to 15 minutes by ciliary movement and replaced by fresh mucus secreted by the nasal cavity and sinus mucosa (1). Ciliary activity can be impaired by a humidity drop, temperature decrease, or cohesion created by opposing mucosal surfaces. Mucociliary transit time is measured by the *saccharin test*. A saccharin pellet is placed in the anterior part of the nasal cavity, dissolves, and is transported by the mucociliary system into the nasopharynx, and then the oropharynx where the sweet taste is detected. Normal transport times are less than 20 minutes, with most subjects detecting the taste within 10 minutes. Other methods are also available (12).

Recurrent sinus infections resulting from increased mucociliary transit time are most commonly associated with primary or secondary ciliary dysfunction. Primary ciliary dyskinesia (PCD) is an autosomal recessive disorder resulting from defective ciliary structure and function. Fifty percent of patients with PCD have Kartagener syndrome with bronchiectasis, sinusitis, and situs inversus. Panrespiratory disease is highly associated with PCD; sinonasal disease is the most common manifestation, but otitis media and pulmonary disorders are also highly prevalent. PCD is diagnosed using the clinical features together with measurement of nasal NO and evaluation of ciliary ultrastructure. On electron microscopic studies, cilia from patients with PCD show a high percentage of anomalous cilia with absent or reduced dynein arms, absent radial spokes, translocation of microtubular doublets, or altered central pairs. Ciliary ultrastructural and functional studies may be normal in some cases of PCD when strong clinical features are present. Conversely, PCD can be excluded if clinical features are weak and NO levels are normal. Cystic fibrosis must be excluded in all cases. PCD and secondary ciliary dyskinesia (SCD) are functionally similar but ultrastructurally different. SCD usually occurs during or after a respiratory infection and is often reversible. SCD is characterized by a low percentage of anomalous cilia and by

a pattern of secondary ultrastructural changes: compound cilia, peripheral microtubule addition or deletion, disorganized axonemes, ciliary disorientation, discontinuity of axoneme membrane, and swollen cilia with excess cytoplasm (14).

The nasal mucosa interfaces with the external environment, interacting with a constant load of bacteria, viruses, and fungi. In the normal individual, the mucosal immune system responds to this stimulation by functioning as a first line of defense against invading pathogens without excessive tissue reaction or collateral damage (15). Two distinct, yet integrated responses to microbial pathogens and foreign proteins have been described: innate and acquired immunity. The innate immune system refers to any inborn resistance that is already present the first time a pathogen is encountered. The innate immune response is modified only in quantitative rather than qualitative terms following repetitive exposure. Respiratory epithelium forms the first line of nasal defense by creating a physical barrier bound with tight junctions. The nasal mucosa secretes enzymes and peptide antibiotics with direct antimicrobial effects in mucus. Neutrophils and macrophages, which phagocytose microbes, form the next line of defense. The epithelium and the phagocytes distinguish self from nonself by soluble and membrane-bound pattern recognition receptors that recognize pathogen associated molecular patterns (PAMPs) found in parasites, viruses, bacteria, yeast, and mycobacteria. These receptors serve two basic functions. First, they may recognize and bind pathogens in the airway mucus and epithelium facilitating phagocytosis (e.g., macrophage mannose receptor). Second, binding to receptors such as the Toll family triggers the secretion of mediators directly affecting pathogen clearance (e.g., interferon) and the attraction of additional phagocytes (16). If the stimulus is sufficiently strong, a secondary acquired immune response will occur.

The acquired immune response across the sinonasal tract is mediated by dendritic cells (DCs), which are phagocytic antigen-presenting cells present in substantial numbers in the nasal mucosa. In the GI tract, DCs perform a sentinel function by sampling the surrounding environment to distinguish invasive pathogens from commensal organisms, apparently through molecular pattern recognition, thereby regulating mucosal immunity (17). Although the normal GI flora usually induces tolerance, an excessive immunologic response to these nonpathogens is believed to result in inflammatory bowel disease. The upper respiratory tract, although not sterile, does not demonstrate the same degree of commensal colonization seen in the GI tract. Nonpathogenic bacteria, pathogenic bacteria, and fungi have been cultured from the upper respiratory tracts of asymptomatic individuals, but it remains unclear whether these organisms always incite an immune response or whether tolerance can develop (18). Moreover, precise characterization of the "normal flora" of the upper respiratory tract is lacking and it is unclear whether the presence of nonpathogenic bacteria serves protective functions by inhibiting the growth of other microbial agents.

The acquired immune response in the nose centers around the processing and presentation of antigen by DCs to T-helper (Th) cells. The interaction between DCs, T cells, and B cells may take place locally in lymphoid mucosal aggregates as well as in draining lymph nodes (15). T and B cells travel to draining lymph nodes and return to effector sites in the mucosa via the bloodstream. The nature of the effector response is heavily dependent on the strength of the PAMP stimulus and resulting cytokine milieu. In the presence of a typical strong PAMP stimulus, a skewed Th1 response is triggered emphasizing a cell-mediated response with potent antiviral and antibacterial effects (19). The Th1 response, with attendant cytokines, facilitates macrophage–phagocytic activity and cell-mediated cytotoxicity. On the other hand, weak PAMP stimuli (or as yet unidentified type 2 specific PAMPs) result in a skewed Th2 response emphasizing IgE and secretory IgA (S-IgA) antibody production with the attraction of mast cells, basophils, and eosinophils (15,19,20). Th2 cells produce cytokines that affect antigen-specific B cells, triggering Ig class switching resulting in IgE- and IgA-secreting plasma cells in the nasal mucosa. S-IgA is the major immunoglobulin in nasal secretions interacting with microorganisms by directly neutralizing some viruses, initiating antibody-dependent cell-mediated cytotoxicity, and interfering with some bacterial growth factors (20). Th2 responses also address multicellular parasites, which are too large to be engulfed by macrophages but demonstrate vulnerability to eosinophils. Th17 responses are thought to play a role in the defense against extracellular bacteria (20). Th1, Th2, and Th17 responses reciprocally inhibit one another; typical chronic *in vivo* immune responses are polarized to one or the other type. Meanwhile, Treg cells have been found to suppress Th1, Th2, and Th17 responses, limiting excessive immune responses (21). Some degree of balance is necessary in contrast to unopposed type 1 or type 2 responses, which manifest as disease in animal models (19). Although the outline of nasal immunity delineated previously is derived from current evidence, one should remember that new data from the rapidly developing area of mucosal immunology will modify these concepts. In particular, the number of Th subsets is likely to expand.

In addition to protective immunity, Th2 effects mediate allergic disorders. AR is an inflammatory disease of the nasal mucosa that initiates the release of mediators from antigen-sensitized immune cells. Allergens are typically protein antigens with weak PAMPs, interacting with DCs to trigger a Th2 response. Activated Th2 cells induce the conversion of B cells to plasma cells that produce IgE specific to that allergen. These specific IgE antibodies attach to the surface of mast cells in the nasal mucosa. At the next exposure, allergen crosslinks the specific IgE antibodies attached to mast cells and induces those mast cells to release preformed inflammatory mediators that result in

the early-phase symptoms of AR. The late-phase symptoms are associated with the subsequent infiltration of inflammatory cells, including eosinophils that further amplify the inflammatory allergic response. Many clinically significant allergens are proteases that attack the epithelial barrier including tight junctions, thus increasing access to DCs and sensitized mast cells (22). The *in vivo* and *in vitro* tests used to diagnose AR demonstrate the presence of systemic IgE, which correlates with an immunologic mechanism for Th2 responses mediated across the nasal mucosa and elsewhere (23). Recent reports have suggested that local Th2-driven or IgE-mediated disease may exist in the nose without evidence of systemic IgE sensitization (24,25). The mechanism as well as the clinical significance for this process remains uncertain.

The sinonasal tract constantly interfaces with the external environment; foreign antigens are encountered and typically cleared. However, in more than 10% of the population, this stimulation triggers a chronic inflammatory infiltrate in the nasal mucosa resulting in the clinical symptoms of CRS (26). The immunodominant antigenic stimuli, presumably microbial, remain unclear although both *Alternaria* fungi and *Staphylococcus aureus* have been proposed (27,28). Much of the current research on CRS, however, has focused interest away from potential pathogens onto identification of defects in the host immune response (29,30,31,32). Increased understanding of the normal immune response of the nasal and sinus mucosa will likely be necessary to make progress in the management of this widely prevalent disorder.

HIGHLIGHTS

- Sinonasal embryology can be divided into two ongoing processes: first, the embryo's head develops into a structure with two distinct nasal cavities; second, the lateral nasal walls then invaginate to create complex folds, known as turbinates, and spaces, known as sinuses.
- The ethmoidal, maxillary, sphenoid, and frontal sinuses make up the paranasal sinuses.
- The complex and variable anatomy of the lateral nasal wall influences approaches to endoscopic sinus surgery.
- A variety of intranasal deformities cause nasal obstruction and evaluation of each of the anatomic causes allows the surgeon to select the best procedure to correct the obstruction.
- The three major functions of the nose are olfaction, respiration, and protection; these functions are aided by the convoluted anatomy of the nasal cavity, which creates a large surface area.
- Turbulent nasal airflow is central to the physiology of the nose. Turbulence increases contact between inspired air and the nasal mucosa enhancing not only the respiratory functions but also olfaction and protection.
- The nasal valve is the narrowest part of the nasal passage with the highest resistance; thus, venous sinusoids of the anterior portion of the inferior turbinate and the nasal septum in the region of the nasal valve most significantly contribute to total nasal airflow resistance.
- Rhinomanometry measures nasal resistance; acoustic rhinometry measures nasal cross-sectional area.
- Coarse nasal hairs, vibrissae, located at the nasal orifice filter out large particles entering the nose, smaller particles impact the mucosa as a result of turbulent flow and stick to the nasal mucus. Mucociliary clearance serves to transport trapped particles including pathogens out of the sinuses and nose.
- Recurrent sinus infections resulting from increased mucociliary transit time are most commonly associated with primary or secondary ciliary dysfunction.
- The nasal mucosa interfaces with the external environment, interacting with a constant load of bacteria, viruses, and fungi. In the normal individual, the mucosal immune system responds to this stimulation by functioning as a first line of defense against invading pathogens without excessive tissue damage.

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Olfaction

24

Eric H. Holbrook *Donald A. Leopold*

Anyone who has experienced complete nasal obstruction from an infection or severe allergic rhinitis has suffered the loss of a sense that is often taken for granted. In other mammals, the sense of smell is absolutely crucial for survival, reproduction, and rearing of young. Although humans can survive without olfaction, the negative impact on quality of life has been well documented with some approaching clinical depression (1–3). As other animals depend on the sense of smell as an alarm system for danger, we also depend on the sense of olfaction to warn us of smoke, natural gas leaks, and spoiled food. On a more frequent occasion, people with smell loss struggle with the blandness of meals and have difficulty with the appropriate use of bodily hygiene products or perfumes. In the food industry, olfaction is crucial to chefs and wine tasters and its loss can be devastating.

The overall prevalence of olfactory dysfunction includes 19% of the population over the age of 20 and 25% of the population over the age of 53 (4,5). If smell loss from aging alone is considered, one out of eight people between the ages of 53 and 91 will acquire an olfactory impairment over a 5-year period (6). Many patients will report a loss in taste when in reality they are experiencing a decrease in flavor due to a lack of sense of smell. Regardless, the effect is the same and especially in the elderly population, the impact on diet and nutrition can be significant (7,8).

This chapter describes the main causes of olfactory disorders and provides a logical guideline to the evaluation and treatment (when available) of patients with smell dysfunction. The following commonly used definitions describe olfactory disorders. The complete absence of a sense of smell is termed anosmia, while hyposmia is a decreased sense of smell. Dysosmias are alterations (decreases or distortions) in smell. A smell perceived in the absence of a true odor in the environment is termed phantosmia, while an altered perception of an odor in the environment different from what is usually experienced for that odor is termed parosmia.

ANATOMY

The nasal cavity is the conduit for odors to reach the specialized neuroepithelium that converts binding of odorant molecules by receptors into electrical signals that extend to the brain. Many studies have looked at airflow properties of the nasal cavity and ability to smell. Although severe nasal obstruction from septal deviation can reduce odorant access to the olfactory nerves, it is rarely the sole cause of olfactory loss. Retronasal presentation of odors during eating has been given increasing importance for adding separate qualities to the overall appreciation of flavor of food (9,10).

Ultimately, odorants need to interact with olfactory receptors that reside in a patch of olfactory epithelium located in the superior/posterior-most aspect of the nasal cavity, the olfactory cleft. This area is variable in size and variable in the extensiveness of small patches of respiratory epithelial replacement. The overall area averages 1 to 2 cm^2 in adults, but covers a much larger region in infants (11). The decrease in olfactory epithelium over time and the presence of respiratory patches within the olfactory epithelium is speculated to be caused by cumulative environmental insult and subsequently a source for olfactory loss with aging. The olfactory epithelium covers a region of the septum below the cribriform plate extending back to the face of the sphenoid (12). A similar sized region apposed to the septal olfactory mucosa is present laterally within the olfactory cleft on the middle and superior turbinates. The narrowness of this space may protect the delicate olfactory neurons from environmental damage, but may increase susceptibility to obstruction from inflammatory processes with resulting smell loss.

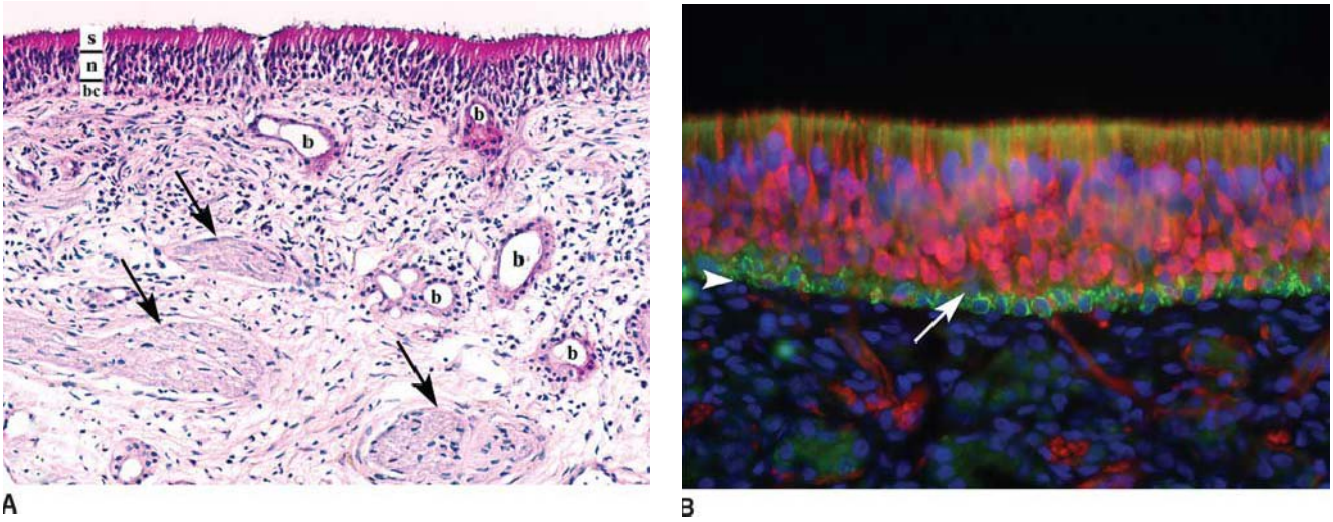


Figure 24.1 Human olfactory mucosa. **A:** Hematoxylin and eosin stain of human olfactory mucosa (200×). The epithelium can be divided into a basal cell layer (*bc*), neuronal layer (*n*), and supporting cell layer (*s*) where the cell bodies of each of these cell types typically reside. The underlying lamina propria contains Bowman glands (*b*) and fila olfactoria (*arrows*) with multiple olfactory receptor axons. **B:** Immunohistochemical staining of human olfactory epithelium (400×). Olfactory neurons with their dendrites and axons are labeled *red* with an antibody directed against PGP9.5. The fine dendrites are seen extending between supporting cells and ending in knobs at the apical surface, while the axons exit through the basal lamina (*white arrowhead*) to converge and join the fila olfactoria. Horizontal basal cells (HBCs) are labeled *green* with antibodies against keratin 5 and reside on top of the basal lamina. Unstained cells between the HBCs and neurons are likely globose basal cells (*arrow*). Supporting cell nuclei are seen as the row of *blue* (DAPI stained) nuclei above the neuronal layer.

The olfactory mucosa is composed of a pseudo-stratified neuroepithelium (Fig. 24.1). Supporting cells populate the apical portion of the epithelium and send foot processes to the basal lamina. The dendritic knobs of the olfactory neurons with their multiple immotile cilia extend above the apical surface of the supporting cells, but the cell bodies of the neurons reside in the midsection of the epithelium with the more mature neurons taking a more apical position. The axons extending from these bipolar cells extend through the basal lamina and converge with other olfactory axons to form bundles (fila olfactoria) that transverse the cribriform plate and innervate the brain within the olfactory bulbs at synaptic collections termed glomeruli. These axons are unique in several aspects: they are true receptor neurons with direct synapses to the brain, they are the only cranial nerve (CN I) with direct exposure to the environment, and they are continually replaced throughout our lifetime. Signal projections from the olfactory bulb travel through the lateral olfactory tracts and synapse on several higher locations including the anterior olfactory nucleus, amygdala, piriform cortex, and entorhinal cortex. Major projections to structures associated with the limbic system and hippocampus explain the often-experienced relationship of specific odors with a strong emotional response or triggering of a vivid memory associated with the odor.

The cells responsible for the replacement of these neurons as well as replacing other cells comprising the epithelium are the horizontal and globose basal cells positioned just above the basal lamina. Unique to the olfactory mucosa are Bowman glands within the lamina propria that send ducts through the epithelium to the apical surface providing mucus that is likely important in the presentation of odorants to the olfactory receptors. Although there is variation in the thickness of the epithelium and less ordered positioning of the olfactory neurons within the epithelium compared to that found in rodents, the architecture and cellular components are remarkably similar in humans (12).

PHYSIOLOGY OF OLFACTION

The detection and identification of a specific odor from the multitude of complex odors present in the environment is only partially understood. The initial site of interaction between an odorant molecule and the olfactory neuron, the olfactory receptor, has now been identified (13). These receptors collectively form a family of similar G proteins (G_{olf}) that when activated stimulate adenylate cyclase to synthesize cyclic adenosine monophosphate (cAMP). cAMP acts as a second messenger to open a cyclic nucleotide-gated ion channel allowing for influx of cations and depolarization of the neuron. There are approximately 1,000 different genes within the olfactory receptor gene family in rodents; many however are pseudogenes. The human olfactory gene family with 339 intact receptor genes and 297 pseudogenes has fewer receptor genes than mice; however, this gene family still comprises one of the largest

gene families in the human genome (14). In rodents, it has been shown that each olfactory neuron expresses only one member of the olfactory receptor genes. Neurons expressing like receptors are restricted to a regional zone oriented from a dorsal–medial to ventral–lateral orientation; however, within these regions, the expression pattern appears random among other receptors expressed in the similar area. These neurons expressing like receptors extend axons that remarkably converge together within the lamina propria to eventually converge exclusively to, on average, two glomeruli within each olfactory bulb (15). In humans, this receptor-to-glomeruli ratio is much broader and calculated to be on the order of 1:16 (16). This receptor-specific patterning is the basis of an odorant map whereby an odorant stimulates a subset of olfactory neurons that in turn activate a specific set of glomeruli in the olfactory bulb (17,18). Therefore, an odor is coded by the multiple receptor neurons it stimulates and in turn the resulting unique pattern of glomerular activation is transmitted in an unclear fashion to higher brain centers and perceived as a smell.

ETIOLOGY OF OLFACTORY LOSS

Numerous causes for a decrease in ability to smell have been described, but multiple reports from various smell and taste centers have consistently recognized similar etiologies (19). The three most common are smell loss relating to head trauma, upper respiratory infection (URI), and chronic rhinosinusitis (CRS). Another large category of smell loss is idiopathic smell loss in which no identifiable source of olfactory dysfunction can be determined. There is also a known progressive loss of sense of smell across the population related to aging with a significant drop in ability after the age of 65 and occurs in greater than one-half of people between the ages of 65 to 80 (20). The cause of this age-related loss is unclear but is independent of neurodegenerative disease. Possible theories for this loss include eventual wear-and-tear of the olfactory neurons from the cumulative effect of exposure to environmental toxins and/or progressive depletion of the regenerative capacity of epithelial basal/stem cells and genetically programmed cell death.

Smell loss related to head trauma is usually easily identified by history; however, even mild injuries to the head can result in significant olfactory disability (21). Often, in severe head trauma, the loss of smell is recognized relatively late in the recovery period due to cognitive alterations and the presence of additional separate severe injuries. The loss is thought to be a result of injury to the frontal lobes and olfactory bulbs through direct injury or commonly from a blow to the back of the head and rebound contusion to the frontal regions through a coup-countre coup injury. Another possible mechanism of traumatic smell loss is through the shearing of olfactory neurons where they transverse the cribriform plate as the brain and olfactory bulbs violently shift during trauma. Recovery from traumatic smell loss is variable but sometimes permanent with rare complete recovery and improvement in only 10% to 35% of patients (22–24). Usually, if return of function occurs, it generally begins within a year of the trauma.

Transient smell loss often occurs with URIs due to inflammatory swelling and obstruction of the olfactory clefts. Less commonly, a longer lasting or permanent deficit occurs after recovery from a URI. Although never confirmed, the loss is thought to be a result of a viral infection. Parainfluenza 3 has been implicated as the possible viral agent based on epidemiologic studies and molecular analysis of nasal epithelium from patients with URI-related anosmia (25,26). Even less clear is the site and mechanism of damage. Epithelial abnormalities have been found in many biopsy studies, but damage isolated to the olfactory bulbs is also possible. Women are afflicted more commonly than men in this type of smell loss, and the elderly may be more susceptible. It more often results in hyposmia instead of anosmia and the chance for recovery is relatively higher than other common forms of smell loss (27) with recovery rates between 32% and 67% (22,23).

CRS is often associated with a decreased or absent ability to smell. This can occur either with or without polyps commonly resulting from obstruction of odorant flow to the olfactory cleft. A description of fluctuating ability to smell with periods of complete return of function is rarely attributed to anything other than CRS; however, patients may also describe a gradual loss or complete anosmia years in duration. Olfaction usually returns, especially in the case of CRS with polyps, with aggressive medical treatment often including systemic steroids. However, inflammation directly involving the olfactory mucosa in patients with CRS has been demonstrated in nasal biopsies, (28–30) and a resulting permanent form of smell loss can occur that is eventually unresponsive to steroids. This CRS-related permanent olfactory loss has been associated with the finding of apoptotic cells within the olfactory epithelium (31) and supports the prudence of aggressive medical and/or surgical management of this disease in order to prevent long-term damage.

Occasionally, patients will present with a history of never experiencing smell, a condition known as congenital anosmia. Their loss is usually recognized through experiences with family or friends or through observation by their parents that they cannot smell a strong odor that others in the same vicinity smell. Although anosmia to specific odors has been identified, patients usually present to physicians with complete anosmia and have no other associated medical conditions. However, a subset of congenital anosmia is associated with Kallmann syndrome (hypogonadotrophic hypogonadism) in which a delay in sexual development can occur, and therefore early recognition of the syndrome is important to allow for hormone replacement therapy. Therefore, pediatric patients presenting with congenital anosmia should be observed for any evidence of delay in development. Mutations covering six genes have

been identified that are associated with Kallmann syndrome and genetic testing can be performed, but genetic testing currently has a sensitivity of only 30% (32,33). Clinical suspicion based on associated findings such as microphallus and/or cryptorchidism in males, hearing loss, or renal agenesis should prompt further workup. An MRI can be obtained to identify agenesis of the olfactory bulbs and rectus gyrus and loss of olfactory sulcus, however, a discussion with the patient's pediatrician and referral to an endocrinologist and/or geneticist is advised. A recent description of a rare congenital smell loss associated with the absence of pain reception in humans has been described that relates to a defect in a voltage-gated sodium channel and may provide insight into more common forms of congenital anosmia (34). Congenital smell loss associated with hypoplastic or absent olfactory bulbs has also been associated with CHARGE syndrome, (35) but other associated deficits other than smell loss are more apparent in this syndrome and the disorder is recognized at an early age.

A different form of congenital anosmia or long-standing smell loss has been identified relating to anatomic narrowing of the olfactory clefts from large concha containing middle and/or superior turbinates. These patients have severe hyposmia or anosmia and are refractory to oral steroids and surgical opening of the olfactory cleft (36,37).

Smell loss can be an early symptom of neurodegenerative diseases such as Alzheimer and Parkinson disease. Schizophrenia has also been associated with smell disorders resulting in difficulty with identification of odors. Environmental toxins associated with smell loss include prolonged industrial exposure to agents such as cadmium, mercury, and formaldehyde (38). Over-the-counter topical zinc nasal spray for treatment of URI has been implicated in causing smell loss in a small percentage of people. Clinically, these patients describe intense nasal burning after use and rapid onset of anosmia (39,40). Although impossible to prove that the smell loss did not develop from the URI, the history of zinc application in humans and animal studies with zinc gluconate suggest a toxic effect on the olfactory neurons (41). The U.S. Food and Drug Administration (FDA) has now advised consumers to stop using zinc-containing nasal products because of the risk of anosmia.

Iatrogenic smell loss frequently occurs with craniofacial resections, but may also occur with commonly performed nasal and sinus procedures. Kimmelman demonstrated mild hyposmia in 32% of patients undergoing an ethmoidectomy, polypectomy, Caldwell-Luc procedure, nasal fracture reduction, rhinoplasty, or septoplasty and anosmia in 1% (42). Damm et al. (43) reported a decreased smell in 20% of patients undergoing septoplasty and turbinate reduction with no reports of anosmia, while 80% improved their olfactory function. Given the alteration and trauma of the nasal mucosa during these surgeries and potential for scarring, it is prudent to include smell loss as a potential complication in preoperative discussion of all nasal–sinus procedures.

EVALUATION

By far, the most useful portion of the evaluation of patients in determining the etiology of smell loss is obtaining a detailed history. Clues as to surrounding circumstances can point to a source of the disorder, and timing can also provide prognostic information. For the most common forms of smell loss, events leading to the smell loss are often obvious. Severe traumatic head injuries preceding a loss of smell are usually brought up by patients without questioning, but patients with anosmia should be asked about any head injury, even mild cases not requiring hospitalization. Traumatic olfactory loss is sudden but often not immediately noticed by the patient because of associated cognitive impairment (44). Sudden onset of smell loss also occurs with URIs. Patients describe a bad "cold" or flu with the usual nasal stuffiness, but with resolution of the associated symptoms, the smell loss remains. These patients are usually very specific in the timing of their smell loss. A report of fluctuation in ability to smell should alert the physician to CRS with polyps as the most likely cause. Associated chronic symptoms of nasal obstruction and drainage are typically present in CRS, and patients typically describe improvement of smell with previous administration of oral steroids for a brief period of time. Many other forms of smell loss described above tend to occur in a more gradual progression. With idiopathic smell loss, patients frequently report a change in the flavor of food over time and are unable recall a specific time of onset or any related event. Smell loss associated with neurodegenerative disorders also present as a gradual onset, and questions regarding memory and cognitive function should be asked in these patients. In the rare case of a nasal mass presenting with gradual smell loss, patients usually complain of unilateral obstruction and often epistaxis. Intracranial masses rarely present with a smell disorder alone, and concomitant diplopia, vision changes, and motor/sensory dysfunction point toward a central cause of anosmia. A complete review of past and current medical conditions, previous surgeries, and list of medications is required in the comprehensive evaluation of smell loss. A complete social history may reveal occupational exposures to olfactory toxins or uncover illicit nasal drug use, such as cocaine.

The physical exam in evaluation of smell disorders includes a thorough head and neck examination with assessment of cranial nerve function. It is important to avoid excessive manipulation of the nose or application of nasal anesthetic agents prior to olfactory testing in order to avoid altering normal responses. Following olfactory testing, particular attention should be given to the nasal airway and possible obstructive causes. Anterior rhinoscopy alone is insufficient in identifying obstructive lesions or polyps (45). Nasal endoscopy with careful inspection of the olfactory cleft for evidence of polyps, mucosal edema, infection, scar formation, or neoplastic lesions is mandatory for evaluating most olfactory disorders.

OLFACTORY TESTING

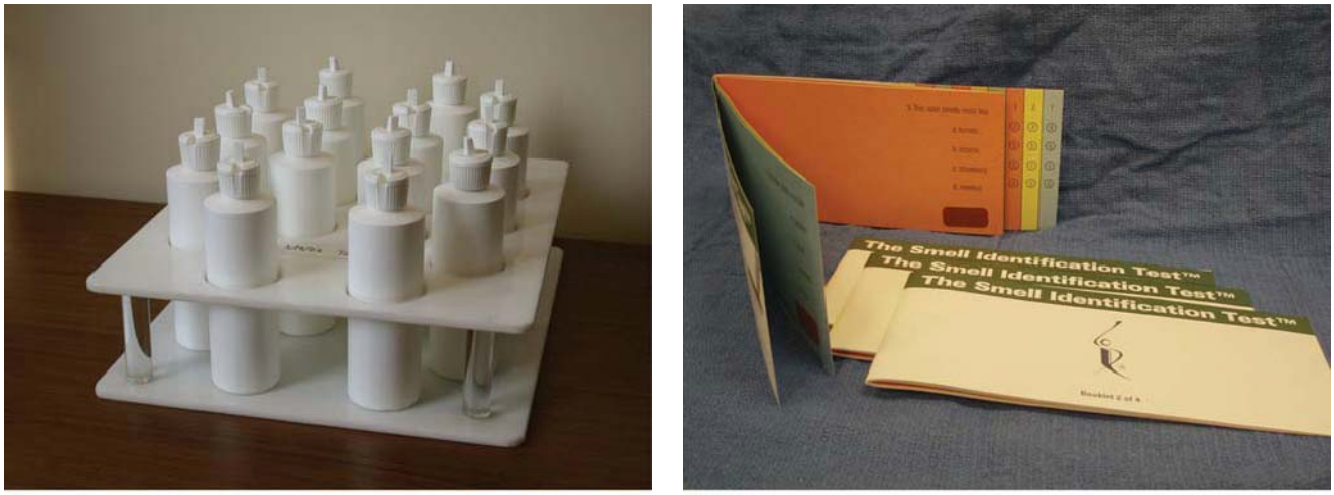
A thorough evaluation of patients with smell disorders includes olfactory testing and helps to determine the severity of the loss. Usually patients are able to recognize changes in their olfactory ability (46), but testing can often assure patients that residual function remains and even recognizes normal function in some overly-concerned patients. It can also provide a baseline measure to compare with postintervention testing, and in some cases, it can help identify malingering, although given the subjective nature of the tests, most conventional testing can be manipulated by patients if they understand the testing format. Many available olfactory tests can be modified for unilateral use to determine asymmetry in function.

Olfactory testing can be divided into psychophysical and electrophysiologic testing. Electrophysiologic tests include electro-olfactograms, which use electrodes to record field potentials during stimulation, and odor event-related potentials, which measure EEG changes during odor stimulation. Currently, these tests are restricted to research centers and are not accessible to most clinicians (47).

Psychophysical tests are more common in clinical practice, many of which are easy to use and the results can be compared to known population standards (Fig. 24.2). Threshold tests measure the ability to detect an odor (such as butyl alcohol) at the lowest concentration compared with a blank (48). Although this testing provides a pure assessment of the ability to detect presence of an odor, it is time consuming and dependent on a knowledgeable administrator. Identification tests determine the ability to correctly identify multiple presented odors. Occasionally, it is incorporated with threshold tests to provide a global assessment of useful olfactory ability. The Sniffin' Sticks test is an example of such a combined test that is widely used throughout Europe. It comprises multiple odor-impregnated felt-tipped pens that allow tests for detection threshold, identification, and discrimination. A composite score is calculated and compared to normative data (49). It too requires a test administrator and can be time consuming. Probably the most widely used test of olfactory ability is the University of Pennsylvania Smell Identification Test (50). This test is commercially marketed as the Smell Identification Test (SIT, Sensonics, Haddon Heights, NJ, USA). It is a self-administered test that utilizes microencapsulated beads that release an odor with scratching. Subjects are required to choose odors from a list of four possibilities. The test correlates well with odor threshold testing and has been extensively studied. The lack of requirement for a test administrator allows the physician to see other patients and frees up ancillary office personnel making this test very popular in the clinical setting. Cultural bias may be a problem with the standard 40-item test, but a Cross-Cultural SIT has been created with odors recognizable across multiple cultures (51) and culture-specific modifications to other common smell tests have also been developed.

IMAGING STUDIES

Because a detailed history provides the underlying etiology of olfactory disorders in the majority of cases, imaging studies are usually not needed. A clear history of



A B

Figure 24.2 Olfactory tests. **A:** The butanol threshold test consists of a series of progressively stronger butanol dilutions (outer 10 bottles) and blank controls (center four bottles). Patients are asked to identify the bottle containing butonal after smelling a puff of air squeezed from the dilution and a blank. The concentration consistently identified is compared with what responses are known for the normal population and for those with olfactory loss. (Photo courtesy of R. Costanzo, VCUHS Smell and Taste Disorders Center, Richmond, VA.) **B:** The 40-item SIT (Sensonics, Inc., Haddon Heights, NJ) consists of 40 scratch-and-sniff samples matched with the names of four possible odors the patient can choose from. The number of correct responses correlates with the degree of olfactory ability.

URI-related anosmia with absence of findings on physical exam requires no further imaging studies, although they are commonly obtained to rule out an intracranial mass and usually for medical–legal reasons (52). A sinus computed tomography (CT) is helpful for the assessment of CRS and obstruction of the olfactory cleft. In cases where the olfactory cleft cannot be visualized with nasal endoscopy and there is no evidence of CRS on history or exam, a CT scan may be useful to rule out anatomical narrowing of this region due to obstruction from large middle and superior turbinate conchas (36). Patients with traumatic head injury and loss of smell commonly present with multiple imaging studies that were performed in the acute setting. These images can be reviewed to look for extent of intracranial damage to the frontal lobes and olfactory bulbs, but the ability to identify olfactory axonal damage due to shearing forces alone cannot be visualized with current methods (53). There appears to be an associated loss of olfactory bulb volume as measured by magnetic resonance imaging (MRI) in many forms of olfactory loss, but this significance is mostly of research interest (54–56). Similarly, functional MRIs are currently used for research purposes without a clear role in the clinical setting. We reserve ordering MRIs when the olfactory disorder occurs (a) in the absence of a clear etiology, (b) with an unusual presentation, (c) under suspicion of intracranial lesion based on history and exam, (d) with suspicion of a neurodegenerative process, or (e) in congenital anosmia for assessment of the olfactory bulbs and gyrus rectus.

PHANTOSMIA/DYSOSMIA CONSIDERATIONS

Anosmia and hyposmia refer to quantitative changes in perception of smell intensity. Qualitative olfactory changes related to perceived distortions of inhaled odorants are called parosmia while the perception of smell when there is no odorant in the environment is known as phantosmia or olfactory hallucination. Hallucinations almost always are short-lived events (seconds), may precede a seizure, and may be associated with electroencephalography (EEG) abnormalities. Phantosmia is a type of qualitative change that is almost always associated with a loss of smelling ability. In a survey of 193 patients with olfactory complaints, Landis et al. (57) noted that patients with parosmia frequently have a close temporal history of head trauma or URI, while those patients with phantosmia have no such related etiologic association. Both parosmia and phantosmia often start for no apparent reason, and tend to affect females more frequently.

Parosmic patients can have the distortion intermittently or continuously. Phantosmics typically have a history of bad smell perceptions lasting only a few minutes in the beginning, but with a progression over months to having daily episodes, often lasting hours. Some phantosmia patients can stop the phantom smell with single or bilateral nostril occlusion, while others cannot (58).

Parosmia patients almost always say that the distortion is unpleasant, and use words like "rotten" or "chemical." Phantosmia patients also typically have unpleasant distortions, like "burned rubber" or "spoiled food." In one study of the natural history of these qualitative disorders, the authors found that after an average of 12 months, almost a third of the parosmic patients reported relief, whereas about half of the phantosmic patients lost their phantom smell (59). In another study looking at the 5-year result for phantosmia, about one-third lost the bad smell, and about one-fourth had improvement. Less than 5% were worse (60).

TREATMENTS

Reliably effective treatment for quantitative olfactory losses is only available for the conductive type where odorant molecules cannot physically access the olfactory receptors. In this conductive group, which includes patients with nasal polyps and nasal mucosal edema due to allergies, treating the inflammation with saline lavage, oral or topical steroids, antihistamines, antibiotics, or surgery can be very effective.

For neural quantitative losses, there are generally no effective therapies. There is no documented return of smell in patients with complete congenital olfactory loss. With some types of congenital olfactory loss, however, immature olfactory neurons have been found on biopsy, and theoretically these conditions could be improved (61). For the two most common types of neural losses, post head trauma and URI-related loss, there is no predictably effective therapy. One study from Germany showed some improvement in this group with oral prednisone therapy at 40 mg tapered over 21 days (62). We have been unable to duplicate their success with this therapy, and the side effects of the prednisone on the patient must be considered. In a more recent publication, this same group does not mention this prednisone therapy (63). Other forms of therapy such as zinc, alpha-lipoic acid, and theophylline have been suggested, but controlled trials have either shown lack of efficacy (as with zinc) or provided insufficient data to show conclusive results.

It is sometimes difficult to determine whether an olfactory loss has a conductive or neural etiology. Oral steroid administration is useful in distinguishing between a conductive loss that will improve as opposed to a neural loss that will not respond (45). There are, however, patients who have open nasal airways to the olfactory area, but yet only have olfactory ability while on oral steroids (64).

Olfactory training has been recently touted as an effective therapy for those who have some remaining olfactory ability (hyposmia, not anosmia). Daily exposure to strong

odorants like rose, cinnamon, lemon, or cloves has been shown to have some beneficial effect (65). Encouragement for continued use or active practicing should be counseled to those with smell loss since there appears to be a relationship with recovery to some degree.

Qualitative changes in olfaction are typically more bothersome to patients, and its treatment is less well known. As stated above, both parosmias and phantosmias typically resolve in 11 months (23). Although these olfactory distortions typically require some peripheral input to the brain, the smell perception is likely produced in the olfactory bulbs or central brain. We have found that therapy can be directed to both places. Because nostril occlusion can sometimes relieve the unpleasant odor, we have had some success with the patients instilling saline drops in their nostril(s) while kneeling with their head on the floor. This likely occludes the upper nasal airways due the surface tension of the liquid. Olfactory relief experienced from applying these drops can last minutes, to hours, to days. In more severe cases, we have had some success treating olfactory distortions with neurologically active medications like gabapentin, pregabalin, or anti-depressants, although unpleasant side effects limit the usefulness of these medications. Finally, for those rare patients severely affected by these qualitative olfactory changes refractory to more conservative approaches, the endoscopic removal the olfactory epithelium may be beneficial and is associated with less morbidity than olfactory bulb resection through a craniotomy (66).

Counseling to protect the anosmic or hyposmic patient is an important responsibility of the physician. Patients with olfactory loss must employ the use of smoke and natural gas detectors in their homes and offices. If possible, converting to an "all electric" home would be a good option. Educating patients' family members so that they are able to inform the patient if the milk in the refrigerator smells foul are extra safeguards the anosmic patient should practice. If the patient lives alone it is particularly important to use proper refrigeration and storage techniques and remove food at their expiration dates.

Quality of life remains forefront in these patients' minds as olfaction gives them the ability to appreciate food, flavor, etc. In this respect, training to appreciate remaining sensory modalities such as texture of food, color, pungency, residual taste, and mouth sensation is beneficial. Additionally, in patients with hypsomia, training the patient to think about the proximity of the smell and intensify the smell by bringing it closer offers value (67). Likewise, encouraging patients to increase food options and trials of different foods is warranted. Adding hot sauces or eating Asian or ethnic foods may better stimulate the trigeminal nerve promoting additional sensation. The use of excess sweeteners or salt is a natural adaptation by many patients with smell loss, and they need to be aware of the detrimental health effects that can result.

HIGHLIGHTS

- Disorders of smell are not infrequent and have a significant impact on quality of life for those who are afflicted.
- Olfactory receptor neurons are unique in their direct connection to the brain and the regenerative capacity of the olfactory epithelium to replace them throughout the life of the organism.
- URIs, head trauma, CRS, and aging are the most common identifiable etiologies for smell loss. In many cases, a cause for smell loss is never identified.
- A careful history and nasal endoscopy are crucial in the evaluation of patients complaining of smell disorders.
- Validated tests of smell are available for use by all physicians and allow for a subjective assessment of the degree of impairment.
- Besides olfactory loss related to CRS, treatment options and effectiveness for other common forms of smell loss are limited.
- Phantosmia and parosmia commonly occur with olfactory loss, but usually resolve spontaneously.
- Physicians evaluating patients with smell disorders need to discuss hazards associated with smell loss and potential dietary effects such as decreased nutrition and effects of increased salt or sugar intake.

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Immunology and Allergy

25

Mohamad Raafat Chaaban *Robert M. Naclerio*

Understanding immunology is fundamental to understanding the pathophysiology, diagnosis, and treatment of many diseases. Allergic rhinitis (AR), with its symptoms of itch, sneeze, rhinorrhea, and congestion, is a classic example of an immunologically mediated disease. We focus on understanding the immunology of AR, which provides broader insights into the immunology of other disease processes that are important to otolaryngologists.

The prevalence of allergic disease in the United States is 20%, and appears to be increasing (1). A nationwide survey published in 2006 showed that 54.6 % of people in the United States tested positive for at least one allergen (2), highlighting the fact that many more people have positive allergy tests than have AR.

AR affects both children and adults, compromising their quality of life (3). The symptoms are either seasonal or perennial in nature. AR (4) is uncommon before the age of 5 (5,6) with the peak incidence occurring between 17 and 22 years (7).

The profound economic impact of allergy is also increasing. Between 2000 and 2005, the cost of treating AR almost doubled from $6.1 billion to $11.2 billion, with more than half of this money spent on prescription medications (8). Costs related to lost productivity and missed work, and health care costs incurred by exacerbation of coexisting medical conditions caused by allergy are more difficult to quantify (9).

THE UNIFIED AIRWAY

In the past several years, there have been some interesting developments in the field of immunoglobulin E (IgE)-mediated diseases. Several studies have shown pathophysiologic parallels between AR and asthma after challenge with antigen. These include hyperresponsiveness to irritants, cell types recruited to sites of inflammation, cytokines produced (10,11), and adhesion molecules expressed after challenge (12).

Increased recognition of the link between the upper and lower airway has led to various terms for respiratory disease involving both, including: "the unified airway," "the united airway," "chronic allergic respiratory syndrome," and "allergic inflammatory airway syndrome" (13). Although the linkage has not been fully characterized, there is speculation that a bidirectional linkage exists. Rhinitis can affect asthma by way of the nasobronchial reflex, secreted cytokines, upregulation of circulating cells, or microaspiration (14,15).

In addition to pathologic studies, several studies have shown that AR is a risk factor for the development of asthma, and increasingly so with greater severity of rhinitis (16–18). In a retrospective study of health claims for asthma patients, those patients with concurrent rhinitis doubled their annual medical resource utilization and costs (19).

The clinical practice guidelines for asthma entitled Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, developed by the National Asthma Education and Prevention Program of the National Heart, Lung and Blood Institute released in August 2007, stated: "The Expert Panel recommends that clinicians evaluate patients who have asthma regarding the presence of rhinitis/sinusitis diagnosis or symptoms. it is important for clinicians to appreciate the connection between upper and lower airway conditions and the part the connection plays in asthma management" (20). Treatment of rhinitis may enhance asthma control (21–24), and early treatment of allergies may prevent the development of asthma (22–24).

Interestingly, patients treated with low-dose fluticasone propionate nasal spray had a significantly lower risk of experiencing an asthma-related hospitalization and incurred lower asthma-related and overall health care costs

compared with those who used montelukast (25), further demonstrating the connection between the upper and lower airways.

THE IMMUNE RESPONSE

The immune system identifies and destroys elements foreign to the body while recognizing and protecting self-components. The inability to properly recognize "self" results in the broad class of diseases known as autoimmunity disorders. Many autoimmune disorders affect the ear, nose, and throat. For example, a cell-mediated immune response is thought to be the etiologic precipitant for the development of relapsing polychondritis, a rare multisystem autoimmune disease, which targets cartilaginous tissues and often involves the nose. Wegener granulomatosis, a vasculitic disease that can be accompanied by ulceration of the nasal mucosa, is also thought to have an autoimmune etiology. Evidence points to auto-reactive T cells aiding in the production of antineutrophil cytoplasmic antibodies, which may be pathogenic in cell-mediated induced injury.

INNATE AND ADAPTIVE IMMUNITY

Innate Immune System

The innate immune system is the first line of defense against foreign substances. It comprises both physical barriers and an array of receptors and antimicrobial compounds. The sinonasal barrier comprises ciliated epithelial cells, subepithelial glands, goblet cells, and the mucus blanket. This epithelium provides a barrier via tight junctions that prevent passage of pathogens across the mucosal surfaces and mucociliary transport to eliminate pathogens trapped in secreted mucus. Nasal glandular products such as lactoferrin, defensins, and lysozyme are the initial defense against infection and function irrespective of prior exposure to the pathogens. Impairment of the innate immune system provides one theory as to how inflammation leads to the development of chronic rhinosinusitis (CRS) (26).

The cells associated with innate immunity include neutrophils, monocytes, mast cells, eosinophils, basophils, and dendritic cells (DCs). These cells are activated in the presence of microbes and work to rid the body of infection. They use pattern recognition receptors (PRRs) found on their surfaces, intracellular compartments and secreted in the bloodstream to opsonize bacteria, activate coagulation and complement cascades, induce phagocytosis and apoptosis, and implement proinflammatory signaling pathways (27).

There are several classes of PRRs: Toll-like receptors (TLRs), RIG-I-like receptors, Nod-like receptors, and C-type lectin receptors (27). PRRs recognize highly conserved DNA sequences that are necessary for the survival of many microorganisms. These highly conserved sequences, known as pathogen-associated molecular patterns (PAMPs), include peptidoglycan and lipoteichoic acid from gram-positive bacteria, lipopolysaccharide (LPS) from gram-negative bacteria, and RNA from viruses. The responses of the innate immune system against the PAMPs signal the adaptive immune system to develop memory and subsequent longer-lasting immune responses. TLRs, first described in 1994, are the most studied of the various PRR classes. They are transmembrane glycoproteins with an extracellular N-terminal leucine-rich domain and an intracellular C-terminal domain, which is itself known as Toll/interleukin (IL-1) receptor (TIR) because of its homology to IL-1 (28).

Recognition of the various PAMPs by TLRs on the surface of monocytes, macrophages, DCs, and mast cells initiates inflammatory responses, which induce cytokine signaling that can be Th1 or Th2. This signaling can be categorized as either myeloid differentiation primary response (MyD88)-dependent (Fig. 25.1), which is used by all TLRs except for TLR3, or TIR containing adaptor-inducing interferon (IFN)-γ-dependent pathways (29). TLRs respond to specific conserved sequences or to molecules present on invading microbes; for example, TLR4 responds to lipid A, a component of LPS, whereas TLR3 recognizes double-stranded RNA. Inflammatory cells express different classes of TLRs, depending on their lineage and maturity (30). The spatial distribution of TLRs ultimately determines the microbes they encounter and whether these elements are recognized as being self or nonself (31,32). Some TLRs are expressed on the cell surface, whereas others are expressed intracellularly within endosomes (Table 25.1).

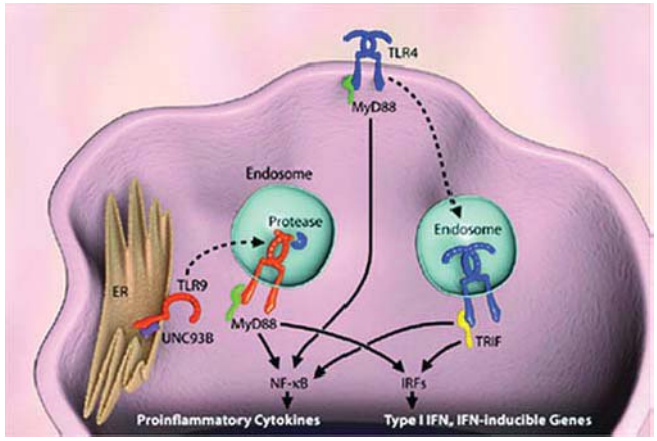


Figure 25.1 Cell biology of TLR signaling. TLR4 is located at the plasma membrane and translocates to the endosomal compartment on stimulation. Although MyD88-dependent signaling occurs without endosomal translocation of TLR4, TIR-domain-containing adapter-inducing interferon-β (TRIF)-dependent signaling requires dynamin-dependent translocation. In a resting cell, TLR9 is localized at the endoplasmic reticulum (ER), but is translocated to the endosome on stimulation, where a protease or proteases cleave TLR9. IRF, interferon regulatory factor; TRIF, Toll/IL-1 receptor domain containing adaptor-inducing interferon-β. (Adapted from Kumagai Y, Shizuo A. Identification and functions of pattern-recognition receptors. *J Allergy Clin Immunol* 2010;125:985–992.)

TABLE 25.1 SUMMARY OF TLRS

	TLR Location	PAMPs Recognized
TLR1	Cell surface	Triacyl lipopeptides (bacteria and mycobacteria)
TLR2	Cell surface	Hemagglutunin protein (viruses), peptidoglycan, and LTA (Gram-positive bacteria), lipoarabinomannan (mycobactria)
TLR3	Endosome	ssRNA, dsRNA viruses
TLR4	Cell surface	LPS (Gram-negative bacteria), glycoinositolphospholipids (*Trypanosama*), mannan (*Candida*), fusion protein (respiratory synctial virus)
TLR5	Cell surface	Flagellin, an important protein in bacteria motility, adhesion, and invasion
TLR6	Cell surface	LTA (Gram-positive bacteria), zymosan (*Saccharomyces*)
TLR7	Endosome	ssRNA viruses
TLR8	Endosome	ssRNA viruses
TLR9	Endosome	dsDNA viruses, unmethylated CpG motifs
TLR11	Cell surface	Profilins from toxoplasmosis gondii, uropathogenic *Escherichia coli*

dsDNA, double stranded deoxyribonucleic acid; LPS, lipopolysaccharide; LTA, lipoteichoic acid; PAMP, pathogen-associated molecular patterns; ssRNA, single stranded ribonucleic acid; TLR, toll-like receptor. Adapted from Ooi EH, Psaltis AJ, Witterick IJ, et al. Innate immunity. *Otolaryngol Clin N Am* 2010;43: 473–487.

Natural killer (NK) cells originate in the bone marrow and participate in the innate immune system. NK cells simultaneously express both T-cell markers (CD3, T-cell receptor [TCR]-αβ) and NK cell markers (CD56, CD16, CD95, and CD178) (33). A large fraction of NK cells are referred to as invariant NK cells, and they are characterized by the expression of a single unique TCR-α rearrangement. Upon activation of NK cells, they are capable of rapid and substantial production of cytokines, including IL-4, which is an important cytokine in allergic pathogenesis (34).

NK cells were first known for their capability to lyse tumors without any prior priming or immunization. They have been shown to have diverse functions ranging from secreting cytokines such as INF-γ, TNF-α, and granulocyte monocyte-colony stimulating factor (GM-CSF) and chemokines (lymphotactin, RANTES (Regulated upon Activation, Normal T-cell Expressed, and Secreted), and macrophage inflammatory protein [MIP]-1α/MIP-1β) after activation (35) to serving as intermediaries between the innate and adaptive immune systems.

NK cell precursors express IL-2 receptor once they commit to the NK lineage. As they mature, further receptor diversity is procured, and the mature NK cell exhibits specific major histocompatibility complex (MHC) receptors, including 2B4, CD38, CD7, and killer-cell immunoglobulin (Ig)-like receptor. Upon completion of maturation, NK cells migrate to the peripheral blood and congregate in the spleen, lymphoid organs, lungs, and liver. There are two different types of NK cells—those that participate in killing and those that focus on cytokine production (36).

Another feature of innate immunity is the complement system. The complement system is the primary humeral mediator of antigen–antibody reactions. Initially, complement was thought to play a major role only in innate immunity against invading pathogens. It was discovered subsequently that the complement system plays an important role in the adaptive immune system by being involved with both T and B cells (37). It has also been shown to play a role in tumor growth (38), tissue regeneration, and in diseases like hemolytic uremic syndrome and age-related macular degeneration (39).

The complement consists of at least 30 chemically and immunologically distinct proteins, which can interact with each other, with antibodies, and with cell membranes. The proteins exist either as soluble in the blood or as membrane-associated. There are three routes by which the complement system is activated: the classical pathways, the lectin pathway, and the alternative pathway. All of the pathways converge at C3 (which is the most abundant complement protein found in the blood), resulting in the formation of activation products and the membrane attack complex (C5b-9) (40).

The biologic activity of complement is manifested in three ways. First, certain complement proteins bind to or opsonize foreign particles. Specific cellular receptors for these complement proteins then mediate the binding and uptake of the opsonized particles by polymorphonuclear leukocytes and monocytes. Second, the small fragments of proteolytic cleavage from complement proteins diffuse readily, and they can bind to neutrophils and macrophages, causing chemotaxis and cell activation. Similar receptors on lymphocytes and antigen-presenting cells bind antigen–antibody complexes and enhance specific immune responses such as phagocytosis and clearance of apoptotic cells. Third, complement causes lysis by the

insertion of a hydrophobic "plug" into lipid-membrane bilayers, allowing osmotic disruption of the target cell. Deficiencies in complement lead to severe infectious or autoimmune diseases.

Complement may play a role, in the nasal mucosa, in an immediate-type hypersensitivity reaction by stimulating mast cells. Studies of asthma have implicated increases of anaphylatoxins C3a and C5a at sites of inflammation after segmental allergen provocation of the bronchus in asthma patients (41), which can contribute to cellular recruitment of inflammatory cells.

Another important player in the innate immune response is the numerous antimicrobial peptides that are expressed in the sinonasal and lower airway epithelium (26). These include lactoferrin (42), lysozyme (43), cathelicidin (44), defensins (45), SP-A and -D (surfactant protein) (46,47), acid mammalian chitinase (47), collectins (48), serum amyloid A (49), and secretory leukocyte proteinase inhibitor (50). The most abundant of the antimicrobial peptides in nasal secretions are the lysozyme, lactoferrin, and secretory leukocyte proteinase inhibitor (51). In addition to being referred to as endogenous antibiotics by being secreted in response to microbes, these peptides also play a role in activating or suppressing effector cells of the innate and adaptive immune system. Human cathelicidin, LL-37, is chemotactic for neutrophils, monocytes, and T cells (52). It has also been shown that SP-D can cause a shift from a Th1 to a Th2 cytokine response, inhibit lymphocyte proliferation (53), and regulate DC responses (54).

The defensins, composed of α-defensins and β-defensins, are expressed on cells such as neutrophils, monocytes, epithelial cells, and paneth cells (55). Paneth cells, which are located at the base of intestinal glands, secrete α-defensins when exposed to bacteria and thus contribute to the gastrointestinal barrier. Degranulation of cells that express defensins occur in a dose-dependent manner as part of the host defense in response to infection at epithelial surfaces (55). It is well known that phagocytes and leukocytes are recruited to sites of infection via chemotactic factors (56). Defensins induce chemotaxis of the immature DCs to the sites of infections (56).

The mRNA of HD5, an α-defensin, is expressed in variable amounts in nasal epithelial cells (57). β-Defensins in mice induce maturation of DCs via TLR4 (58). Because DCs are involved in both antigen (Ag)-specific immune responses and Th1/Th2 polarization, defensins may contribute to interactions between the innate and the adaptive immune system via their influence on DCs. Cathelicidin is an antimicrobial protein expressed by epithelial cells, monocytes, NK cells, mast cells, and γδT cells. LL-37, a cathelicidin peptide, participates in host antimicrobial immunity by recruiting phagocytes, immature DCs, and T cells to sites of inflammation (52). Both LL-37 and human β-defensin-2 cause mast cell degranulation, with consequent histamine release (59). Eosinophil-derived neurotoxin is implicated in antiviral roles and has been shown to play a role in DC development, and like defensin, it may also play a role in bridging of the innate system with the adaptive immune system (60).

Other roles of the antimicrobial peptides have been postulated. Biofilms, which are implicated as a possible cause of CRS (61,62), are organized communities of microbial cells that are attached to living surfaces and are composed of exopolysaccharide matrix encased in a self-produced exopolysaccharide matrix and attached to an inert or living surface (63). *In vitro*, synthetic Cathelicidin LL-37 shows antibiofilm properties at subbactericidal concentrations when cultured with Pseudomonas aeruginosa (64). In animal models, synthetic LL-37 successfully eradicated biofilm of Pseudomonas sinusitis (65).

Adaptive Immune System

Innate immunity controls and eliminates infection with the help of the complement system, NK cell activation, and TLR activation. If the innate immune system is unable to mount an inflammatory response sufficient to remove pathogens, the adaptive immune response is activated. The adaptive immune system, in contrast to the innate immune system, is highly specific in nature and benefits from gene rearrangement. Developing B and T lymphocytes obtain randomly assembled Ig receptors and TCR from specific gene segments. The variable, diversity, and joining (VDJ) segments that are flanked by recombination signal sequences are recombined with either addition or subtraction of nucleotides, creating immense variability in the receptor (66). Whereas the remodeling process that regulates chromatin accessibility of target gene segments remains unclear, it is evident that these processes tremendously expand the diversity of antigen recognition.

The adaptive immune system utilizes many of the same cells as the innate immune system. One major difference between the two responses is the mode of recognition of antigens. Whereas the innate immunity recognizes microorganisms through components present on their cell walls via broad receptor recognition, the adaptive immune system recognizes specific antigens that are processed and presented by antigen-presenting cells in the context of MHC receptors. In cell-mediated adaptive immunity, priming occurs during the first exposure to antigen by MHC II on antigen presenting cells (APCs) with the help of costimulatory molecules. TCR receptors on the T cell associate with the CD3 receptor and, in turn, activate a series of phosphorylation steps within the cell, resulting in the formation of either CD4+ or CD8+ T cells. Activation of T-helper (Th) cells allows the secretion of many cytokines and mediators which, in turn, activate effector cells such as macrophages. Also, in humeral adaptive immunity, the primed Th cell comes into contact with B cells expressing the same antigen. Interaction between these two cell types and linking of CD40 and CD40L on B and activated Th cells, respectively,

causes B-cell activation and differentiation into antibody-secreting plasma cells (67).

A major difference between the adaptive and the innate immune system is the capability of memory in the adaptive system. Most activated T cells function as effector cells and later undergo apoptosis. Some of them, however, differentiate and persist in the host for many years to provide rapid protection on subsequent antigen exposure. The exact mechanism by which certain subsets of T cells become memory cells, and under what signaling conditions, is under investigation.

THE LINK BETWEEN THE INNATE AND ADAPTIVE IMMUNE SYSTEMS

There has been increasing evidence regarding the cross talk between the innate and adaptive immune responses. TLRs, being part of the innate immunity, play an important regulatory role in the function of antigen-presenting cells (68). It has been found that the signals that spur the induction of the adaptive immune system are many, but ample evidence now suggests that activation of TLRs on APCs results in upregulation of costimulatory molecules that induce type-I INF responses and facilitate APC–T-cell interactions that are necessary for the adaptive immune system (69). In one study, Jang et al. (70) found that IL-6 and IL-10 produced by DCs in response to *Mycobacterium tuberculosis* occurred largely as a result of the contribution of TLR2 responses.

DCs express TLR, which are able to recognize pathogen-derived molecules or endogenous signals released by damaged or dying cells (71). Immunologic tolerance results from exogenous antigen presentation of DCs in the absence of direct PRR stimulation (72). PRRs on DCs also play an essential role in driving the cell production of Th1 and Th17-polarizing cytokines such as IL-12, IL-6, transforming growth factor (TGF-β), and IL-23 (68–71). There is also evidence that DCs can be primed for Th-2 polarization through OX40/OX40 ligand interactions, which are thought to be facilitated by the basophil production of IL-4 (71,72).

TLR activation through several pathways contributes to polarization to Th1 immune responses—leading to the hypothesis that this polarization may prevent Th2 immune responses and allergy. Studies in allergen-challenged TLR4-defective mice showed reductions in airway inflammation with eosinophils, allergen-specific IgE levels, and Th2 cytokine production, compared with wild-type mice (73). TLR activation may also lead to Th2 responses. TLR-2-stimulated DCs *in vivo* produce abundant IL-10, which favors a Th2 response (74). All of these developments have led to hypotheses that TLRs play a role via DCs in linking the innate immune system to adaptive immune deviation in allergy.

Trompette et al. (75) reported on a more intimate link discovered between TLR4 signaling and allergic sensitization to specific antigens. The major allergens of house dust mites are homologs of MD-2, the secreted LPS-binding member of the TLR4 signaling complex. Functional homology suggests that Der p2/LPS may drive airway Th2 inflammation *in vivo* in a TLR4-dependent manner, retaining this ability in the absence of MD-2. These data further suggest that Der p2 tends to generate effector lymphocyte responses because of its ability to activate the innate immune system through TLR4 signaling (76–79). A further understanding of the influence of TLRs on Th1/Th2 is likely to help us better understand the mechanisms of allergy.

Immunohistologic studies on sinonasal biopsy specimens have shown that TLR4 is localized in the submucosal seromucinous glands and the TLR2 in the stroma deep to the epithelial surface (80). Reduced mRNA expression of TLR2 was reported in turbinate tissue biopsies of patients with allergic or non-AR as compared to controls (81). It has also been shown that the TLR2 mRNA expression of TLR3 and TLR4 mRNA was reduced in patients with nasal polyps and with fungal colonization, which may represent a link between fungus and TLR expression in nasal polyps (82).

Another link between innate and adaptive immunity is through the NK cells. They have been found in several studies either to activate DC maturation (83), or they are activated by DCs to increase in numbers, secrete IFN-γ, and then to modulate or, in essence, create negative feedback of the afferent limb of the immune response by killing immature DCs (84). This concept is important in that it suggests a complex interplay of cells in the innate regulation of the immune response by NK cells prior to their activation in the adaptive immune response.

CELLS OF THE IMMUNE SYSTEM

The cells of the immune system are derived from pluripotent hematopoietic cells. They develop along two distinct lineages: the myeloid and the lymphoid. The myeloid stem cell lineage is further divided into granulocytes, megakaryocytes, platelets, and erythrocytes. Granulocytes play an important role in allergic responses as early responders in inflammation; they phagocytose bacterial pathogens and secrete important cytokines.

Pluripotent stem cells also differentiate along the lymphoid stem cell line, of which T cells, B cells, and NK cells are major players in the immune response to allergy (85).

Neutrophils

Blood neutrophils are composed of two interchangeable subpools: the "circulating pool" and the "marginal pool." For the "circulating pool" of neutrophils to reach the site of acute inflammation, they must pass through a series of coordinated steps that include adherence to endothelium, extravascular migration, chemotaxis, membrane recognition, attachment to foreign particles, phagocytosis, fusion of lysosomes, degranulation, and a burst of oxidative metabolism.

Neutrophils are recruited and activated by Th17 cells in either a direct or an indirect way. The direct way is through IL-8 production, and the indirect way is by inducing the production of CSF and CXCL8 (86,87). For their adhesion to the vascular endothelium, they need chemokines and selectins.

Once they reach the site of inflammation, the neutrophils recognize particles by the opsonins attached to them. These opsonins include Igs to which the neutrophils exhibit Fc receptors and the C3b fragment of complement. After phagocytosis, the processes described for mononuclear phagocytes also apply to neutrophils.

In regard to their role in allergy, neutrophils are recruited during the late response to antigen challenge, but they are rarely seen to increase during seasonal allergen exposure, making their role in allergic disease uncertain.

Eosinophils

Eosinophils are produced in the bone marrow from CD34+ hematopoietic precursors. They circulate in the blood and localize to inflamed tissues. Many cytokines are important in the recruitment of eosinophils to sites of inflammation, but the most important are IL-1, IL-5, and TNF (88). Eosinophils possess adhesion molecules (ligands), which assist in their movement toward chemokines such as RANTES, MIP-1α, eotaxin, and monocyte chemoattractant protein-4 (MCP-4), secreted by inflamed tissues (85).

Eosinophil function results from elaboration of a variety of cytokines, proteins, peroxidases, and enzymes. One of these, a major basic protein, is cytotoxic and helminthotoxic. Also elaborated are eosinophil peroxidase, eosinophil-derived neurotoxin, Charcot-Leyden crystal protein, and eosinophil cationic protein (85).

Survival of eosinophils in tissues is based upon their need for several growth factors, such as IL-5, IL-3, and GM-CSF. In the absence of growth factors, they undergo programmed cell death (apoptosis). IL-33 enhances the survival of eosinophils, causes the production of superoxide anion, and activates eosinophils as effectively as does IL-5 (89). Blocking of the receptors of IL-33, namely ST2, reduced the survival of eosinophils and the production of IL-8 (89).

Konya et al. (90) reported that endothelial cell-derived prostaglandin (PG) I-2 attenuated the migration of eosinophils *in vitro*. In addition, upon treatment of the endothelial cells with a cyclooxygenase inhibitor, eosinophil migration and adhesion were blocked. These results suggest that selective PGI-2 receptor agonists might have beneficial effects in allergic inflammation.

Basophils

Basophils are granulocytes that possess high-affinity IgE receptors. They contain histamine and other mediators, including cytokines. They can contribute to anaphylaxis by releasing histamine. They express IL-4, and contribute to allergic reactions at tissue sites such as the nose, lungs, and skin (91,92).

Monocytes

Monocytes originate in the bone marrow from pluripotent stem cells and then are released into the blood. They produce PGs, IFNs, proteases, and cytokines. They play a role in immunomodulation with their expression of histamine H4 receptor, which is involved in the perpetuation of allergic inflammation. Histamine H4 mediates mast cell migration toward CXCL12, which is a constitutive chemokine (ligand of CXCR4 and CXCR7) that is expressed in the skin and in the airway epithelium and plays a significant role in allergic airway diseases (93,94).

Upon migration from the blood into tissues, monocytes mature into macrophages or APCs, which are either dendritic or Langerhans cells interspersed in the epithelial layer of the nasal mucosa and skin. It has been found that this maturation is associated with upregulation of H-1 (histamine) receptors (95). In the proliferation of immature macrophages, mitogens such as CSF, which is produced by fibroblasts, lymphocytes, and monocytes, play an important role. During inflammation, both migration and proliferation increase dramatically (96).

Macrophages are the most abundant immune cell in the airways in the absence of inflammation (96). They play an important role in the initiation and regulation of the immune response by producing Th1-type cytokines (IL-12, IL-18, TNF-α, and IFN-α/β). Macrophages that produce IL-12 increase the bronchial responsiveness associated with eosinophil migration. Macrophages producing IL-1 stimulate T-cell function, and present immune molecules to lymphocytes (97), displaying the same major histocompatibility determinants used by T cells (98). IL-1 increases production of PGs and leukotrienes, which may alter vascular permeability and bronchial tone. IL-1 also induces the production of acute-phase proteins, including complement components, fibrinogen, and clotting factors, and increases the activity of adhesion proteins (e.g., intracellular adhesion molecule [ICAM]-1). Substances chemotactic for macrophages include C5a anaphylatoxin, bacterial products such as *N*-formylmethionyl peptides, and products from stimulated B and T lymphocytes (99).

Also important are substances that inhibit migration away from sites of inflammation: lymphokines (macrophage inhibitory factor and macrophage activation factor) and proteolytic enzymes produced during activation of complement (factor Bb).

The capacity for macrophages to recognize opsonized particles resides in their receptors, which bind the Fc portion of Igs and the C3 components of complement, which facilitate phagocytosis and subsequent killing of ingested microbes and tumors as follows. Particles bound to specific or nonspecific membrane receptors are surrounded

by the macrophage cell membrane, forming phagocytic vesicles. Endocytic vacuoles become secondary lysosomes after fusion with primary lysosomes. Within the lysosomal compartment, the contents are digested at acid pH by more than 40 hydrolytic enzymes. After ingestion of particles, macrophages as well as neutrophils undergo a respiratory burst, observed as a dramatic increase in the consumption of oxygen and activation of a membrane-associated oxidase. This oxidase reduces molecular oxygen to superoxide anion, which, in turn, dismutates to hydrogen peroxide. Superoxide and hydrogen peroxide interact to give rise to hydroxyl radicals and singlet oxygen. These reactive metabolites of oxygen exert antimicrobial and antitumor effects.

Another group of effector molecules synthesized by macrophages includes nitric oxide and reactive nitrogen intermediates. The macrophage itself is protected from these oxygen metabolites by its glutathione peroxidase and catalase. Numerous soluble agents, including antigen–antibody complexes, C5a, ionophores, and tumor promoters, can trigger the respiratory burst without phagocytosis (97).

Lymphocytes

T Lymphocytes

The cells primarily responsible for immune recognition are lymphocytes, which have surface-specific receptors for antigenic determinants of foreign molecules. Certain lymphocytes confer the ability to recognize host cells that are infected with intracellular microorganisms through recognition of epitopes presented on the cell's surface. It is therefore imperative that lymphocytes also retain the ability to recognize self-antigens in addition to foreign elements in order to be effective in targeted destruction.

The T cells make up 60% to 70% of peripheral lymphocytes. They are concentrated in zones where they are likely to meet antigen, namely, the paracortical areas of lymph nodes and of the spleen. They originate in the thymus and participate in cell-mediated immunity. T cells confer high degrees of specificity within the clone, and variability across all T cells through the recombination of the antigen-specific portion of their CD3-TCR. In addition to CD3, T cells have a variety of other surface markers that are important in allergy. CD4 and CD8 are markers on certain subsets of T cells and enhance the signal that occurs when a T cell comes into contact with an appropriate antigen-MHC complex borne by APCs. A second signal is provided via CD28 that interacts with the costimulatory molecules B7-1 and B7-2 that are present on APCs (97).

When the T cells leave the bone marrow, they leave as the pre-T cells CD4-CD8-DN (double negative) cells. It is not until gene segment rearrangements occur during their maturation that they will have a gene coding a full-length TCR protein. From a pre-T cell, sequential rearrangements of two TCR genes leads to surface expression of an αβ or γδ TCR (100). Double positive T cells, that is, T cells that are both CD4 positive and CD8 positive, only survive if they are able to recognize self-antigens presented in that particular individual's MHC molecules. They thus undergo positive selection. The T cells then drop either the CD4 to become CD8+, or cytotoxic T cells, or retain only the CD4+ molecules, to become CD4+ T helper cells. Deeper in the thymus, negative selection occurs, which selects for T cells that bind too strongly to self-antigens and causes these cells to apoptose. These two selection processes allow for tolerance of self by the immune system as well as positive selection of T cells that are able to recognize peptides displayed in that individual's unique MHC I and MHC II molecules.

γδ T cells, which only comprise 2% of T cells, are thought to play a role in mucosal immune defense because they accumulate in epithelial sites of inflammation and in some mouse models, γδ T cells do play a role in allergic inflammation (101), however, evidence for the role of γδ T cells in allergic inflammation is conflicting.

CD4+ T Cells

CD4+ T cells interact with cells in the context of MHC-II protein, which is present on APCs. These cells develop into Th1 and Th2 cells. Upon leaving the thymus, CD4+ cells enter the lymphoid organs, where their naïve TCR receptor comes into contact with antigen-MHC complexes on APCs. The type of APC, the costimulatory molecules produced, in addition to the local cytokine environment, all play a role in determining whether the Th cell will become a Th1 or Th2 cell (102). Th1 and Th2 cells are only able to be distinguished from each other by the substances they produce. Th1 cells secrete IFN-γ, IL-2, TNF-α, and TNF-β, which are important for eliminating intracellular pathogens. In contrast, Th2 cells secrete IL-4, IL-5, IL-6, and IL-13, which are important for the elimination of extracellular organisms.

It is also important to mention that peptides are not the only target of T-cell response, as T cells recognize a variety of lipid antigens by means of a family of nonpolymorphic genes (CD1) (103) that evolved to present lipids and glycolipids to the mammalian immune system (104,105). CD1a is expressed on DCs and macrophages. The CD1 protein is implicated in pollen capture and processing (106,107). It is speculated that this recognition by CD1+ DCs and CD1-restricted T cells is involved in the rapid handling of the foreign inhaled grain and initiates the allergic response (107).

CD8+ T Cells

CD8+ cells interact in the context of MHC-I, which is present on all cells. The role of CD8+ cells in allergy is not clear, although some studies hypothesized that CD8+ cells may prevent the development of airway hyperresponsiveness (108,109). CD8+ cells secrete cytokines of the Th1 type and function primarily as cytotoxic cells promoting the death of recognized infected cells.

Dichotomous findings with respect to CD8+ cells led to attempts to further characterize the subpopulations of

CD8+ cells. One study showed the different cytokine profiles of CD8 cell subpopulations stimulated by dendritic cell 1 (DC1) and dendritic cell 2 (DC2). Specifically, IL-10 producing-CD8 cells activated by DC2s were presumed to play a regulatory and possibly an immunotolerant role in the immune response (110). CD8 cells are thought to prevent the induction of immune responses early in the sensitization process, but had a limited role once airway sensitization had occurred (111). Other studies point to the homing capabilities of CD8 cells. Those cells that migrate to lymphoid organs are named central memory cells, whereas those that home to nonlymphoid tissue are called effector cells in inflammatory processes. Elucidation of how and when activated T cells commit to memory cell lineage is still unknown. One interesting development is that memory CD8+ T cells are more efficient in TCR signaling and better augment downstream signaling than are naïve or effector cells (112). This supports the finding that symptoms of AR may continue to increase in patients later in the allergy season despite decreasing allergen counts.

T_{reg} Cells

T cells previously called T suppressor cells, are now called T regulatory (T_{reg}) cells. T_{reg} cells are CD4+CD25+ T cells that express the IL-2 receptor marker (CD25). Previously known for taking part in preventing autoimmunity and transplant rejection, they are now recognized as immunomodulators in the Th1/Th2 paradigm. The T_{reg} subset called Tr1 cells (inducible T_{reg} cells) can produce large amounts of IL-10 and TGF-β (113), which can down regulate allergen-specific Th1 and Th2 responses (114).

T_{reg} cells play a role in areas of tolerance. Children who outgrew their milk allergy (called tolerant children) demonstrate significantly higher peripheral T_{reg} cells compared to children who continued to experience allergy to cow's milk (115).

In a cohort study of over 150 children at age 6 from atopic families, CD4+CD25+ T cells were highest during pollen allergy season, which suggests that these cells represent a mixture of regulatory and activated cells (116). Furthermore, in another study, the number of T_{reg} cells to dust mite allergen were found to be similar in both nonatopic and atopic individuals, cautioning against a simplistic view that atopic diseases are caused only by a deficiency of T_{reg} cells (117). T_{reg} cells also play a role in immunotherapy by secreting IL-10 and TGF-β and inducing B cell Ig class switch toward IgA and IgG4 (Fig. 25.2).

B Lymphocytes

B lymphocytes, like T lymphocytes, leave the bone marrow and localize to peripheral lymphoid tissues. They aggregate in follicles within lymphoid organs, where they coordinate the humeral response. When stimulated by antigen via their IgM surface receptors or B cell receptors (BCRs), BCRs associated ligands aggregate to form signaling complexes, whose strength is modulated and propagated via second

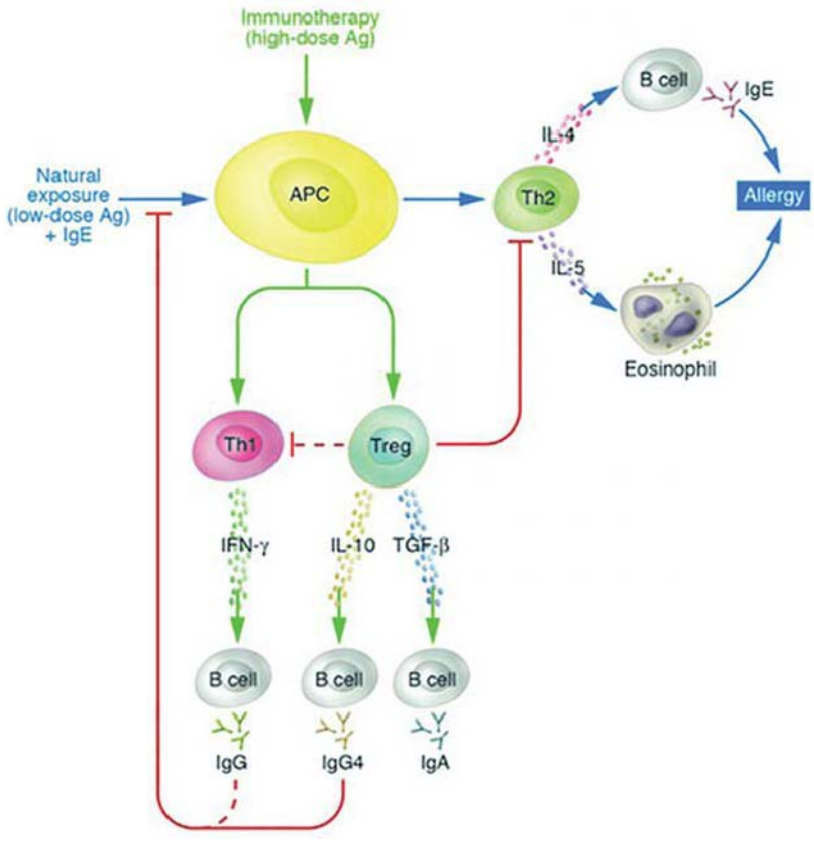


Figure 25.2 Potential mechanisms of conventional allergen immunotherapy. High-dose allergen exposure during immunotherapy results in both immune deviation of Th2 responses in favor of a Th0/Th1 response and the generation of IL-10– and TGF-β–producing CD4+CD25+ T cells, and possibly T_{regs}. IFN-γ–induced activation of bystander macrophages and/or other cells represents an alternative source of these inhibitory cytokines. During subsequent natural environmental exposure to allergens, the activation and/or maintenance of the usual atopic Th2 T cell response is inhibited. Additionally, these cytokines induce preferential switching of B cell responses in favor of IgG and IgG4 antibodies (and possibly IgA antibodies under the influence of TGF-β). IgG may also inhibit IgE-facilitated allergen binding to antigen-presenting cells with subsequent downregulation of IgE-dependent Th2 T-lymphocyte responses. *Blue arrows* represent immune response pathway to natural exposure (low-doses Ag and IgE); *green arrows* represent immune response pathway to immunotherapy (high dose Ag); *red blocked lines* represent inhibition (high-dose Ag); *dotted lines* represent possible means of action not yet proven. (Adapted from Robinson DS, Larché M, Durham SR. Tregs and allergic disease. *J Clin Invest* 2004;114:1389–1397.)

messengers such as diacylglycerol, inositol triphosphate, and intracellular calcium release. B cells differentiate into plasma cells. Plasma cells are responsible for secreting different classes of Igs that mediate humeral immunity. The synthesis of Igs together with heavy chain class switching can occur in the nasal mucosa (118) and be induced in response to allergen exposure (119). IL-4, IL-13, and CD40 are the elements necessary to promote synthesis of IgE and Ig heavy chain class switching in the nasal mucosa. Wise et al. (120) and Durham et al. (121), showed activation of these mediators following allergen provocation. Secondary lymphoid organization can also be seen within nasal polyps (122). Thus class switching can occur outside lymph nodes (123,124), and in the sinonasal tissue.

Dendritic Cells

DCs express receptors such as members of the TLR family that enable them to recognize pathogen-derived molecules or endogenous signals released by dying or damaged cells (125). DCs also express receptors of cytokines like TNFs or IFNs, allowing these cells to recognize a wide spectrum of pathogens like viruses or parasites.

DCs are thought to have two distinct origins. The majority are from a myeloid progenitor, which bears CD11c, CD33, and CD13 cell surface markers and is called myeloid DCs. A smaller subset of DCs are called "plasmacytoid DCs" (pDCs) because of their similarity to antibody-secreting plasma cells. These cells bear a high number of CD123 cell surface markers, which respond to IL-3 and, in turn, produce type I IFN. Characteristics of the pDCs link them to both lymphoid and myeloid precursors (125). The mechanism by which DCs help establish T-cell memory and tolerance, has yet to be determined, but at least in a mouse asthma model, if pDCs are depleted and animals are exposed to an allergen, then IgE sensitization, airway eosinophilia, and Th2-cell cytokine production occurs, which is not seen in mice with pDCs (126).

In AR, cytokines such as IL-4, IL-5, and IL-13 produced by activated cells play a role in inflammation. In cultures of pDCs and CD4+T cells of grass pollen allergic patients, IL-2, IL-5, IL-10, and IL-13 production is increased and upon exposure to grass allergen, CD4+ cells grow and pDCs will produce IL-4, IL-5, and IL-13 with repeated stimulation (127). This further supports the theory that pDCs have effects on stimulating allergen-specific (memory) Th2 responses in the presence of mucosal inflammation.

In their immature forms, DCs in the periphery of the body primarily function to sample antigen. The maturation of DCs occurs after TLR-ligand stimulation (128), upregulation of MHC classes I and II, and upregulation of costimulatory molecules such as CD40, CD80, and CD86 (129). These mature DCs then go on to interact with naïve CD4+ and CD8+ cells.

Another role of DCs is polarizing of T cells into Th2-type effector cells. In animal models of allergic airway inflammation, dendritic-cell–like APCs resembling epidermal Langerhans cells preferentially uptake antigen and present it to CD4+ cells locally in the lung (130), supporting the work of others showing that DCs act to induce Th2 responses (131,132) and that they are necessary to induce a chronic inflammatory eosinophilic response (133,134).

Langerhans cells, another subset of DCs, are the subpopulation that plays a role in T-cell responses in the nasal submucosa in seasonal allergies (135). Other studies comparing functional DC subtypes in normal human upper airways as opposed to the characterizations made in mouse models found that the majority expressed a macrophage-like phenotype (CD11b+CD14+CD64+CD68+RFD7+) (136).

IMMUNOGLOBULINS

Igs are glycoproteins composed of 82% to 96% polypeptide and 4% to 18% carbohydrate components. They account for approximately 20% of the total plasma proteins. Igs function to tag and aggregate toxins and bacteria. They facilitate the activation of the complement system as well as the activation of macrophages, neutrophils, and lymphocytes to clear foreign materials. Binding of antibody to the Fc receptor of mast cells sensitizes these cells for immediate type hypersensitivity.

Ig diversity is attained via multiple processes. The human heavy chain (V_H), D, and junctional (J_H) heavy chains are found on chromosome 14. There are 46 functional V_H segments per haploid genome, with considerable polymorphism within certain segments. V segments vary in two specific regions called complimentarily-determining regions that form part of the antigen-binding site of antibodies. There are seven families of D segments that code for diversity in the Ig repertoire. Functional J_H segments, six in number, are located downstream of the D region. Combinatorial rearrangement of this large number of genes codes for diversity by utilization of recombinant activation genes (*RAG1* and *RAG2*) to facilitate binding to recombinant signal sequences. DNA strand breakage and rejoining at splice sites account for much of the diversity observed in Ig function; however, the recombination process incorporates additional methods that greatly increase the variety of expressed antibodies, which includes the addition or removal of nucleotides to segments and somatic point mutation of rearranged genes. All completely assembled Ig molecules contain an equal number of heavy (H) and light (L) polypeptide chains (Fig. 25.3). In a healthy individual, there are nine isotypes of Igs and four different classes, they are: IgG, IgA, IgM, and IgE.

In normal adults, IgG, which has the most prominent role in memory immune responses, constitutes approximately 75% of the total serum Igs. The relative concentrations of the four subclasses are as follows: IgG1, 60% to 70%; IgG2, 14% to 20%; IgG3, 4% to 8%; and IgG4, 2% to 6%. IgG can fix complement, with the subclasses' ability to fix complement as follows: IgG3 > IgG1 > IgG2. IgG4,

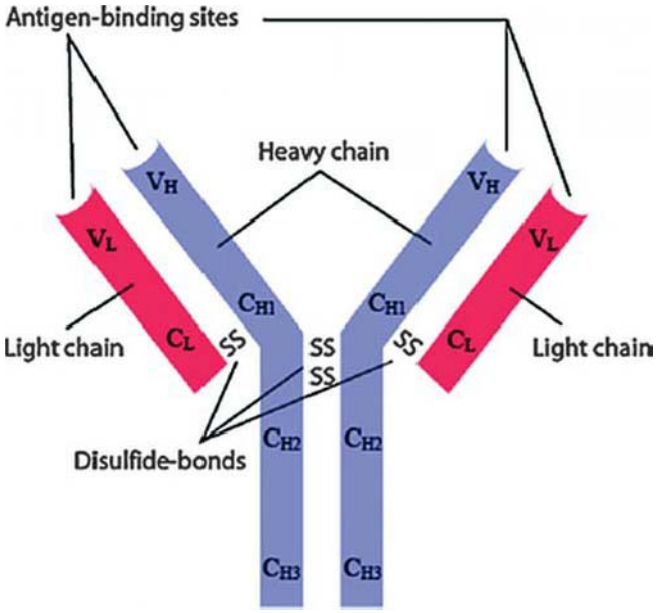


Figure 25.3 Antibody structure. Antibodies are Y-shaped, flexible molecules consisting of two heavy and two light chains linked together by disulfide bonds. The light and heavy chains are composed of constant (CL, CH1, CH2, CH3) and variable (VL, HL) regions. (Adapted from Moser M, Leo O. Key concepts in immunology. *Vaccine* 2010;31;28(Suppl 3):C2–C13.)

although unable to fix complement by the classic pathway, can utilize the alternative complement pathway. IgG4 also plays a role in immunotherapy, as shown in Figure 25.2.

IgA, constituting approximately 15% of the total serum Igs, predominates in body secretions. There are two subclasses, IgA1 and IgA2. The helper T cells in the lymphoid tissues of the gastrointestinal and respiratory tracts switch the B cells from IgM to IgA secretion. Secretory IgA, because of its abundance in saliva, tears, and bronchial and nasal secretions, as well as mucous secretions of the small intestine, provides the primary defense mechanism against local mucosal infections. Its main function may be to prevent access of foreign substances to the general immunologic system. Besides its traditional role in extracellular antibody function, IgA can neutralize viruses intracellularly, can provide an internal mucosal barrier by intercepting antigens and ferrying them through the epithelium, and, after binding to the surfaces of some leukocytes, can activate the alternate pathway of complement activation. Its role in food tolerance to antigens in the digestive system is currently under study. In a study by Frossard et al. (137), a significant increase in the antigen-specific IgA-producing cells was seen in a group of mice tolerized to food allergy.

IgM constitutes 10% of serum Igs and normally exists as a pentamer with a molecular weight of 900,000. IgM antibody predominates in the early immune response and along with IgD is the major Ig expressed on the surface of B cells and is far and away the most efficient Ig in complement fixiation. The enormous size of this pentamer Ig can cause dangerous obstruction in high concentration in areas such as small venules. After an early rise, the IgM response declines and is replaced by IgG of the same antigen specificity. The fetus makes IgM before birth, but maternal IgM is too large to cross the placenta. Thus, IgM antibody to a specific organism in newborn serum indicates intrauterine infection.

IgD is a monomer that is normally present in serum in trace amounts (0.2% of total Igs) and whose function remains unknown. IgD (with IgM) predominates on the surfaces of human B lymphocytes, and thus its most important role may be as a receptor.

Normally, IgE comprises only 0.004% of the total serum Igs, but it binds with very high affinity to mast cells and basophils via the Fc region, thus playing an important role in allergic responses. Like IgD and IgG, IgE normally exists in monomeric form. IgE is produced by B cells after the initiation of two important signals: IL-4 or IL-13 targeting of the *Cε* gene that causes switch recombination, and interaction of activated-T-cell CD40 ligand (CD40L) with CD40 on the surface of B cells to initiate deletional switch recombination (138). Although these mechanisms are not fully understood, the formation of IgE in the atopic or allergic patient plays a major role in the disease process. IgE is also produced locally in nasal mucosa in patients with AR (139).

IgE antibodies fixed to mast cells undergo cell surface cross-linking upon combination with allergen, which then triggers the release of preformed inflammatory mediators such as histamine, tryptase, and protease from mast cells and basophils. IgE probably promotes the survival of mast cells by binding to its high-affinity receptor, *FcεR I*, on the mast cell, which leads to increased expression of antiapoptotic molecules (140). The continued survival of proinflammatory cells in the context of allergic inflammation may be a factor in the chronic symptomatology of the disease even after the removal of allergens. A subunit of the FcεRI receptor, the β chain, probably promotes transport of FcεRI to the surface of mast cells and basophils and hence amplifies the downstream events of the allergic response several-fold in those cells (141). The role of *FcεRIβ* as a candidate gene for atopy modulation is unclear.

IgE also binds to macrophages, neutrophils, eosinophils, and DCs via low affinity receptors. In macrophages, *FcεRI* cross-linking results in production of IL-10. Expression of cell surface *FcεRIα* is present on neutrophils from asthmatic patients (142), indicating that neutrophils may play a role in the allergic response via an IgE-dependent activation mechanism. Human eosinophils were found to secrete IL-10 upon engagement of the receptor (143). Targeting IgE has proven clinically useful, as demonstrated by omalizumab, a monoclonal antibody against IgE, which decrease serum and cell-surface IgE levels and has been useful in the care of severe allergic asthma since approved by the U.S Food and Drug Administration (FDA) in 2003.

Also important are strategies for modulating IgE synthesis by blocking of transcription factors for IgE production. In a mouse model of asthma, mice lacking T-cell–specific

T-box transcription factor (T-bet), a transcription factor that skews toward Th1 and away from Th2 differentiation, had airway changes resembling an asthma phenotype (144). Other studies that under way are those of blocking synthesis of cytokines such as IL-4 and IL-13 that promote production of IgE. Anti-CD23 antibodies in their role of inhibiting IgE production are also being studied.

CYTOKINES, INTERFERONS, AND CHEMOKINES

Cytokines are soluble mediators that have growth, differentiation, and activation functions for immune responses. Cytokines can be grouped into those that are predominantly APCs or T-lymphocyte derived; that predominantly mediate cytotoxic (antiviral and anticancer), humeral, cell-mediated (Th1 and Th17), or allergic immunity (Th2); or that are immunosuppressive (T_{reg} cells) (145). Table 25.2 lists the cytokines produced by lymphocytes, and Table 25.3 is a complete list of cytokines.

Chemokines are a group of small (8 to 12 kD) proteins with the ability to affect cell migration or chemotaxis. These cells include the neutrophils, monocytes, lymphocytes, eosinophils, fibroblasts, and keratinocytes. To date, 52 chemokines and 20 chemokine receptors have been described, which are listed in Table 25.4, and their involvement in diseases in Table 25.5.

TABLE 25.2 Th LYMPHOCYTE FAMILIES

Family	Cytokine Repertoire	Cytokines Involved in Differentiation	Transcription Factors Involved in Differentiation
Th1	IFN-γ, TNF-α, TNF-β, GM-CSF, IL-2, IL-3	**IL-12:** activates STAT4, leading to expression of T-bet; induces IL-18R expression **IL-18:** upregulates IL-12R, further induces IFN-γ expression **IL-27:** activates STAT4, leading to increased expression of T-bet and IFN-γ **IFN-γ:** increases expression of T-bet by increasing expression of STAT1; negative regulator of Th17 and Th2	**T-bet:** master regulator of Th1 cells; potentiates production of IFN-γ and IL-12Rβ2; suppresses Th2 and Th17 differentiation **STAT4:** produced in response to IL-12 and potentiates production of IFN-γ **STAT1:** increases expression of T-bet; negative regulator of Th17
Th2	IL-2, IL-3, IL-4, IL-5, IL-9, IL-13, IL-24, IL-25, IL-31, TNF-α, GM-CSF	**IL-4:** activates STAT6, leading to expression of GATA-3; negative regulator of Th17, IL-19, IL-25, IL-33 **TSLP:** promote differentiation and survival of Th2-like cells	**GATA-3:** master regulator of Th2 cells; potentiates IL-4 expression; suppresses expression of Th1 differentiation and cytokines expression (IFN-γ) **MAF:** contributes to IL-4 production once a Th2 program is established; inhibition of Th17 differentiation **STAT6:** promotes Th2 cell differentiation; negative regulator of T-bet expression and Th1 differentiation **NFAT:** increases transcription of IL-4
Th9	IL-4, IL-9	**TGF-β:** induces the high IL-9 phenotype of Th2-like lymphocytes	
Th17	IL-17 (IL-17A), IL-17F, IL-21, IL-22	**IL-6:** differentiation factor for the generation of Th17 cells TGF-β, IL-21 **IL-23:** support the differentiation and function of Th17 cells in the additional presence of IL-6	**RORγt** (retinoic acid-related orphan nuclear receptor) is the master regulator of Th17 cell differentiation **STAT3:** activated by IL-6 and essential for Th17 differentiation
nT_{reg}/iT_{reg}	IL-10	**TGF-β:** differentiation factor for the generation of nT_{reg} cells **IL-10:** important for differentiation of peripheral iT_{reg} cells, role in nT_{reg} development uncertain **IL-2:** promotes survival, proliferation, and survival of nT_{reg} cells through their constitutive expression of CD25	**FOXP3:** master regulator of thymus-derived nT_{reg} cells
Th3	TGF-β, IL-10		

Adapted from Commins SP, Borish L, Steinke JW. Immunologic messenger molecules: cytokines, interferons, and chemokines. *J Allergy Clin Immunol* 2010;125(2 Suppl 2):S53–S72.

TABLE 25.3 CHARACTERISTICS OF CYTOKINES

Cytokine	Structure	Size Molecular Weight	Receptors	Cell Sources	Cell Targets	Major Functions	Disease Association
IL-1α, IL-1β	Heterodimer	17 kD	IL-1RI, IL-1RII	Macrophages, monocytes, lymphocytes, keratinocytes, microglia, megakaryocytes, neutrophils, fibroblasts, synovial lining cells	T cells, fibroblasts, epithelial and endothelial cells	Induction of proinflammatory proteins, hematopoiesis, differentiation of Th17 cells	Wide range of autoimmune and inflammatory diseases, RA, IBD, psoriasis
IL-1Ra (antagonist)	Heterodimer	16.1–20 kD	IL-1RI, IL-1RII	Monocytes, macrophages, fibroblasts, neutrophils, endothelial and epithelial cells, keratinocytes	T cells, fibroblasts, epithelial and endothelial cells	Antagonism of IL-1	Wide range of autoimmune and inflammatory diseases, RA, IBD, psoriasis
IL-2	Monomer	15.5 kD	IL-2R	CD4+ and CD8+ activated T cells, DCs, NK cells, NKT cells	CD4+ and CD8+ T cells, NK and B cells	Proliferation of effector T and B cells, development of T_{reg} cells, differentiation and proliferation of NK cells and growth factor for B cells	T-cell-mediated autoimmune and inflammatory diseases, X-linked severe combined immunodeficiency 1
IL-3	Monomer	15 kD	IL-3Rα + β c (CD131)	T cells, macrophages, NK cells, mast cells, eosinophils, stromal cells	Erythroid progenitors, granulocyte-macrophages progenitors, CD34+ progenitor cells, basophils, eosinophils	Hematopoietic growth factor, activation of basophils and eosinophils	Role in allergic diseases, different types of cancers, lymphocytic and acute myeloid leukemias
IL-4	Monomer	15 kD	IL-4R type I, IL-4R type II	Th2 cells, basophils, eosinophils, mast cells, NKT cells, γ/δ T cells.	T and B cells	Induction of Th2 differentiation, IgE class switch, upregulation of class II MHC expression on B cells, upregulation of CD23 and IL-4R, survival factor for B and T cells, role in tissue adhesion and inflammation	Inflammatory and autoimmune diseases (allergy/asthma and diabetes mellitus), chronic lymphocytic leukemia diseases
IL-5	Dimer	15 kD	IL-5R	Th2 cells, activated eosinophils and mast cells, Tc2 cells, γ/δ T cells, NK and NKT cells, CD4– ckit– CD3ε– IL2Rα– (Peyer patches)	Eosinophils, basophils, and mast cells	Differentiation and function of myeloid cells, increment of chemotactic activity and adhesion capacity on eosinophils, remodeling and wound healing	Allergy/asthma, hypereosinophilic syndrome
IL-6	Homodimer	19–26 kD	IL-6R, (sIL-6R) gp130	Endothelial cells, fibroblasts, monocytes/macrophages	Hepatocytes, leukocytes, T cells, B cells, hemopoietic cells	Liver: synthesis of acute phase proteins; leukocytes: trafficking, activation; T cell: differentiation, activation, survival; B cell: differentiation, production of IgG, IgM, IgA hematopoiesis	Autoimmune disease, chronic inflammatory disease, B-cell malignancy, SLE, Castleman disease, plasmacytoma/multiple myeloma

IL-7	Monomer	25 kD	IL-7R and sIL-7R	Epithelial cells, keratinocytes, DCs, B cells, and monocytes/macrophages	B, T, and NK cells	Proliferation of pre-B and pro-B cells (mice), megakaryocytes maturation, VDJ recombinations, naive T-cell survival, synthesis induction of inflammatory mediators in monocytes	Allergy/autoimmunity and psoriasis
IL-8	Homodimer	16 kD	CXCR1 and CXCR2	Monocytes, macrophages, neutrophils, lymphocytes, endothelial cells, epithelial cells, fibroblasts, keratinocytes, chondrocytes, synovial cells, hepatocytes	Neutrophils, NK cells, T cells, basophils, eosinophils, endothelial cells	Chemoattractant for neutrophils, NK cells, T cells, basophils, eosinophils; mobilization of hematopoietic stem cells; angiogenesis	Increased levels during inflammatory diseases (RA, psoriasis, bacterial and viral infections)
IL-9	Monomer	14 kD	IL-9R	Th2, Th9, mast cells, and eosinophils	B, T, and mast cells	T and mast cells growth factor, inhibition of Th1 cytokines, proliferation of CD8+ T cells and mast cells, IgE production, chemokine and mucus production in bronchial epithelial cells	Helminth infections, Hodgkin lymphoma, asthma, food allergy
IL-10	Homodimer	20.5 kD, predicted size of precursor protein; 18.6 kD, predicted size mature protein, monomer	IL-10R1/ IL-10R2 complex	T cells, B cells, monocytes, macrophages, DCs	Macrophages, monocytes, T cells, B cells, NK cells, mast cells, DC, and granulocytes	Immune suppression	Cancer, autoimmunity, allergy
IL-11	Monomer	19 kD	IL-11Rα + gp130	Stromal cells: fibroblasts, epithelial cells, endothelial cells, vascular smooth muscle cells, synoviocytes, osteoblasts	Myeloid, erythroid, and megakaryocyte progenitors, osteoclasts, epithelial cells, hepatocytes, macrophages, neurons	Growth factor for myeloid, erythroid, and megakaryocyte progenitors; bone remodeling; protects epithelial cells and connective tissue; induction of acute-phase protein; inhibition of macrophage activity; promotion of neuronal development	Increased during allergic asthma
IL-12 (p35/p40)	Heterodimer	IL-12a p35, 35 kD; IL12b p40, 40 kD	IL-12Rb1 and IL-12Rb2	Monocytes, macrophages, neutrophils, microglia, DCs, B cells	T cells (Th1 cells), NK cells	Induce Th1-cell differentiation and cytotoxicity	Impaired Th1 response with higher susceptibility to intracellular pathogens, use as anticancer agent
IL-13	Monomer	10 kD	IL-13R1α1 and IL-13R1α2	T, NKT, and mast cells, basophils, eosinophils	B cells, mast cells, epithelial cells, eosinophils, smooth muscle cells and macrophages	Switching to IgG4 and IgE, upregulation of CD23, MHC-II on B cells, induction of CD11b, CD11c, CD18, CD29; CD23, and MHC-II on monocytes, activation of eosinophils and mast cells, recruitment and survival of eosinophils, defense against parasite infections	Asthma, AR, fibrosis

(Continued)

TABLE 25.3 CHARACTERISTICS OF CYTOKINES (*Continued*)

Cytokine	Structure	Size Molecular Weight	Receptors	Cell Sources	Cell Targets	Major Functions	Disease Association
IL-14	Monomer	53 kD	IL-14R	T cells, T-cell clones, B-lineage and T-lineage lymphoma cell lines	B cells, certain leukemia cells	Proliferation of activated B cells	Autoimmunity, lymphoma genesis
IL-15	Monomer	14–15 kD	IL-15R	Monocytes, activated CD4+ T cells, keratinocytes, skeletal muscle cells	T, NK, and NKT cells	T-cell activation, proliferation and activation of NK cells, differentiation of γ/δ T cells, suppression of IL-2 induced AICD of T cells, homeostasis of CD8+ memory, NK and NKT cells, enhancement of Th2 differentiation and suppression of AR	Autoimmune and inflammatory diseases
IL-16	Homotetramer	56 kD	CD4	T cells, eosinophils, mast cells, eosinophils, monocytes, DCs, fibroblasts, epithelial cells	T cells, monocytes, macrophages, eosinophils	Chemotaxis, modulation of T-cell response	Increased during various inflammatory and infectious diseases including atopic eczema, allergic asthma, Crohn disease, RA, hepatitis C infection, tuberculosis; inhibits HIV infection
IL-17A	Cysteine knot, homodimer or heterodimer	35 kD	IL-17RA (=IL-17R)	Th17 cells, CD8+ T cells, NK cells, NKT cells, γδ T cells, neutrophils	Epithelial/endothelial cells, fibroblasts, osteoblasts, monocytes, macrophages	Induction of proinflammatory cytokines, chemokines, and metalloproteases; recruitment of neutrophils	RA, MS, IBD, psoriasis, allergic asthma, atopic dermatitis, contact hypersensitivity
IL-17B,C,D	Cysteine knot, homodimer	41, 40, 52 kD	For IL-17 B, IL-17RB (=IL-17H1, IL25R); for IL-17C and D, not known	IL-17B: neuronal cells, chondrocytes; IL-17C: immune cells under certain conditions; IL-17D: resting B and T cells	Monocytes, endothelial cells, myofibroblasts	Induction of proinflammatory cytokines, chemokines, and metalloproteases; IL-17B: chondrogenesis and osteogenesis	RA, allergic asthma, inflammatory cardiomyopathy, Wegener granuloma
IL-17F	Cysteine knot, homodimer or heterodimer	44 kD	IL-17RA (=IL-17R) and IL-17RC (=IL-17RL)	Th17 cells, CD8+ T cells, NK cells, NKT cells, γδ T cells, neutrophils	Epithelial/endothelial cells, fibroblasts, osteoblasts, monocytes, macrophages	Induction of proinflammatory cytokines, chemokines, and metalloproteases; recruitment of neutrophils	IBD, psoriasis, allergic asthma
IL-18	Heterodimer	22.3 kD	IL-18R	Wide range of cells, mainly macrophages, Kupffer cells, keratinocytes, osteoblasts, astrocytes, DCs	Variety of cells, T cells, NK cells, macrophages, epithelial cells, chondrocytes	Induction of IFN-γ in presence of IL-12, enhances NK cell cytotoxicity, promoting Th1 or Th2–cell responses depending cytokine milieu	Autoimmune diseases or inflammatory disorders, RA, psoriasis, MS, type I diabetes

IL-19	Monomer	20.5 kD, predicted size of precursor; 17 kD, predicted size of mature protein; 35–40 kD, found in transfected cells, glycosylated	IL20R1/IL-20R2	Monocytes, keratinocytes, airway epithelial cells and B cells	Keratinocytes	Unknown	Psoriasis
IL-20	Monomer	20 kD, predicted size of precursor; 17.5 kD, predicted size of mature protein	IL-20R1/ IL-20R2 and IL-22R1/ IL-20R2	Monocytes, keratinocytes, epithelial and endothelial cells	Keratinocytes, monocytes	Role in skin biology	Psoriasis, RA, atherosclerosis
IL-21	4-Helix bundle, monomer	15 kD	IL-21R	T cells (predominantly Th17), NKT cells	CD4+ T cells, CD8+ T cells, B cells, DCs, macrophages, keratinocytes	Regulation of proliferation, differentiation, apoptosis, antibody isotype balance, cytotoxic activity	Cancer, SLE, RA
IL-22	6 Antiparallel α-helices, monomer	23 kD	IL-10R2 chain and IL-22R1 chain	Activated T cells (predominantly Th17), NKT cells (NK-22)	Tissue cells like keratinocytes, subepithelial myofibroblasts	Pathogen defense, wound healing, tissue reorganization	Psoriasis, IBD, cancer
IL-23 (p19+p40)	Heterodimer	IL-12b p40, 40 kD; IL-23 p19, 19 kD	IL-12Rb1 and IL-23R	Macrophages, activated DCs	T cells (Th17 cells) and macrophages	Stimulate production of proinflammatory IL-17 and promote memory T-cell proliferation	Susceptibility to extracellular pathogens, exacerbate organ-specific autoimmune inflammation
IL-24	Homodimer and monomer	23.8 kD, predicted size of unprocessed precursor; 18 kD, unglycosylated mature protein; 35 kD, observed size of secreted IL-24, glycosylated	IL20R1/IL-20R2 and IL-22R1/ IL-20R2	Melanocytes, T cells, monocytes	Cancer cells	Tumor suppression	Melanoma, psoriasis
IL-25 (IL-17E)	Homodimer	17 kD	IL-17RA and IL-17RB	Th2 cells, mast and epithelial cells, eosinophils and basophils from atopic individuals	Th2 memory cells	Induction of Th2 responses, IgE, IgG1, IL-4, IL-5, IL-13, and IL-9 production	Gastrointestinal disorders, asthma
IL-26	6 α-Helices, homodimer	38 kD	IL-10R2 chain and IL-20R1 chain	Activated T cells (predominantly Th17), NKT cells	Epithelial cells	Activation and regulation of epithelial cells	IBD
IL-27 (p28+EBI3)	Heterodimer	IL-27a p28, 28 kD; IL-27b EBI3, 25.4 kD	WSX-1 and gp130	Activated DCs, macrophages, epithelial cells	T cells, NK cells	Induction of Tbet promoting Th1-cell differentiation, inhibition of Th17-cell response via STAT1	Immune pathology because of uncontrolled inflammatory response
IL-28A/B/ IL-29 (IFN λ family)	Monomer	IL-28A, 22.3 kD; IL-28B, 22.2 kD; IL-29, 21.9 kD	IL-28R1/ IL-10R2	Monocyte-derived DCs	Most cell types	Antiviral immunity	Role in allergic and autoimmune diseases
IL-30 (p28 subunit of IL-27)							

(Continued)

TABLE 25.3 CHARACTERISTICS OF CYTOKINES (*Continued*)

Cytokine	Structure	Size Molecular Weight	Receptors	Cell Sources	Cell Targets	Major Functions	Disease Association
IL-31	4-Helix bundle	24 kD	IL-31RA/ OSMRβ	Activated CD4+ T cells (mainly Th2) and CD8+ T cells	Keratinocytes, epithelial cells, monocytes, eosinophils, basophils	Induction of IL-6, IL-8, CXCL1, CXCL8, CC chemokine ligand 2, and CC chemokine ligand 8 production in eosinophils, upregulates chemokine mRNA expression in keratinocytes, expression of growth factors and chemokines in epithelial cells, inhibition of proliferation and apoptosis in epithelial cells	Atopic dermatitis, allergic contact dermatitis, prurigo nodularis, chronic spontaneous urticaria, nonatopic eczema, asthma, other inflammatory disorders
IL-32	Unknown	14.9–26.6 kD	Unknown	Monocytes, macrophages, NK cells, T cells, epithelial cells	Macrophages, DCs, T cells, PBMCs, monocytes	Induction of TNF-α, IL-8, and IL-6, apoptosis	RA, IBD, autoimmune diseases
IL-33	β-Trefoil fold	30 kD (active form, 18 kD)	ST2	Necrotic cells and nuocytes	Basophils, mast cells, eosinophils, NK cells, NKT cells, Th2 cells, DCs, nuocytes	Transcriptional repressor activity, induction of Th2 inflammation on mucosal tissues	Autoimmune and cardiovascular diseases, asthma, gastrointestinal tract and lung disorders
IL-34	Homodimer	39 kD monomers	CSF1R	Heart, brain, liver, kidney, spleen, thymus, testes, ovary, small intestine, prostate, colon, most abundant in spleen	Monocytes, macrophages	Proliferation	
IL-35 (p35+EBI3)	Heterodimer	60 kD	Unknown	T_{reg} cells	Different T-cell subsets	Proliferation of T_{reg} cells and inhibition of Th17-cell function, suppression of inflammatory responses	IBD, collagen-induced arthritis
IL-37	Unknown	17–24 kD	IL-18Rα?	Monocytes, tonsil plasma cells, breast carcinoma cells	Intracellular mechanism manner and DC	Suppression of proinflammatory cytokines and inhibition of DC activation	RA
IFN-γ	Homodimer	34 kD	IFNGR1/ IFNGR2	NK and NKT cells, macrophages, myelomonocytic cells, Th1 cells, CTL and B cells	Epithelial cells, macrophages, DCs, NK cells, T and B cells	Antiviral properties, promotes cytotoxic activity, Th1 differentiation, upregulation of MHC class I and II, inhibition of cell growth, proapoptotic effects and control of AICD, regulation of local leukocyte–endothelial interaction, and enhancement of microbial killing ability	Susceptibility to intracellular pathogen infection and tumor development, type 1 diabetes, RA, experimental autoimmune encephalomyelitis

AICD, Activation-induced cell death; CTL, cytotoxic T lymphocyte; NK, natural killer; OSMRb, oncostatin-M receptor b; sIL-6R, soluble IL-6 receptor; STAT1, signal transducer and activator of transcription.

Adapted from Akdis M, Burgler S, Crameri R, et al. Interleukins, from 1 to 37, and interferon-g: receptors, functions, and roles in diseases. *J Allergy Clin Immunol* 2011;127:701–721.

TABLE 25.4 CC, C, CXC, CX3C CHEMOKINE/RECEPTOR FAMILIES

Systematic Name	Human Chromsome	Common Name	Receptor	Physiological Features
CC Chemokine/receptor family				
CCL1	17q11.2	I-309	CCR8,R11	Inflammation
CCL2	17q11.2	MCP-1, MCAF	CCR2	Inflammation
CCL3	17q11–q21	MIP-1α/LD78 α	CCR1,R5	Inflammation, homeostasis
CCL3L1	17q21.1	LD78β	CCR5	Inflammation
CCL4	17q11.2	MIP-1β	CCR5	Inflammation
CCL4L1	17q12	None	CCR5	Inflammation
CCL4L2	17q12	None	CCR5	Inflammation
CCL5	17q11.2	RANTES	CCR1, R3, R4, R5	Inflammation
CCL6	(mouse)	C-10	CCR1, R2, R3	Unknown
CCL7	17q11.2	MCP-3	CCR1, R2, R3	Inflammation
CCL8	17q11.2	MCP-2	CCR1, R2, R5, R11	Inflammation
CCL9	(mouse)	MRP-2/MIP-1γ	CCR1	Unknown
CCL10	(mouse)	MRP-2/MIP-1γ	CCR1	Unknown
CCL11	17q11.2	Eotaxin	CCR3	Inflammation, homeostasis
CCL12	(mouse)	MCP-5	CCR2	Unknown
CCL13	17q11.2	MCP-4	CCR1, R2, R3, R11	Inflammation
CCL14	17q11.2	HCC-1	CCR1	Inflammation
CC Chemokine/receptor family				
CCL15	17q11.2	HCC-2, Lkn-1	CCR1, R3	Inflammation
CCL16	17q11.2	HCC-4, LEC	CCR1	Inflammation
CCL17	16q13	TARC	CCR4	Inflammation, homeostasis
CCL18	17q11.2	DC-CK1, PARC	Unknown	Homeostasis
CCL19	9p13	MIP-3β,ELC	CCR7, R11	Homeostasis
CCL20	2q330q37	MIP-3α,LARC	CCR6	Inflammation, homeostasis
CCL21	9p13	6Ckine, SLC	CCR7, R11	Homeostasis
CCL22	16q13	MDC, STCP-1	CCR4	Inflammation, homeostasis
CCL23	17q11.2	MPIF-1	CCR1	Inflammation
CCL24	7q11.23	MPIF-2, Eotaxin-2	CCR3	Inflammation
CCL25	19p13.2	TECK	CCR9, R11	Homeostasis
CCL26	7q11.23	Eotaxin-3	CCR3	Inflammation
CCL27	9p13	CTACK, ILC	CCR2, R3, R10	Homeostasis
CCL28	5p12	MEC	CCR3, R10	Inflammation, homeostasis
C Chemokine/receptor family				
XCL1	1q23	Lymphotactin	XCR1	Inflammation
XC12	1q23	SCM1-b	XCR1	Inflammation
CXC Chemokine/receptor family				
CXCL1 (ELR)	4q12–q13	GROα, MGSA-α	CXCR2>R1	Inflammation, homeostasis
CXCL2 (ELR)	4q12–q13	GROβ, MGSA-β	CXCR2	Inflammation
CXCL3 (ELR)	4q12–q13	GROγ, MGSA-γ	CXCR2	Inflammation
CXCL4 (non-ELR)	4q12–q13	PF4	CXCR3	Inflammation
CXCL4L1 (non-ELR)	4q12–q21	PF4V1	CRCR3	Inflammation
CXCL5 (ELR)	4q12–q13	ENA-78	CXCR1, R2	Inflammation
CXCL6 (ELR)	4q12–q13	GCP-2	CXCR1, R2	Inflammation
CXCL7 (ELR)	4q12–q13	NAP-2	CXCR2	Inflammation
CXCL8 (ELR)	4q12–q13	IL-8	CXCR1, R2	Inflammation
CXCL9 (non-ELR)	4q21.21	Mig	CXCR3	Inflammation
CXCL10 (non-ELR)	4q21.21	IP-10	CXCR3	Inflammation
CXCL11 (non-ELR)	4q21.21	I-TAC	CXCR3	Inflammation
CXCL12 (non-ELR)	10q11.1	SDF-1α/β	CXCR4, R7	Inflammation, homeostasis
CXCL13 (non-ELR)	4q21	BLC, BCA-1	CXCR3, R5	Inflammation, homeostasis
CXCL14 (non-ELR)	5q31	BRAK, bolekine	Unknown	Homeostasis
CXCL15 (ELR)	(mouse)		Unknown	Unknown
CXCL16 (non-ELR)	17p13	SR-PSOX	CXCR6	Inflammation
CXCL17 (non-ELR)	19q13.2	VCC1,DMC	Unknown	Inflammation, homeostasis
CX3C chemokine/receptor family				
CXCCL1	16q13	Fractalkine	CR3CR1	Inflammation

Adapted from Commins SP, Borish L, Steinke JW. Immunologic messenger molecules: cytokines, interferons, and chemokines. *J Allergy Clin Immunol* 2010;125(2 Suppl 2):S53–S72.

TABLE 25.5 CHEMOKINE/CHEMOKINE RECEPTOR INVOLVEMENT IN HUMAN DISEASE

Chemokine/Chemokine Receptor	Disease
CCR5, CCL3L1, CCL4L1, CXCR4	HIV/AIDS
CXCR4	WHIM syndrome
CX3CR1, CX3CL1, CXCL1, CXCL8, CXCR2, CCL2	Atherosclerosis
CCL2, CCL5, CCL7, CCL11, CXCL8	Asthma, allergic diseases
CXCR4,CXCL1,CXCL12	Cancer metastases
CXCL4	Heparin-induced thrombocytopenia
CCL26	Eosinophilic esophagitis
CCR5	Rheumatoid arithritis
CCR5	Renal allograft rejection
CCR5	West Nile virus infection
Duffy antigen receptor for chemokines	Malaria (Plasmodium vivax infection)

WHIM, Warts, hypogammaglobulinemia, infection and myelokathexis. Adapted from Commins SP, Borish L, Steinke JW. Immunologic messenger molecules: cytokines, interferons, and chemokines. *J Allergy Clin Immunol* 2010;125(2 Suppl 2):S53–S72.

DEVELOPMENT OF ALLERGY

The development of AR, as that of other allergic conditions, pivots on the interplay between genetic predisposition and the timing of environmental exposures. The environmental triggers include dust mite, molds, animal dander, and the pollens of trees, grasses, and weeds (146). A family history of atopic diseases is a risk factor for the development of AR, asthma, and atopic dermatitis. Studies on AR among twins and within atopic individuals clearly indicate a genetic contribution for its development (147). In monozygous twins, a 45% to 60% concordance for AR is observed, which drops to 25% in cases of dizygotic twins (148).

Subjects with a family history of asthma, eczema, hay fever, and urticaria and a positive skin test are referred to as atopic. Allergic parents have a higher than usual proportion of allergic children; 50% of children with two allergic parents will develop an allergy. With only one allergic parent, the chance is about 30%. Thus, the family history represents an important risk factor for allergic disease and indicates an important question to address when evaluating a child with possible allergies.

The genetics of asthma has received more attention than the genetics of AR (149). Among these studies, a number of candidate genes and their polymorphisms have been targeted with variable effect, sizes, and levels of significance (Table 25.6). A meta-analysis for the genetics of AR provided evidence for an overall association between the A allele of IL13 SNP (single nucleotide polymorphism) and an increased risk of AR, especially in mixed-age populations (150).

There are several environmental changes that are epidemiologically linked with allergy and affect fetal gene expression and immune function (151–154). These include, but are not limited to, the microbial burden (155,156), dietary changes (157,158), and environmental pollutants (159,160). These epigenetic changes can be passed on to subsequent generations (Fig. 25.4).

Lifestyle changes that occurred in the past few decades probably increased the development of atopy and increased the prevalence of allergy in the Western countries (161). Maternal diet, including decreases in polyunsaturated fatty acids (152), soluble fiber (162), antioxidants (163), and folate (164) during pregnancy, is associated with an increase in asthma and allergic disease. Vitamin D may affect the development of allergies and asthma early in life although the studies are conflicting (165). High maternal intake of vitamin D during pregnancy and by infants in their first year of life was shown to be associated both negatively (166,167) and positively (168) with wheeze or asthma in children. Paracetamol (Tylenol) use increased the risk of asthma (169–172), especially when used in the first year of life (173). Paracetamol reduces the levels of the antioxidant glutathione in immune cells, which results

TABLE 25.6 CANDIDATE GENES TARGETED IN GENETIC STUDIES OF AR

CCXCR1 (6)	CXCL9 (7)	IL28RA (8)	FOXJ1 (9)	ADRB2 (10)
CCR1 (6)	CXCL10 (7)	IL13 (10–17)	FCγRIIA (18)	IL18 (19, 20)
CCR2 (6)	CXCL11 (7)	GATA3 (11, 21)	IL4 (14, 15, 22–25)	IL2(14)
CCR3 (6)	RANTES (26)	EPO (27–29)	IL4R (10, 12, 14, 17, 30, 31)	IL6 (14)
CCR5 (6)	Eotaxin 2,3 (32)	LTC4S (33)	ICOS (34)	CTLA4 (25)
SDAD1 (7)	SFTPD (35)	CD14 (36, 37)	IL5 (10)	IL12B (38)
ADAM33 (39)	TNF-α (22)	Fαr11β (22–24)	IL10RA (40)	TIM1 (41)
FLG (42)	TLR2 (43)	TLR4 (43)	RNAse3 (44)	FOXP3 (45)
PIP (46)	WNT2B (46)	CLC (46)	PLUNC (46)	IFN-γ (47)

Adapted from Bunyavanich S, Shargorodsky J, Celedo JC. Meta-analysis of Th2 pathway genetic variants and risk for allergic rhinitis. *Pediatr Allergy Immunol* 2011;22(4):378–387.

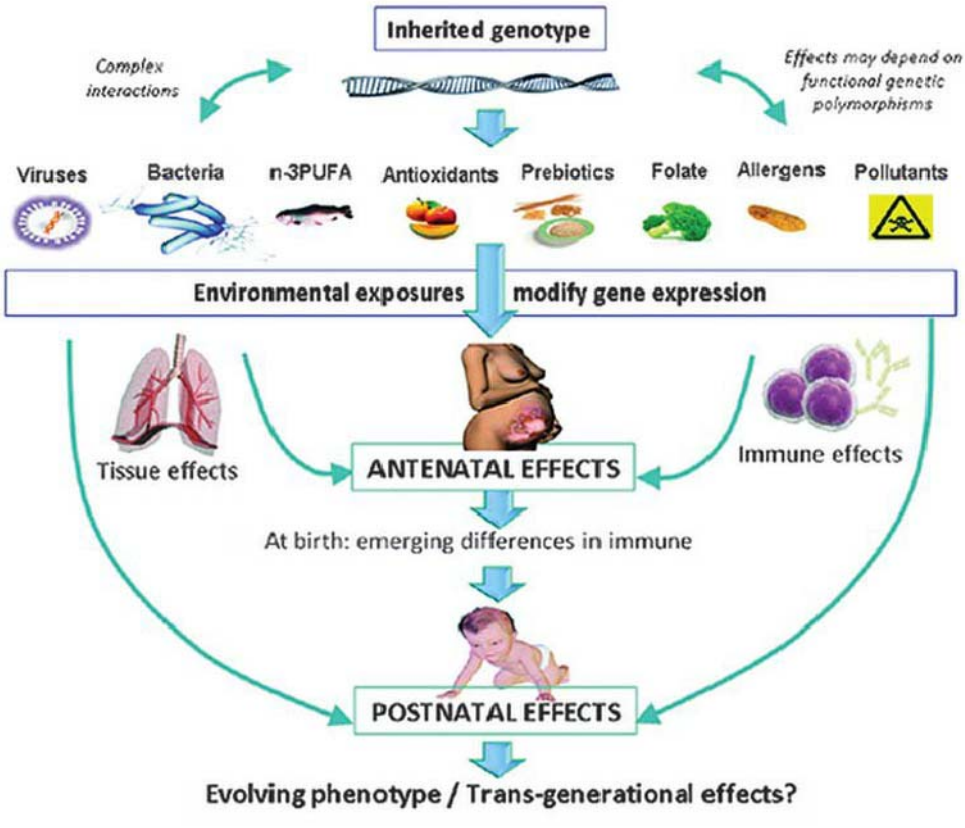


Figure 25.4 Complex gene-environmental interactions modify gene expression and phenotype during early development. PUFA, polyunsaturated fatty acid. (Adapted from Martino D, Prescott S. Epigenetics and prenatal influences on asthma and allergic airways disease. *Chest* 2011;139(3):640–647.)

in increased oxidative stress, decreased antioxidant effects, and could lead to the promotion of Th2 allergic inflammation (169), as well as increased viral loads (174).

The Hygiene Hypothesis

Epidemiologic studies provide evidence for the "hygiene hypothesis" that associates reductions of infectious diseases in developed countries with the rise of allergic and atopic diseases. The "hygiene hypothesis" postulates that infections during infancy may protect against AR and atopy by downregulating the production of IgE (175–180). There is an inverse relationship between number of siblings and atopy, which implicates greater exposure to infectious agents as being protective toward the development of atopy later in life; that is, the youngest sibling has the least likelihood of developing allergic disease. Pet ownership decreases the development of asthma later in life, in a dose response relationship, with the greater the number of pets, the less the risk of later asthma. However, Svanes et al. (181) showed that cat ownership increased the development of adult asthma in sensitized children, with a stronger association in communities with less exposure to cats. In contrast, they found that dog ownership seemed to promote the development of nonallergic asthma in adulthood, but protected against allergic asthma (181).

In a cross-sectional study of rural farming communities in Austria, Germany, and Switzerland, exposure of children less than 1 year old to stables and farm milk was associated with increased protection against the development of asthma, AR, and atopic sensitization (182). The farming environment is associated with reduction in Th2-dependent antibody isotype switching on exposure to common inhalant allergens in human subjects. This process is thought to be mediated by exposure to endotoxin acting through TLR4. Genetic variants at the TLR4 receptor are associated with a blunted response to lipopolysaccharide in humans (183).

In a study of TLR4-deficient mice, sensitization and challenge with ovalbumin (OVA) produced significantly reduced OVA-specific IgG1 and no IgE antibody responses (184). In the same study, investigators showed that different doses of LPS conferred divergent abilities to develop Th1- or Th2-predominant responses. The inverse association between farm milk consumption and allergic diseases is mediated via CD 14-activated innate-immune mechanisms (185).

Other supporting evidence for the hygiene hypothesis includes early day care attendance, before 3 months of age, with a reduction in the development of asthma and atopy in later childhood, and reduction of IgE levels (186). In another large cohort study conducted in northern Europe, individuals were tested for seven

common infections. It was shown that those with less than three specific IgG antibodies were almost twice as likely to have atopic symptoms (187). Controversy still exists on the use of antibiotics in infancy and the development of asthma (188). Although these and other studies are impressive, the "hygiene hypothesis" as the primary reason for the increased prevalence of AR is controversial.

The Allergic Response

AR develops after sensitization to allergens. Allergens such as pollens, grasses, dander, and mold are deposited on mucosal surfaces. After antigen deposition, DCs sample antigen and migrate to the lymph nodes, where they present antigen to sensitize T cells. Recent studies have implicated certain cytokines as aiding in the sensitization process. Iwasaki et al. (189) showed that, in TNF-α knockout mice, sensitization was less robust than that induced in wild-type mice. Decreased mRNA production of IL-4, IL-10, and eotaxin in the nasal mucosa as well as eosinophil recruitment in TNF-α knockout mice, point to a potential contribution of TNF-α to the development of AR.

When an allergen binds to a specific IgM on an APC, such as Langerhans cells in the epidermis, the allergen is internalized, broken up in lysosomes, and presented as small fragments in the context of cell-surface MHC-II complexes. During this interaction in the local lymphoid tissue, the complexes are presented to Th cells. Th cells subsequently secrete cytokines such as IL-4. T cells exhibit IL-4 receptor and CD40 ligand on their surfaces. IL-4 from T cells binds to the IL-4 receptor on B lymphocytes. Allergen sensitization in the nose results in IgE production in the context of these cytokines.

Germ line transcription of the heavy chain locus results in an isotype switch from IgM to IgE and the synthesis of IgE (118) (Fig. 25.5). Interestingly, it is now thought that allergic individuals possess a mucosal environment that favors class switching from IgG to IgE, and indeed, that the isotype switch occurs within the local environment of the mucosa (139). The importance of IgE in the allergic reaction was clearly demonstrated by the successful reduction of the allergic reaction by use of anti-IgE antibodies (190).

IgE-mediated nasal mucosal responses in response to antigen challenge occur in an early and a late phase. In the early response, mast cells predominate (Fig. 25.6). Activation of mast cells produces the cardinal symptoms of sneezing, itching, rhinorrhea, and congestion. The late response occurs hours after the early response, during which numerous cells are recruited and interact. These interactions not only generate symptoms, primarily congestion, but lead to the production of additional allergen-specific IgE and to increased responsiveness to subsequent allergen (priming) and exposure to irritants (hyperresponsiveness) (191–193).

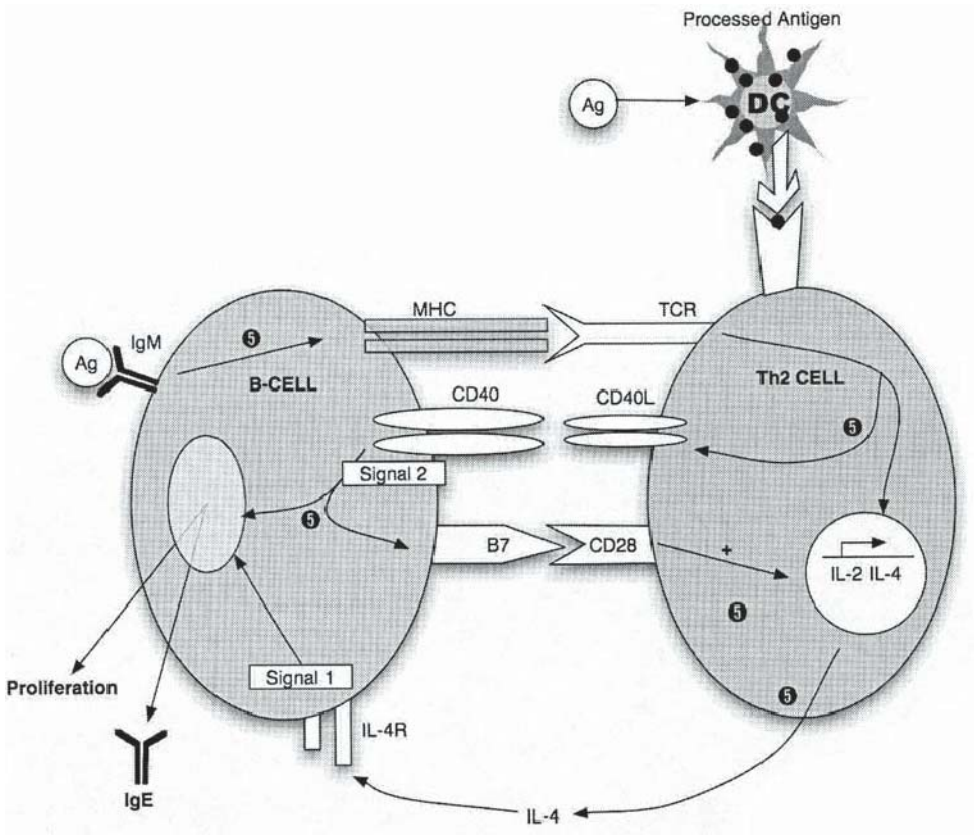


Figure 25.5 IgE development: Signal 1: IL-4 interaction with IL-4 receptor on B cell. Signal 2: costimulatory signal of CD40 on B cell with CD40L on Th2 cell.

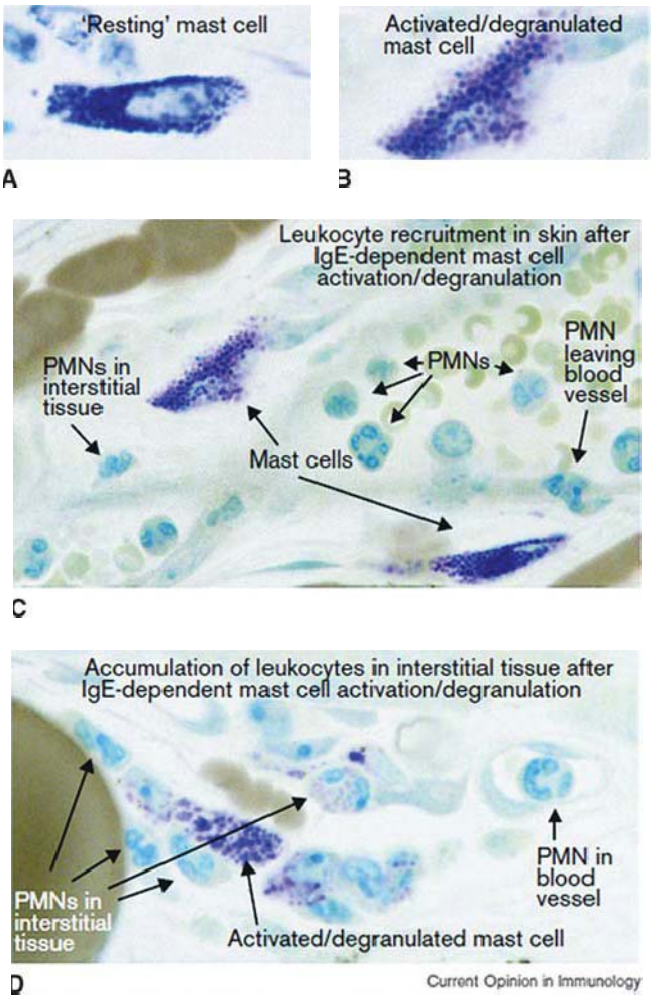


Figure 25.6 IgE-dependent activation of mast cells can induce leukocyte recruitment to sites of allergic responses. The figure shows the degranulation of mast cells and the subsequent recruitment of leukocytes (particularly polymorphonuclear leukocytes [PMNs]) from adjacent vessels. Mice were sensitized by intradermal injection of DNP-specific IgE and were challenged 24 hours later with DNP–HAS intravenously. **A:** Resting and **(B)** activated mast cells can readily be distinguished. The figure illustrates that mast cells **(C)** not only contribute to leukocyte recruitment and migration out of blood vessels in the early phase of an allergic response, but **(D)** are also involved in orchestrating the accumulation of leukocytes in the interstitium of the dermis; these are also characteristic features of later stages of allergic inflammation in humans (i.e., during LPRs and chronic allergic inflammation). Photomicrographs (by J Wedemeyer) are of 1 mm, Epon-embedded, Giemsa-stained sections of ear skin **(A)** before, **(B and C)** at 6 hours, or **(D)** at 8 hours after induction of IgE-dependent passive cutaneous anaphylaxis. Original magnifications were approximately 2,000× **(A and B)** and approximately 1,000× **(C and D)**. (Adapted from Wedemeyer J, Tsai M, Galli SJ. Roles of mast cells and basophils in innate and acquired immunity. *Curr Opin Immunol* 2000;12:624–631.)

The Early Response

The early response in a sensitized host occurs within minutes after exposure to antigen. Patients first sense itching, followed by sneezing, rhinorrhea, watering of the eyes, and then, nasal congestion. A large part of this response except for the congestion is due to the release of histamine and results in vasodilation, vasculature leakage of fluids, glandular, and neural stimulation.

Role of the Mast Cell

Mast cells are divided into two subtypes based upon their content of proteases. Both subtypes contain histamine and exist in the nasal mucosa. Products of mast cells include, but are not limited to, histamine, lipid mediators such as PGs and leukotrienes, chemokines such as eotaxin and RANTES, as well as cytokines IL-3, IL-4, TNF-α, GM-CSF, and MIP-1α.

Mast cells are affected by local cytokines that influence their development, maturation, and death. The cytokine responsible for mast cell growth and proliferation is the stem cell factor (SCF or c-kit ligand) (194). SCF induces histamine release from mast cells, but inconsistently from basophils, and is derived from bone marrow stromal cells, endothelial cells, and fibroblasts. Other cytokines also play a role in mast cell proliferation, including IL-3, IL-5, IL-9, IL-10, IL-11, and nerve growth factor (NGF) (195–199).

Mast cells play important roles in the early response and may play a role in the late response to allergen challenge, as demonstrated in Figure 25.6. Antigen-specific IgE has the ability to bind with high-affinity receptors on mast cells on mucosal surfaces. On exposure to antigen, the antigen-specific IgE on the surface of mast cells cross-links, causing an influx of calcium ions. This process results in the exocytosis of granular content, with the release of preformed mediators such as histamine, heparin, and proteolytic enzymes (tryptase and β-glucosaminidase).

The Late Response

The late response to nasal challenge with antigen refers to the symptoms and inflammatory events that occur hours after antigen exposure. The eosinophils respond to IL-5 produced by T cells, and T cells are likewise activated to facilitate a cascade of events that precipitate the local inflammatory reactions seen in the late response. IL-4 released by mast cells and T helper cells, also contributes to this cascade of events.

In response to IL-4, IL-1β, or TNF-α, local epithelia upregulate very late antigen 4 and ICAM-1 on their surfaces (Fig. 25.7). In concert, T cells, basophils, monocytes, and eosinophils are recruited via vascular cell adhesion molecule 1 (VCAM-1) or lymphocyte function-associated antigen 1 ligands to sites of inflammation. In particular, VCAM-1 and E-selectin have been found to be increased on vascular endothelium of patients with AR, whereas ICAM-1 was found to correlate with E-selectin upregulation (200). RANTES and eotaxin act to recruit T cells and eosinophils into the nasal mucosa. TGF-β has also been found to be upregulated on epithelia of the inferior turbinates of atopic patients and patients with rhinitis, suggesting a possible role for TGF-β in chemoattraction and retention of mast cells in rhinitis (201). Eotaxin in nasal lavages of patients with AR, in particular, was found to correlate with eosinophil recruitment in the mucosa (202). Eotaxin administered intranasally to patients with AR increased eosinophil levels in the mucosa (203).

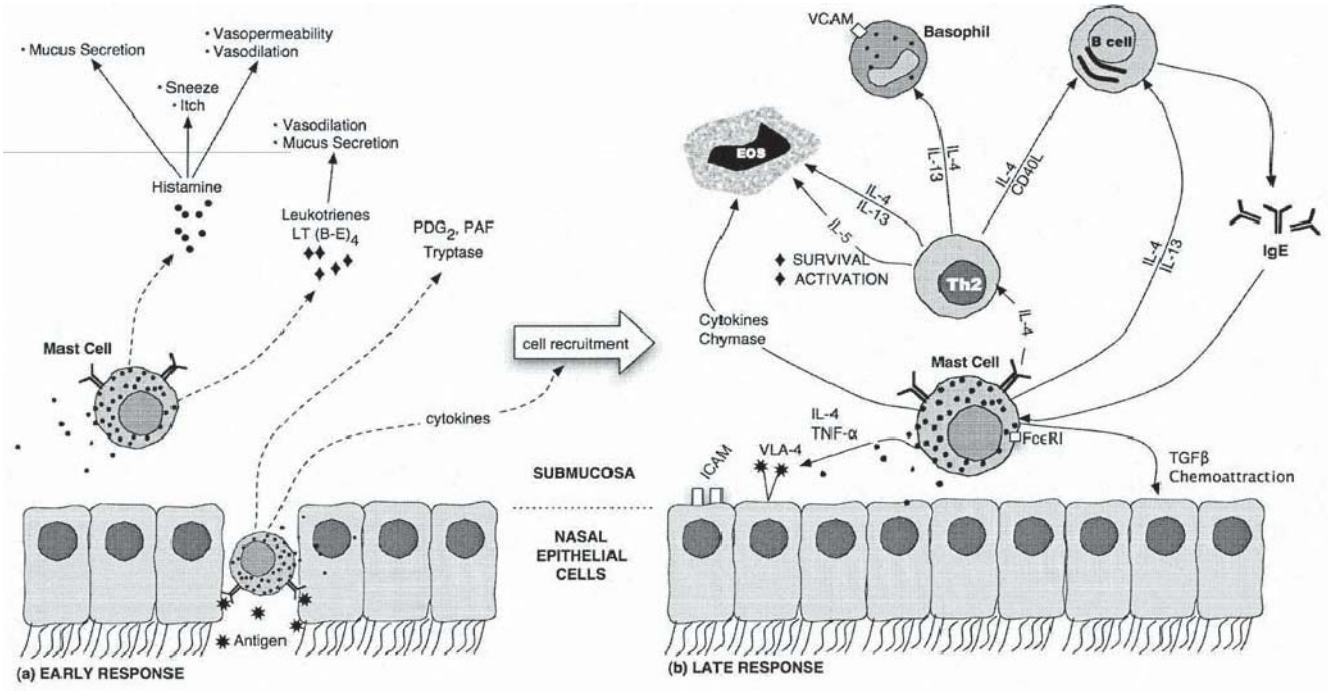


Figure 25.7 **A:** Early response: In the early response to nasal allergen challenge, mast cell activation causes symptoms secondary to mediator release. **B:** Late response: In the late response to allergen challenge, cell recruitment via cytokines causes the accumulation of multiple inflammatory cells in the mucosa, which in turn release mediators that lead to symptoms, hyper responsiveness to irritants, and priming (increased responsiveness to antigen). PAF, platelet activating factor; VLA, very late antigen.

Intracellular and cell-surface changes on endothelium facilitate transendothelial migration of cells. Platelet endothelial cell adhesion molecule 1 (PECAM-1)-deficient endothelium *in vitro* and *in vivo* showed delayed resolution of vascular permeability, suggesting that proinflammatory conditions are conducive to transmigration of inflammatory cells (204). Vascular endothelium cadherin is a transmembrane actin-associated, calcium-dependent adhesion molecule localized at endothelial junctions, and is thought to modulate endothelial permeability (205). During the last decade, there has been general agreement that cells are tethered via interactions between leukocytes and endothelial ligands and are slowed down by "rolling" along the surface of the endothelium, at which point they adhere and are then transmigrated through gap junctions of endothelial cells, a process termed the paracellular pathway. An alternative theory was also reported when leukocytes were shown to cross the endothelium in a transcellular pathway. Figure 25.8 demonstrates these two theories (206).

As highlighted above, the inflammatory processes are numerous, and they overlap in function, adding to complexity and increasing the difficulty in individually defining the exact contribution and importance of each mediator. Interactions that occur during the late response will not only generate symptoms, but lead to the production of additional allergen-specific IgE and to increased responsiveness to subsequent allergen (priming) and irritant exposure (hypersensitivity).

Nonspecific hyperresponsiveness is one of the clinical characteristics of allergic inflammation. Upon infiltration of the nasal mucosa with eosinophils, it becomes hyperactive to normal stimuli and causes nasal symptoms such as sneezing, rhinorrhea, nasal itching, and obstruction (207). Patients with AR will exhibit hyperresponsiveness to nonspecific stimuli such as tobacco or cold, dry air.

THE NEURAL COMPONENT OF ALLERGY

The nose is innervated by afferent, efferent, and postganglionic autonomic nerves. An example of a coordinated neural response is the nasal cycle, a physiologic phenomenon observed more than a century ago (208) that has been confirmed with the use of acoustic rhinomanometry (209) and magnetic resonance imaging (MRI) (210). The nasal cycle is the periodic congestion and decongestion of the nasal venous sinusoids that lead to partial obstruction and patency of each nostril, in reciprocating manner over approximately 4 to 6 hour intervals. Normal individuals are unaware of it because the total nasal resistance remains constant. Patients with rhinitis often describe alternating nasal congestion, which represents the nasal cycle in a compromised airway.

The nasonasal reflex refers to the unilateral stimulation of one nasal passage that ultimately leads to bilateral efferent reflexes, which are identified by their effects in the contralateral nostril. It occurs in response to allergen, histamine, cold, dry air, and capsaicin. The contralateral nostril secretions are 60% of the challenge side after

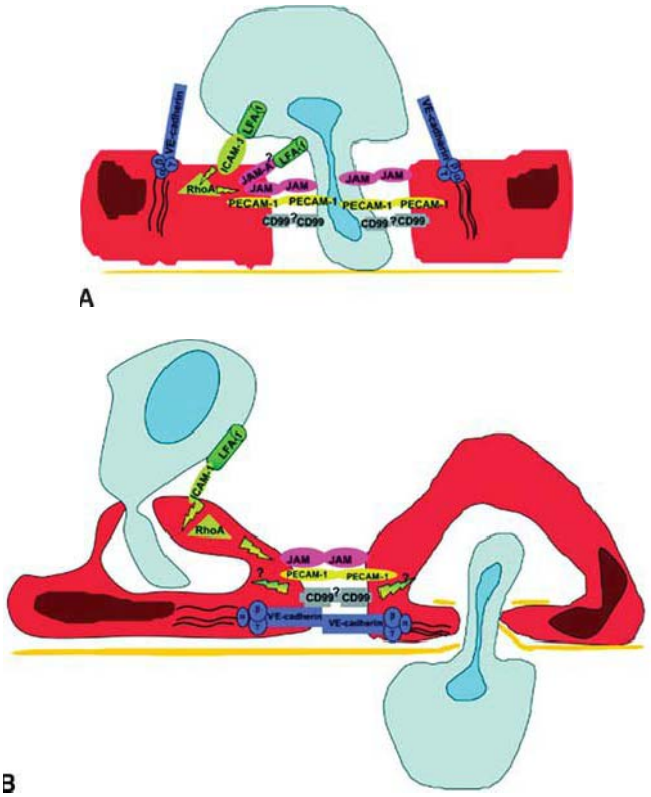


Figure 25.8 Alternative passageways of leukocyte migration across the endothelium. Leukocytes firmly adhere to endothelial ICAM-1, which, via its cytoplasmic tail, delivers a RhoA-mediated signal into the endothelial cell, allowing the leukocyte to migrate either paracellularly through the interendothelial cell junction or transcellularly through the endothelial cell proper. **A:** During paracellular migration, leukocytes encounter homophilic interactions with junctional molecules such as PECAM-1, members of the JAM family, and perhaps CD99 and guiding them through the intercellular cleft, whereas VE-cadherin redistributes to the endothelial cell surface. **B:** Although there is a lack of specific molecular proof for a transcellular route of leukocyte migration across the endothelium, it is speculated that the same molecules investigated for junctional migration trigger the intraendothelial signals required for transcellular migration. (Adapted from Engelhardt B, Wolburg H. Mini-review: transendothelial migration of leukocytes: through the front door or around the side of the house? *Eur J Immunol* 2004;34:2955–2963.)

unilateral histamine provocations. This reflex was shown to be inhibited by cocaine anesthesia to the ipsilateral trigeminal nerves with the efferent limb (parasympathetic) blocked by topical anticholinergic drugs or vidian neurectomy (211).

A nasal–ocular reflex has been shown to exist. Stimulation of the nasal mucosa produces both nasal and ocular symptoms. A topical antihistamine applied in the nose reduces the nasal ocular reflex, suggesting that histamine released in the nose initiates the reflex. The reflex explains how intranasal steroids can eliminate ocular symptoms without being absorbed systematically (212).

Neuropeptides and Neurogenic Inflammation

The secretion of neuropeptides such as tachykinins and neurokinin A (213) are thought to play a modulating role in the pathogenesis of AR through a mechanism called neurogenic inflammation. NGF plays a role in the early response to allergens by inducing maturation, stimulation, and consequent activation of mast cells and release of mediators (214).

NGF promoted allergic responses in a mouse model of asthma by increasing eosinophil and lymphocyte recruitment into the lungs, as well as by the local generation of IL-4 and IL-5, after OVA challenges (215), and is increased in bronchial biopsy specimens after allergen challenge (216).

NGF augments the production of substance P (SP) by neurons and SP is increased in mucosal nerve fibers of patients with seasonal AR (217). SP's actual role in modulating inflammatory migration is unclear (218). Although SP does increase TNF-α and IL-12 production by monocytes and macrophages, it can degranulate mast cells (219).

Neurotrophins, a family of homologous growth factors initially discovered in the nervous system, such as NGF and brain-derived neurotrophic factor, are highly upregulated during allergic inflammation. Neurotrophins are secreted by eosinophils and submucosal glands of the nasal mucosa increase angiogenesis and prolong eosinophil survival in the lungs, increase production of specific IgE, and promote Th2 cytokine predominance (220,221).

Diagnosis

The history and physical examination suggest the diagnosis of AR and both *in vivo* and *in vitro* assays are available to test for allergy; however, there are many more positive allergic tests than allergic individuals (2). The gold standard for allergy testing is *in vivo* antigen-specific skin testing, which is a semiquantitative measurement of the early-phase hypersensitivity reaction. The antigens chosen for testing are based on the patient's medical history plus a screen of common antigens in the local environment. On skin testing, in a sensitized patient, a wheal and flare will occur and usually reach a maximum size in about 20 minutes. Allergy skin testing is suppressed by antihistamines. Thus patients are asked to avoid antihistamines for at least 72 hours before testing. The risk of anaphylaxis with skin testing is small, while large local reactions are more common and all together are reported at a rate of 0.02% to 1.40% (222,223).

In patients with a history of anaphylaxis or inability to be skin tested because of antihistamine use or dermatographism, *in vitro* testing of allergen-specific IgE antibody can be measured from serum. Specific IgE is quantified by plotting of values on a curve for total serum IgE. Historically, the first IgE-specific test was the radioallergosorbent test. The suspected allergen was bound to an insoluble material, and the patient's serum was added. Antibodies to the allergen in the serum would bind. When radiolabeled antihuman IgE antibody was added, it would bind to those IgE antibodies bound to the insoluble material. Subsequently, the unbound antihuman

IgE antibodies were washed away. The resultant amount of radioactivity present quantifies the serum IgE for the specific allergen. This test, however, is currently not being used because it requires a radioactive isotope and expensive equipment. Although other tests have been developed such as the MAST (multiple allergen simultaneous test) and the capsulated hydrophobic carrier polymer system that can provide more accurate *in vitro* tests and test multiple allergens, these tests are less sensitive and more expensive than the *in vivo* skin testing for allergy detection (223,224).

Management

Avoidance

Total avoidance of allergens is the safest and most effective therapy of AR, however, compliance can be difficult since this affects patients daily life activities, dwellings, and life styles and can be expensive to implement. Measures include, but are not limited to, pet avoidance, use of allergen-impermeable encasings on the bed and all pillows, use of an air conditioner, and keeping the windows closed to reduce pollen exposure (225). There have been few studies demonstrating the effectiveness of avoidance in patients with AR. The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (226) report that there is lack of sufficient evidence for the effectiveness of avoidance of house dust mites or pet animal dander (227). This is in contrast to the mandatory avoidance by patients with occupational rhinitis, as illustrated by the European Academy of Allergy and Clinical Immunology, which stated that the safest and most effective treatment for occupational AR is the strict avoidance of the offending allergens (228). Avoidance is an example that what makes sense does not always translate into effective treatment.

Pharmacotherapy

Therapy for AR is usually step-wise, depending on the severity and duration of the symptoms. Figure 25.9 shows the stepwise pharmacologic management of AR as proposed by the ARIA guidelines (226). The medications used are: oral antihistamines, intranasal antihistamines, intranasal steroids, leukotriene receptor antagonists, intranasal cromolyn, decongestants, and saline irrigations.

Oral antihistamines are effective in relieving most allergic nasal symptoms except for nasal congestion. The 2008 ARIA guidelines (226) recommended the use of second-generation antihistamines over the first-generation antihistamines because of the sedative effects of the earlier first-generation antihistamines such as diphenhydramine. Topical steroids are the most effective drug for the treatment of pediatric and adult AR. Many studies have looked at the combination of an intranasal corticosteroid with an antihistamine or leukotriene receptor antagonist, but most have concluded that combination therapy is no more effective than monotherapy with intranasal corticosteroids (229,230). One published study showed that the combination of fluticasone and azelastine was superior to treatment with either alone in patients with moderate to severe AR (231). This type of combination is supported by several other currently unpublished clinical trials. For this reason, combination therapy should be considered in patients who have moderate to severe symptoms, who respond incompletely to monotherapy with an intranasal steroid.

A summary of the pharmacologic treatment guidelines is shown in Tables 25.7 and 25.8. Patients are usually evaluated after 2 to 4 weeks for response to medical treatment. If they have an excellent response, the medications should be continued with gradual step down. If there is a partial response, persistent symptoms should be addressed and treated. Whereas allergic eye symptoms frequently improve with nasal steroids or oral antihistamines, isolated or residual eye symptoms often respond to topical ocular antihistamines. If ocular symptoms persist, it warrants referral to an ophthalmologist to consider other ocular diseases, which mimic AR.

Considerations in Select Populations

More systemically bioavailable nasal corticosteroids, such as beclomethasone temporarily reduce linear growth in children (232–234). Monitoring of growth in children receiving these agents is recommended. In the elderly, who may have increased susceptibility to somnolence from antihistamines, nonsedating antihistamines are recommended. The major symptom of elderly patients with rhinitis is often profuse watery rhinorrhea, which is most responsive to anticholinergic agents.

In pregnant patients, the greatest concern for congenital malformation is present during the first trimester. FDA pregnancy risk categories guide usage in this population. Nasal cromolyn is the safest medication in pregnancy. Cetirizine, chlorpheniramine, loratadine, and tripelennamine are FDA pregnancy category B, whereas many other antihistamines have a category C rating. Category B medications have not shown any adverse effects on pregnancy or the fetus, usually based on animal studies. Intranasal budesonide has a category B rating, whereas other nasal corticosteroids are rated category C (235). Oral decongestants should be avoided in the first trimester because of the risk of gastroschisis in the newborn (236). Systemic decongestants are also banned for use in competing athletes.

Immunotherapy

Allergen-specific immunotherapy (SIT) provides relief for patients who have severe symptoms. It modulates the immune system, and has the potential to alter the natural history of the disease. Immunotherapy is still clinically effective even several years after cessation (237). Pollen immunotherapy in children with seasonal allergic rhinoconjunctivitis decreases bronchial hyperresponsiveness

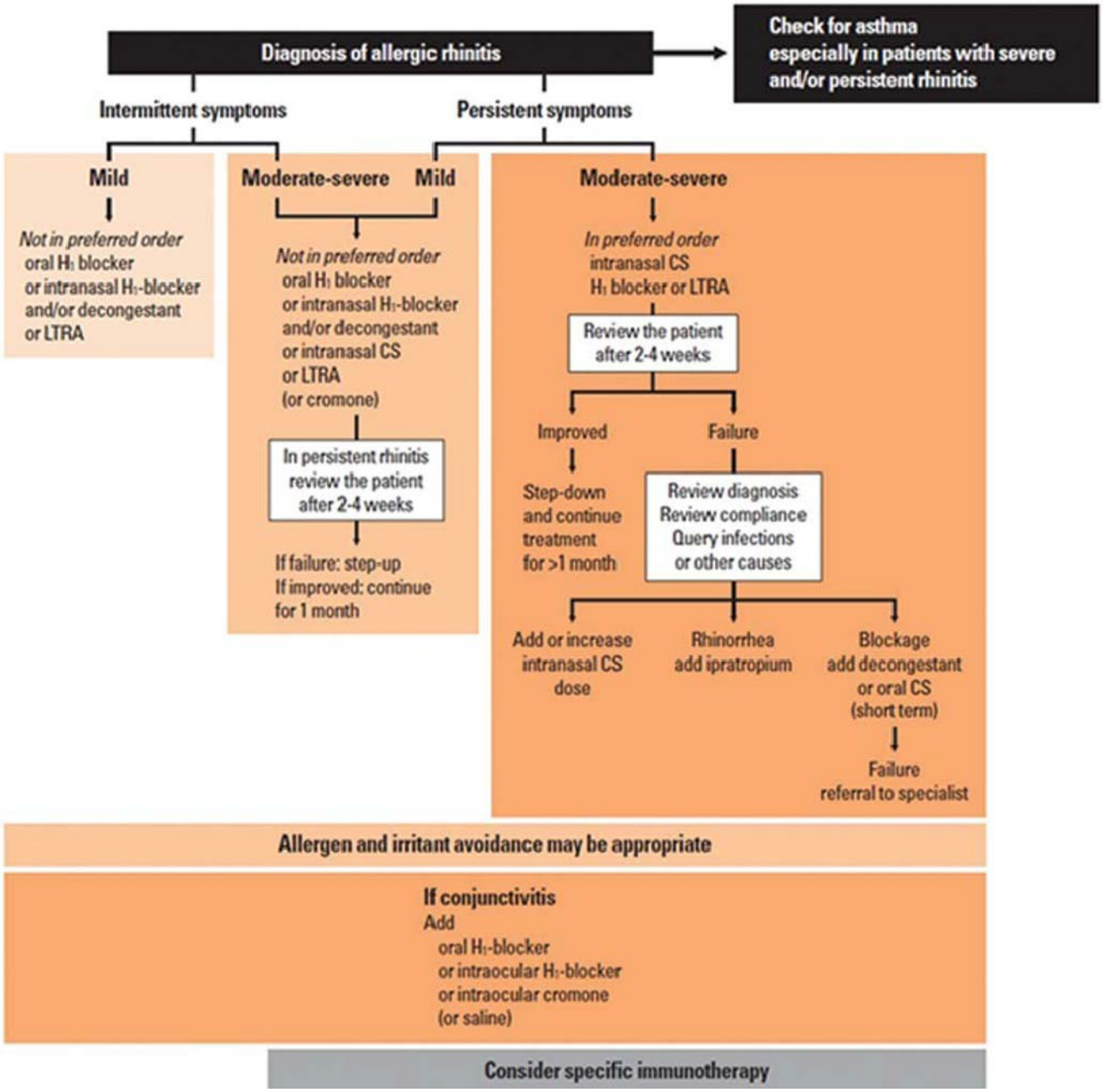


Figure 25.9 Rhinitis management. (Adapted from Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;63(Suppl 86):8–160.)

and development of asthma symptoms for at least 2 years after treatment (238). A Cochrane Systematic Review and meta-analysis of 15 trials on the efficacy of SIT for seasonal allergy with standardized allergens (22) found an overall significant reduction in symptom scores. The ARIA (239) concluded that injection immunotherapy for inhalant allergens was effective for seasonal and perennial AR. In a double-blinded, placebo-controlled trial of the effect of grass and birch pollen found that a combination of SIT, and omalizumab was superior to either treatment alone in reducing nasal and ocular symptoms (240).

The immune mechanisms involved in successful immunotherapy are not fully known. One of the first measurable changes with immunotherapy is an increase in allergen-specific IgG4. In SIT, allergen-specific IgE increases initially during treatment, then steadily decreases to pretreatment levels during maintenance (241,242). The IgG4 antibodies block IgE activity, which is consequently associated with decreased mast cell and basophils activation and release of preformed mediators. In the late response, these "blocking" antibodies prevent the IgE-mediated presentation of antigen to T cells (243,244). In addition to changes in IgE

TABLE 25.7 CLINICAL RECOMMENDATIONS FOR THE TREATMENT OF AR

Clinical Recommendation	Evidence Rating
The initial treatment of mild to moderate AR should be an intranasal corticosteroid alone, with the use of second-line therapies for moderate to severe disease.	A
Compared with first-generation antihistamines, second-generation antihistamines have a better adverse effect profile, including less sedation (with the exception of cetirizine [Zyrtec]).	A
The adverse effects and higher cost of intranasal antihistamines, as well as their decreased effectiveness compared with intranasal corticosteroids, limit their use as first- or second-line therapy for AR.	A
Although safe for general use, intranasal cromolyn (Nasalcrom) is not considered first-line therapy for AR because of its decreased effectiveness at relieving the symptoms of AR and its inconvenient dosing schedule.	C
Nasal saline irrigation is beneficial in treating the symptoms of chronic rhinorrhea and may be used alone or as adjuvant therapy.	B
Although dust mite allergies are common, studies have not found any benefit to using mite-proof impermeable mattress and pillow covers.	A
Interventions without documented effectiveness in the prevention of AR include breastfeeding, delayed exposure to solid foods in infancy, and the use of air filtration systems.	B

A, consistent, good-quality patient-oriented evidence; B, inconsistent or limited-quality patient-oriented evidence; C, consensus, disease-oriented evidence, usual practice, expert opinion, or case series.
For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.
Adapted from Sur DK, Scandale S. Treatment of allergic rhinitis. *Am Fam Physician* 2010;81(12):1440–1446.

and IgG, B lymphocytes increase IgA and IgM production. Theoretically, this boosts the barrier function against antigen penetration at mucosal surfaces (245,246). The IgA increase with subcutaneous immunotherapy (SCIT) is of the subtype IgA2, and has been correlated with an increase in nasal TGF-β and monocyte IL-10 expression, which in turn are associated with the development of tolerance in allergic patients (238).

Immunotherapy induces allergen tolerance by a number of mechanisms. Some studies have shown a shift away from a Th2 to a Th1 cytokine profile with the production of IL-10 locally and peripherally, whereas others have shown that this occurs locally only in the nose (247–249). Tolerance may occur as a result of the increase in the number of allergen-specific suppressor T cells, T_{reg} cells, following immunotherapy (250–254). The production of IL-10 by T lymphocytes was also found to be important in successful immunotherapy (255).

Successful grass pollen immunotherapy in a study by an increase in the ratio of IFN-γ to IL-5 mRNA+ cells in the nasal mucosa was present in one study in patients experiencing symptom relief with grass SCIT, providing evidence for T-cell-subset switching at the protein level (256). Successful SCIT-treated patients showed a rise of signaling lymphocyte activation molecule, a Th1-associated gene with *in vitro* stimulation of T lymphocytes with pollen and mite-sensitive asthmatics, successfully treated with SCIT, demonstrated an increase in the IFN-γ to IL-4 ratio again showing the shift away from an allergic Th2 profile to that of a Th1 profile (257).

TGF-β downregulates T-cell inflammatory and cytotoxic inflammation. It also affects B cells and macrophages (252). SIT is effective because it immunoregulates or suppresses the allergic response.

Adverse reactions to SIT were divided by Calderon et al. (239) into local reactions and systemic reactions. The systemic reactions were further divided into early (occurring within 30 minutes) and late (after 30 minutes). Local reactions not requiring treatment occurred in 92% of the active immunotherapy group versus 33% of the placebo group. Local reactions requiring treatment occurred in 10% of the active SIT group and in 4% of the placebo group. Systemic reactions required adrenaline in 0.13% of the cases in the active SIT group. Within the anaphylaxis group, fatalities occur in around 4 per year (258). The risk of anaphylaxis and the rare risk of death, require that SIT be regulated and only administered by those trained to perform to the highest safety standards.

Sublingual Immunotherapy

Another promising treatment is sublingual immunotherapy (SLIT). Numerous studies demonstrate SLIT effectiveness in decreasing symptoms and use of medications (259) in AR, and in reducing the development of allergic asthma in children (260). Prolonged treatment appears to show persistent efficacy after stopping (261,262). It appears to be as effective as SIT for certain populations and antigens, and less so in others. ARIA (263) reported strong evidence for SLIT efficacy in AR. One of the most attractive features of SLIT is its safety profile, with most adverse reactions consisting of mild and self-resolving throat pain or itching; however, at least three nonfatal anaphylactic reactions have been reported with SLIT (264–266). Other systemic side effects include abdominal pain, conjunctival itching, rhinitis, and urticaria.

Calamita et al. (267), in a meta-analysis found SLIT beneficial in treating asthma treatment, but that the magnitude of improvement was small.

TABLE 25.8 AR TREATMENT BASED ON SYMPTOMS

Treatment Type	Ocular Symptoms	Nasopharyngeal Itching	Sneezing	Rhinorrhea
Intranasal corticosteroids	✓	✓	✓	✓
Oral antihistamines	✓	✓	✓	✓
Intranasal antihistamines	—	✓	✓	✓
Decongestants	✓	—	—	✓
Intranasal cromolyn (Nasalcrom)	—	✓	✓	✓
Intranasal anticholinergics	—	—	—	✓
Leukotriene receptor antagonists	✓	—	—	✓
Nasal saline irrigation	—	—	—	✓
Immunotherapy	✓	—	✓	✓

Adapted from Sur DK, Scandale S. Treatment of allergic rhinitis. *Am Fam Physician* 2010;81(12):1440–1446.

CONCLUSION

The development of AR pivots on the interplay between genetic predisposition and environmental exposure. The pathophysiology of AR illustrates the complexity of the immune system and the importance of a basic understanding of immunology for the otorhinolaryngologist. Many of the cells and cytokines implicated in allergic diseases are involved in other disease processes as well. An understanding of AR pathophysiology is foundational to understanding the management and treatment of this highly prevalent, bothersome, and quality of life impairing disorder.

HIGHLIGHTS

- AR, is classically characterized by itching, sneezing, rhinorrhea, and congestion, and is mediated by IgE or type I hypersensitivity.
- AR is a risk factor for the development of asthma, and the risk increases with the greater severity and persistence of rhinitis.
- Impairment of the innate immune system is probably one cause of CRS.
- The cells associated with innate immunity include neutrophils, monocytes, mast cells, eosinophils, basophils, and DCs and is a first line defense against newly encountered pathogens.
- Innate immunity controls and eliminates infection with the help of the complement system, NK-cell activation, and TLR activation. If the innate immune system is unable to remove pathogens, the adaptive immune response is activated.
- The adaptive immune system, in contrast to the innate immune system, is highly specific in nature, and it benefits from gene rearrangement, and, unlike the innate immune systems, is capable of developing memory.
- Igs, glycoproteins composed of mostly polypeptides and a small carbohydrate component, account for 20% of total plasma proteins. Igs function to aggregate toxins or bacteria. In normal adults, IgG, which has the most prominent role in memory immune responses, constitutes approximately 75% of the total serum Igs.
- AR is an immediate hypersensitivity reaction that is mediated by IgE in response to an otherwise innocuous antigen.
- The development of AR pivots on the interplay between genetic predisposition and environmental exposure. Environmental triggers include allergens such as dust mite, molds, animal dander, and the pollens of trees, grasses, and weeds.
- A family history of atopic diseases is a risk factor for the development of AR.
- The early response to the allergen occurs within minutes and is characterized by mast cell degranulation and the release of preformed mediators, including histamine and proteases, which leads to vasodilatation, vasculature leakage of fluids, and glandular and neural stimulation. It is symptomatically characterized initially by itching, then sneezing, rhinorrhea, watering of the eyes, and then, nasal congestion.
- The late response to nasal challenge with antigen occurs hours after antigen exposure with a recrudescence of allergic symptoms mediated by influx of cellular elements such as eosinophils (responding to the early phase release of IL-5) and activated T cells.
- The history, and physical examination provide the basis for further evaluation in AR. The gold standard for allergy testing is *in vivo* antigen-specific skin testing although both false positives and false negatives can occur. Treatment of AR involves avoidance usually with implementation of environmental controls, medications. and/or immunotherapy.

- Intranasal steroids are the most effective drug for the treatment of pediatric and adult AR.
- Allergen-SIT is used for seasonal and/or perennial AR, and is usually employed in patients with severe, prolonged, or refractory symptoms. SIT modulates the immune system via mechanisms not completely understood, but probably involve IL-10 and T_{reg} cells, and a shift from Th2 to a Th1 bias. SIT and SLIT are the only interventions with the potential to alter the natural history of the disease.

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26 Allergy Testing

James W. Mims

Allergic rhinitis is one of the most common conditions that otolaryngologists treat (1). While the diagnosis of allergic rhinitis is founded on clinical impression, allergy testing plays an important role in distinguishing allergic rhinitis from nonallergic inflammation. Inhalant allergies may also play a role in comorbidities that are disproportionately represented in otolaryngology patients including allergic asthma, atopic dermatitis, allergic conjunctivitis, sinusitis, allergic ear disease, and allergic laryngeal manifestations. While history and physical exam provides the clinical suspicion of hypersensitivity, allergy testing is necessary to determine which allergens are most likely causing the allergic symptoms.

INFLUENCES ON ALLERGY TESTING ACCURACY

Before discussing different types of allergy testing, there are four principles that help to understand and interpret allergy test results. Each complicates our tendency to interpret allergy testing as a "black/white" decision where a positive test represents clinical disease and a negative test removes allergy from the differential diagnosis. We also look at research from food and venom allergy to clarify these points. The four principles are as follows:

Positive Tests Prevalence and Allergic Disease Prevalence

Positive allergy test results are more common than clinically bothersome allergic symptoms.

The Center for Disease Control evaluated a sample of 10,508 individuals selected to represent the U.S. population with skin prick tests (SPT) as part of the Third National Health and Nutrition Survey. Common aeroallergens were used with appropriate positive and negative controls. They reported at least one positive test in 53.9% of subjects (2). However, a 2009 national survey by the Center for Disease Control found that 11.8% reported "respiratory allergies."(3) Similarly, a positive SPT for food has a reported unacceptable specificity of about 50% (4). In venom allergy, 3% of the population has systemic allergic reactions to bees, while 20% have positive skin or specific IgE (sIgE) tests (5). Thus allergy testing should only be performed in individuals with symptoms of allergic disease, and test results must be interpreted in the context of the patient's history.

Negative Allergy Tests and Allergic Reactions

Allergic disease, including anaphylaxis, can be seen after negative allergy tests.

Rhinitis symptoms in patients with negative allergy testing are designated as nonallergic rhinitis. However, in food and venom anaphylaxis, there is no designation of nonallergic anaphylaxis. In food allergy, a negative sIgE test for peanut in a child suspected of peanut allergy occurs in about 10% to 20% of children who will have an allergic response on double-blinded placebo-controlled peanut challenge (6). In venom allergy, there are reports of sting anaphylaxis after negative tests, but these events are rare and less likely to be fatal (5). While negative tests are useful, they do not always exclude clinical allergic disease.

There are at least four possible reasons for false negative tests. First, some individuals test positive only during a certain window after exposure, so testing may be negative outside that time frame. Second, allergen extract material used in testing does not always match an individual's "real world" exposures. Third, some hypersensitivity reactions, even anaphylaxis, are not IgE mediated (e.g., contrast dye anaphylactoid reactions are not IgE mediated [7]). Fourth, there is a theory of local allergy in which the immunologic process in the nose may not be mirrored by mast cells in the skin (8).

Sensitivity and Tolerance

Testing sensitivities and clinical tolerance can change over time.

Since positive allergy tests do not always correlate with clinical symptoms, having a positive allergy test is termed an "allergic sensitivity." Those who suffer from IgE-mediated ragweed allergy, should produce sIgE to ragweed, and have bound sIgE to ragweed on their mast cells and basophils. However, it should be noted that when they are treated with immunotherapy for their allergy, the sIgE does not become undetectable (or even consistently reduce) (9). Despite this, their allergy symptoms improve or may resolve. This suggests that the mechanism of developing tolerance does not require a reversal of the sensitization process. Rather, tolerance has a distinct mechanism that likely involves specialized T cell lymphocytes that regulate inflammation, called T-regs (10). Although semantically paradoxical, sensitization and tolerance can coexist.

Studies that have investigated the natural history or development of allergic disease demonstrate that sensitization and tolerance can vary over time (11). The controlling factors in this are not well understood, but exposure to allergen likely plays a role.

Variability in Allergen Extract

All allergy testing relies on source allergen extracts that have significant biologic variability.

Both allergy skin and laboratory testing require use of raw biologic material. For example, testing for ragweed pollen requires the collection, purification, and sterilization of ragweed pollen (12). Creating an allergen extract is an inexact process and biologic diversity exists between different extract manufactures and even different lots of extract from the same manufacturer. Several common allergens are standardized; however, most allergen extracts are not standardized (13). Along with variation in allergen extract, allergic individuals express diversity not only to what source they are allergic to, but differ in the specific molecular epitopes their sIgE binds (14). Most allergenic sources, such as cat, have multiple molecular proteins to which human IgE can bind. This leads to confusion with terminology as an "allergen" can refer to a source (i.e., cat), a particle (dander), a protein (Fel d 1), or a molecular epitope. The allergens defined by the molecule are named by a convention, the first three letters of the genus, first letter of the species, and sequential number of the identified molecule. For cat, *Felis domesticus*, the first molecular allergen was Fel d 1. Cat has eight identified allergens, Fel d 1-8 (15). If more than 50% of the clinically allergic population produces IgE to a specific molecular allergen, it is termed a "major allergen." Fel d 1 is a major allergen shared by more than 80% of the cat allergic population. As such, cat allergen extracts are standardized by their Fel d 1 content (13). If a person allergic to cat was sensitized only to Fel d 4, they could test negative if the extract, standardized to Fel d 1, did not have an adequate concentration of Fel d 4. This is especially problematic for sources without major allergens, with multiple allergens, or with nonstandardized extracts (many of the molds, tree pollens, and nonragweed weed pollens). Individuals sensitized only to the minor allergens are at risk for false negative tests. In conclusion, all allergy testing is only as good as the allergen extract.

If these four concerns are valid, the diagnosis of allergic rhinitis is primarily a clinical diagnosis. In individuals with a clinical history suggestive of allergy, allergy testing is useful and can direct use of medication, guide environmental control strategies, and identify candidates for immunotherapy.

SELECTING ALLERGENS FOR TESTING

Inhalant allergens are generally divided into groups by source. The main groups are pollens, molds, epidermals, and arthropods (16). Allergen qualities that effect their selection in testing include cross-reactivity, potency, and abundance. An example of cross-reactivity is demonstrated in pollens. Timothy and fescue grass pollens come from different plants but are antigenically very similar (17). A sensitized person who tests positive for one will reliably test positive for the other as they bind the same sIgE sites that can be proved through competitive inhibition. As such, it is not necessary to test an individual for both (16). However, many of the molds are antigenically distinct and testing for Alternaria may not cross-react with other regionally antigenic mold spores (16). Potency, or antigenicity, refers to the strength of reaction produced by the exposure. While grass pollen is less abundant than tree pollen, grass pollen is more potent. Generally, if a sensitized person were tested to an equal amount of grass and tree pollen, they would likely develop a larger reaction from the grass pollen. Pine pollen is an example of a pollen that can be very abundant but not potent and tends not to cause symptoms (18). However, small quantities of cat dander can elicit symptoms because it is potent (19). As such small quantities of cat allergen, such as found in dust collected from a school, may be clinically significant. Abundance is obviously important and explains the seasonal and regional allergies to different pollens.

Pollen allergens are subdivided into trees, grasses, and weeds. Allergenic pollens are typically spread by wind rather than by insects (bees). Pollens are relatively large airborne particles that tend to impact in the nose and conjunctiva rather than the lower airways due to size. For this reason, pollens tend to clinically exacerbate allergic rhinitis and conjunctivitis, while smaller mite, dander, and mold allergens play a larger role in asthma. Pollen allergy tends to be intermittent or seasonal (20–22).

Tree pollens tend to be released in the spring and the abundance causes significant clinical allergy (22). Most tree pollen exhibits modest cross-reactivity and usually testing

one allergenic tree from each family is sufficient. The local variety of trees differs across North America. Thus practitioners will need to gather information about their local pollens. Allergen extract providers, publications, botanists, and environmental agencies are often reasonable sources of information. Common allergenic trees include oak, cedar, and birch. Grass pollens exhibit high potency and high cross-reactivity (21). Selecting one grass from each family represented in the region is sufficient. In most areas, three representative grass pollens will suffice. Grass pollen is most prevalent in the summer. Weed pollen is present in the summer and fall. Ragweed is a potent, abundant, and widely distributed pollen that tends to be released in the late summer and early fall. Weed pollens have less cross-reactivity than grass and vary significantly by region (20). It is sensible to research local antigenic weeds and create a panel that accounts for cross-reactivity.

Inhalant mold allergy is produced by the air-borne mold spores. Spore counts typically range between 5,000 and 50,000 spores/m^3 of air (23). A person typically breaths around 3 m^3 daily. (For reference, a moderate grass pollen level would be 5 grains/m^3.) Multiple factors make testing for mold allergy problematic. There are over one million species of mold that have been identified, but less than 80 are known to play a role in respiratory pathology (24). Multiple factors including poor resources to obtain regional mold data, changing taxonomy, and the sheer quantity of routine exposure further complicate mold allergy. Additionally, spores collected from the single mold strain can vary substantially in antigenicity. And, cross-reactivity between molds varies. Molds within the same genus can be antigenically distinct and molds of different families sometimes display significant cross-reactivity. Despite this, mold is a commonly identified sensitivity and immunotherapy for some molds has been shown to be effective (24).

Proteins on animal dander are frequently antigenic. As such, common household pets like cats and dogs are frequently included on testing panels for persistent allergy symptoms. Fel d 1 is the major allergen found in cat saliva and dander but the function of the protein is unknown (19). Cat allergen has been identified in dust collected from schools, and living with a cat is not required to become sensitized (19). Dander tends to be a small particle and is frequently a trigger for allergic asthma. Beyond dog and cat, the patient's history should be used to guide testing. Guinea pigs, laboratory animals, farm animals, and pet birds are other frequent sources of allergic sensitization in exposed atopic individuals (25).

Arthropod allergy mostly encompasses dust mites (26) and cockroach. However, sometimes a careful history can lead to other concerns; an obscure example would be Asian ladybug sensitization for those living in log cabins (27). Dust mite allergy is very common. Dust mites thrive in humid temperate regions and feed on the gram of human skin each person sheds daily. They are found in high quantity in pillows and mattresses but also found in furniture used frequently. They are microscopic and do not cause symptoms in nonsensitized individuals. There are two common dust mite species in the United States, *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus. Blomia tropicalis* can be found in southern regions approaching tropical climates. Cockroach allergy is especially problematic for childhood asthma in urban settings (28).

ANTIGEN SCREENS

Smaller panels of 9 to 15 selected allergens have been shown to correlate well with larger batteries of allergy tests (29,30). Regional antigenically distinct trees and weeds along with a grass from each family represented in the region are commonly selected pollens. Most screening panels would also include dog, cat, *D. farinae*, and *D. pteronyssinus*. Common allergenic molds including *Alternaria*, *Aspergillus*, Hormodendrum, *Helminthosporium*, and *Penicillium* are frequently tested. Sometimes with skin or sIgE screening, several allergens are combined as a mix, for example, tree mix, grass mix, or mold mix.

ALLERGY SKIN TESTING

In 1865, Charles Blackley suspected he had allergic rhinitis, abraded his skin, and bandaged grass pollen grains over the wound. An intense cutaneous response developed and allergy skin testing was discovered (31). Blackley had performed a version of a scratch test, which is today discouraged because of inconsistencies with the technique (32,33). However, skin testing remains the most popular form of allergy testing in the United States. There are two main variables in skin testing: How much allergen is used, and how deeply it is placed into the skin. SPT uses devices with single or multiple tines dipped in allergen extract to place the allergen into the epidermis of the skin (32). Intradermal testing (IT) uses a small needle to raise a wheal intradermally. (The same technique is used in the purified protein derivative test for tuberculosis.)

Skin testing is popular for multiple reasons. Results are available in minutes. Multiple allergens can be tested at once (a weakness of nasal challenge testing). Systemic allergic reactions are rare. Costs are reasonable. For inhalant allergens, it has been argued that it is more sensitive than sIgE tests (32).

However, skin tests are subject to multiple variables. Skin test results vary with the extract, selected device (34), patient age (35), anatomic location (36), medication, season of the year (37), criteria for interpretation, mechanics of applying the test, and coexisting skin conditions (38). A study by Nelson et al. illustrates the variation encountered in one of the above-listed variables, extract potency. Nelson et al. compared standardized extracts for major allergen content in micrograms. They analyzed the micrograms of major allergen in 28 different *D. pteronyssinus* extracts standardized

to 10,000 AU/mL. The micrograms of major allergen varied nearly fivefold from 68 to 385 μg/mL. Variability for cat extract ranged twofold and orchard grass ranged eightfold (39). Nonstandardized extracts have shown up to a 100-fold variability (40). Despite these problems, positive skin allergy tests in patients selected by allergic history and physical findings have correlated with challenge tests and identified patients who benefited from allergen-specific immunotherapy in randomized controlled trials (41).

Skin testing should always be performed with positive and negative controls (42). Positive controls use histamine to generate a response. The most common reason for a negative response to a positive control is medication use by the subject. Antihistamines, tricyclic antidepressants, and systemic beta agonists are known to inhibit skin test responses and should be discontinued 72 hours prior to skin testing. Negative controls contain the diluent used in allergen extracts. This can vary between extracts but many extracts include glycerin as a preservative, phenol for bacteriostasis, and buffered saline. The diluent can cause a nonspecific reaction usually attributed to the glycerin or skin conditions such as dermatographia. It is not uncommon for allergic individuals to have small reactions from negative controls possibly due to the glycerin. When allergen skin tests are measurably greater than the small reactivity observed after negative control, the allergen test can be interpreted as positive at the discretion of the physician (42).

Skin Prick Tests

SPT is performed with a variety of techniques and devices. Most dip a device with single, dual, or multiple tines into concentrated allergen extract and press into the skin of the ventral forearm firmly with a gentle rocking motion. The prick usually leaves an impression without bleeding (Fig. 26.1). The skin should be marked so that the tests can be identified. Test results are read at a set time, usually 20 minutes. A positive response generates a wheal (raised skin) and flare (erythema) response. While the wheal or flare can be used to determine a positive response, generally a wheal 3 or 4 mm greater than the negative control response is used. Historically, a 1+ to 4+ scale has been used but has been criticized as it is not standardized (43). The greater than 3 mm wheal has greater sensitivity and less specificity than the greater than 4 mm wheal. There is a risk that any allergy skin testing could cause a systemic allergic reaction, thus allergy skin tests should be administered where treatment of anaphylaxis is immediately available. Patients undergoing allergy skin testing should be observed 20 to 30 minutes after skin testing. All patients


A


B


C

Figure 26.1 Skin Prick Test. **A:** SPT applied with a device that places eight tests simultaneously. **B:** Indentations on the skin after a SPT. Of note, no bleeding. **C:** Skin wheal and flare reaction from a positive control (**upper right**) using Histamine base 6 mg/mL. Other sites are negative.

undergoing allergy skin testing require attention to interfering medications and skin conditions, positive and negative control tests, and an environment where anaphylaxis can be managed. There are several excellent reviews of SPT in the current literature (32,42,44).

Intradermal Skin Testing

Allergy extract is diluted before applying intradermally. IT with full strength extracts has an unacceptable risk of systemic reaction, and the results do not correlate well with clinical disease. However, there is no universally accepted dilution for IT. IT is optimally performed using a 26 or 27 gauge unattachable needle joined to a 1 mL syringe to minimize "dead space." The skin is prepped with alcohol and approximately 0.01 mL volume is injected into the dermis to form a 4 mm wheal. The 4 mm wheal will enlarge to a 5 mm wheal by diffusion (not a hyperreactivity response) (42). Wheal and flare determine a positive response and the wheal should be 2 mm or greater than the negative control. (Fig. 26.2) If the negative control is 5 mm, a positive response would be 7 mm or greater read at 10 to 20 minutes (32,42). Another method of measuring a positive response, primarily used in research, is the longest diameter of the wheal or flare added to the orthogonal (or perpendicular) diameter (12). (This convention is used because the wheal and flare responses are not predictably circular.) We discuss the use of IT in three situations: single IT, intradermal dilutional testing (IDT), and in blended techniques.

Single Intradermal Testing

Single IT generally refers to the placement of a single IT after a negative SPT. In theory, the patient has been screened by the negative SPT as not highly sensitive, which allows the IT to be safely placed. There is little agreement on the dilution to use, but a typical scenario might dilute the concentrated extract an additional 25 times. For example, 0.1 mL of a nonstandardized extract labeled 1:20 weight/volume (w/v) could be added to 2.4 mL of diluent creating a 25-fold dilution of strength "1:500 w/v." One paper concluded that SPTs and IT tests were roughly equivalent when

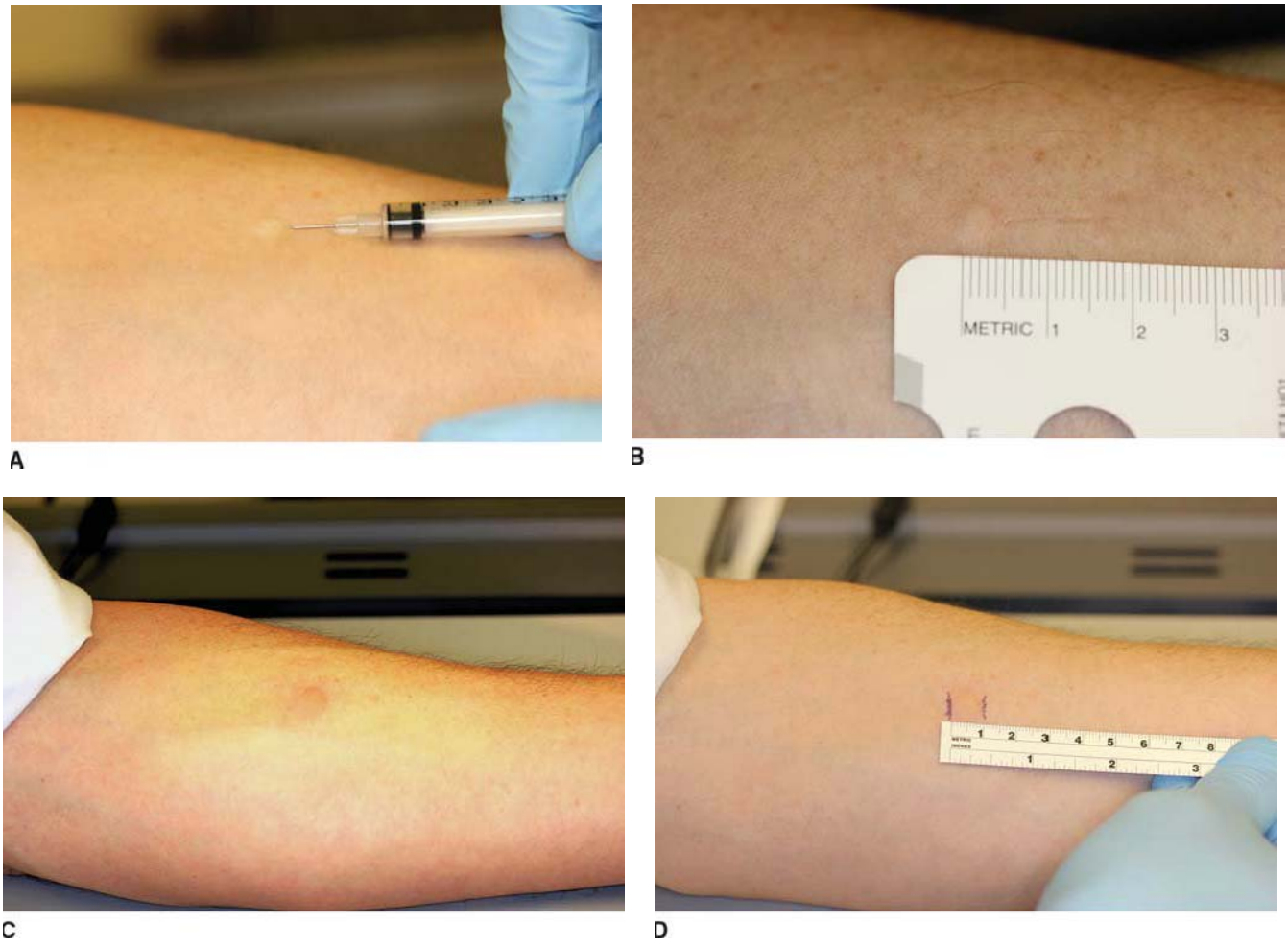


Figure 26.2 Intradermal Test (IT). **A:** Placement of Intradermal allergy test with a 27 gauge needle. **B:** Initial wheal measures 4 mm. **C:** Wheal response to 0.004 mg/mL Histamine base at 10 minutes (positive control). The histamine response will have the same appearance as a positive allergen response. **D:** Measuring the response at 10 minutes.

the IT extract was diluted 1,000-fold (33). For example, Figures 26.1 and 26.2 show similar skin reactions. Figure 26.1 (SPT) uses a histamine base of 6 mg/mL, and Figure 26.2 (IT) uses a histamine base of 0.004 mg/mL (roughly a 1,000-fold difference in concentration).

The clinical interpretation of a positive IT test after a negative SPT for the same extract is controversial (45). Two studies have examined SPT negative, IT positive patients for cat (46), and grass (47) allergy. These studies did not show a significant difference between SPT negative, IT positive patients and SPT negative, IT negative patients for symptoms recorded over the grass pollen season, grass pollen nasal challenges, exposure to a house with cats, or cat extract nasal challenge. These suggested that when the SPT was negative, clinical allergic symptoms were unlikely regardless of the IT result. However, the studies were small and both cat and grass are potent allergens with standardized extracts. When using a nonstandardized extract, a negative SPT might not be as predictive. Ultimately, knowledge of the allergen extract, clinical suspicion based on allergic history and physical findings, and test results must be combined into a clinical impression.

Intradermal Dilutional Testing

IDT (42) does not start with a negative SPT, but rather testing begins with very small amounts of allergen extract placed intradermally (e.g., greater than 100,000-fold dilution). Negative tests are followed by stronger dilutions at 5- to 10-fold intervals until either positive reactions occur or no reaction is observed. IDT is used by the FDA for allergen standardization and in clinical venom allergy testing. IDT, based on the work of Herbert Rinkle (48), was historically the primary allergy test used by many otolaryngologist. While antigen standardization began with ragweed in 1975, most allergen extracts were and still are nonstandardized and based on units of w/v. W/V is the grams of raw material divided by the volume of extract. Similarly, one could describe the strength of a cup of coffee by the weight of the dry coffee and the volume of water used. (Some nonstandardized antigens use Protein Nitrogen Units, a measure of total protein, which can correlate poorly with the small portion of antigenic proteins.) The most common w/v extracts were 1:20 and w/v is still a common unit used. Rinkle used fivefold dilutions of 1:20 w/v extracts diluted six times (Table 26.1).

ITs would begin with Dilution no. 6. If no. 6 was negative, a Dilution no. 5 was placed, then continuing progressively stronger. He observed that clinically allergic individuals tended to develop a 7 mm wheal and if the next more concentrated dilution was placed, a 9 mm wheal would form (Fig. 26.3). This pattern of two consecutive wheals that enlarged 2 mm or more from the prior dilution suggested allergic sensitization. The first wheal that enlarged more than 2 mm was called the "endpoint" and the second wheal the "confirming" wheal. He suggested that when the endpoint wheal was unexpectedly large

TABLE 26.1 FIVEFOLD DILUTIONS OF ALLERGEN EXTRACT

Concentrate	1:20 w/v
Dilution no. 1	1:100 w/v
Dilution no. 2	1:500 w/v
Dilution no. 3	1:2,500 w/v
Dilution no. 4	1:12,500 w/v
Dilution no. 5	1:62,500 w/v
Dilution no. 6	1:312,500 w/v

Nonstandardized allergen extracts frequently use w/v as a unit and the most common extract strength is 1:20 w/v. The Dilution no. 1 can be made by mixing 1 mL of extract "Concentrate" with 4 mL of diluent. Although the Dilution no. 1 is designated as 1:100 w/v by convention, it may not have the same biologic reactivity as an extract produced with 1 g of raw allergen and 100 mL of extracting fluid.

(e.g., 13 mm) or there was no confirming wheal that the test be judged negative or repeated on another date. One of the reasons for the popularity of IDT among otolaryngologists is that the "endpoint" responses can be used to calculate the amount of antigen placed in vials for starting immunotherapy. The IDT results help assure the vials were sufficiently dilute to inject safely. Disadvantages of IDT include that it requires multiple ITs for each allergen, is time consuming, requires technical proficiency, requires preparation of multiple dilutions of each allergen, and is inconsistently reimbursed. Also, IDT is controversial as to what constitutes a negative test. Generally, the controversy surrounds the no. 2 dilution. If only the no. 2 dilution is positive, it is similar to the testing scenario where a patient is SPT negative, but single IT positive discussed above. Thoughtful interpretation is warranted.

Blended Techniques of Skin Testing

The disadvantages of IDT testing caused some authors to look for techniques that provided the quantitative endpoint information of IDT while applying fewer skin tests. Jack Krouse

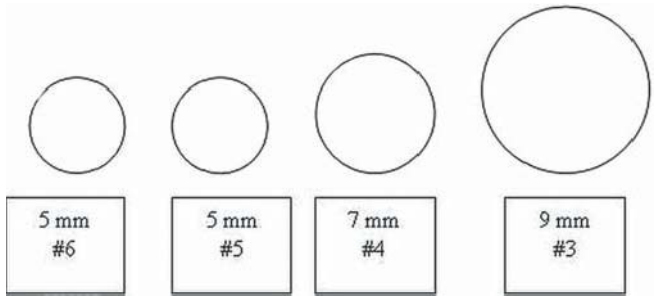


Figure 26.3 IDT example. The circles represent the wheal sizes 10 minutes after placing a 4 mm wheal of fivefold dilutions. The increase from 4 to 5 mm is independent of hypersensitivity and expected. The no. 6 dilution on the left would be placed first, and if negative then a no. 5 dilution placed. In this example, the no. 4 dilution increases to 7 mm suggesting a positive response (the endpoint) and the no. 3 dilution increases greater-than or equal to 2 mm more than the no. 4 "confirming" the reaction is not spurious.

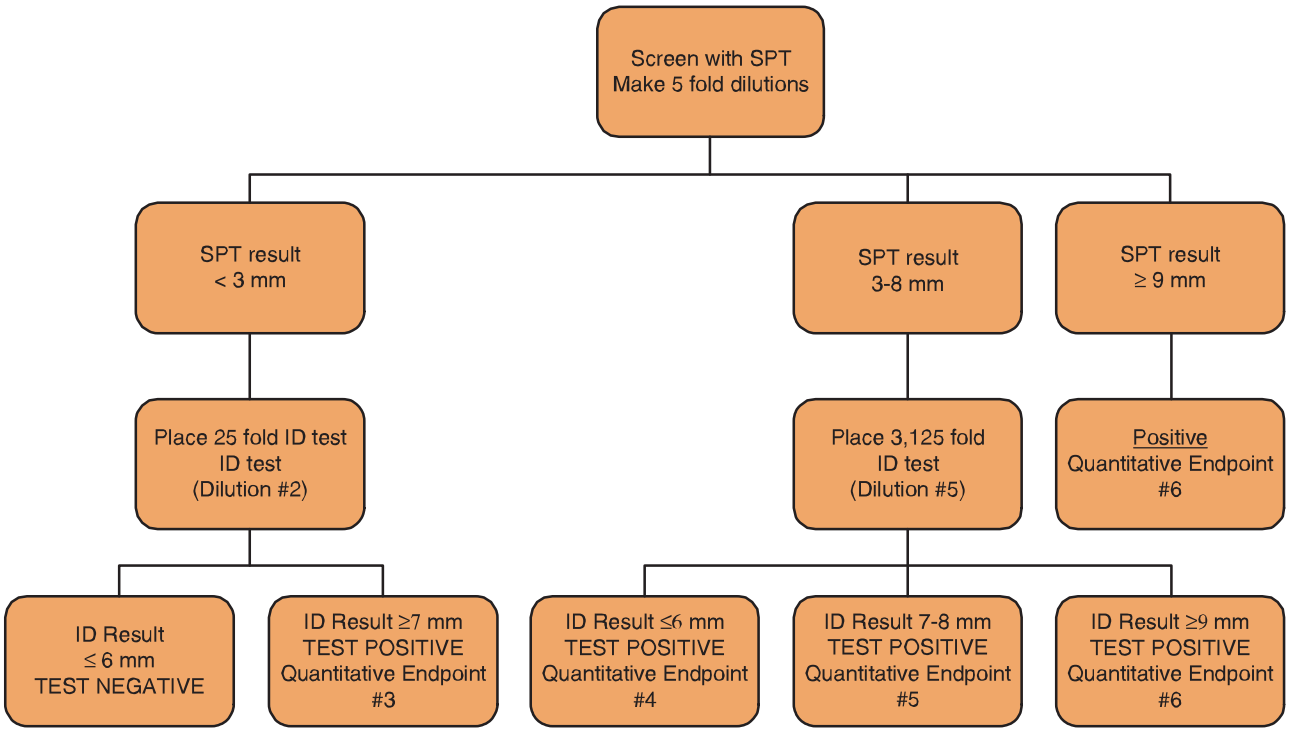


Figure 26.4 MQT testing algorithm Fivefold dilutions are prepared from allergen extract and the initial test is a SPT from the allergen extract. The results of the SPT are read at 10 to 20 minutes and an ID test from the specified dilution is placed according to the algorithm. MQT test provides a postive/negative result and an "endpoint" quantification similar to IDT with fivefold dilutions. MQT, Modified Quanitative Testing; SPT, Skin Prick Test; ID, Intradermal Test. Adapted from Krouse JH, Mabry RL. Skin testing for inhalant allergy 2003: current strategies. *Otolaryngol Head Neck Surg* 2003;129:S33–S49.

advocated "Modified Quantitative Testing" (MQT) (42,49). MQT testing starts with a SPT and depending on the size of the reaction, a dilution is recommended for an ID test. Based on the SPT and ID results, a quantified result is established in addition to a positive/negative result (Fig. 26.4).

Similar to IDT, endpoints provided by MQT can also be used to calculate a safe starting dose for immunotherapy. Of concern, the MQT algorithm can lead to placing a no. 2 IT dilution after a negative SPT test, which is again controversial.

sIgE Testing

In 1921, Prausnitz and Küstner (50) reported temporary tranference of fish allergy after intentional blood transfusion between the authors. The molecule responsible for their observations, IgE, was isolated independently by two groups using differing techniques in the late 1960s (51,52). Methods to assess specific allergies using sIgE in the sera or plasma were developed soon after and have been refined over the years. While different methods are used in different laboratories, they are all held to the same quality controls by the 1998 Clinical Laboratory Improvement Ammendments in the United States.

All sIgE testing has a common strategy. The specific allergen being tested, for example cat dander, is adhered to a fixed substrate (e.g., a paper disk, string, or sponge). The patient's serum or plasma is exposed to the fixated allergen and the patient's IgE specific to that allergen binds. The remaining serum is washed away leaving only IgE bound to the allergen. Labeled monoclonoal IgG molecules are then added and bind to the IgE. The IgG molecules are nonhuman antibodies produced against human IgE. The unbound IgG is washed away and the label is used to semiquantitatively measure the remaining bound IgG, which correlates to the patient's bound IgE. The labels used include radioactive isotopes, flourescent markers, or enzymes that catalyze a reaction that produces a measurable substance (53) (Fig. 26.5).

Initially, sIgE measurements in the 1970s were inconsistent (54,55), but modern sIgE tests agree reasonably well with skin testing (56). But, few studies have directly compared skin testing and sIgE testing to blinded allergen challenges or natural exposures. Many authors have concluded that sIge testing is slightly less sensitive than SPT (53), but the lack of a gold standard for clinical inhalant allergy makes it difficult to know which test is the most accurate.

Advantages of sIgE testing include the ability to test for multiple allergens from a single needle stick, test reults are not influenced by medication use or skin conditions, there is no risk of anaphylaxis, and the test yields semiquantitative information. Disadvantages cited have included cost; however, cost to the patient is not much different per antigen. Other disadvantages include a longer delay for the test

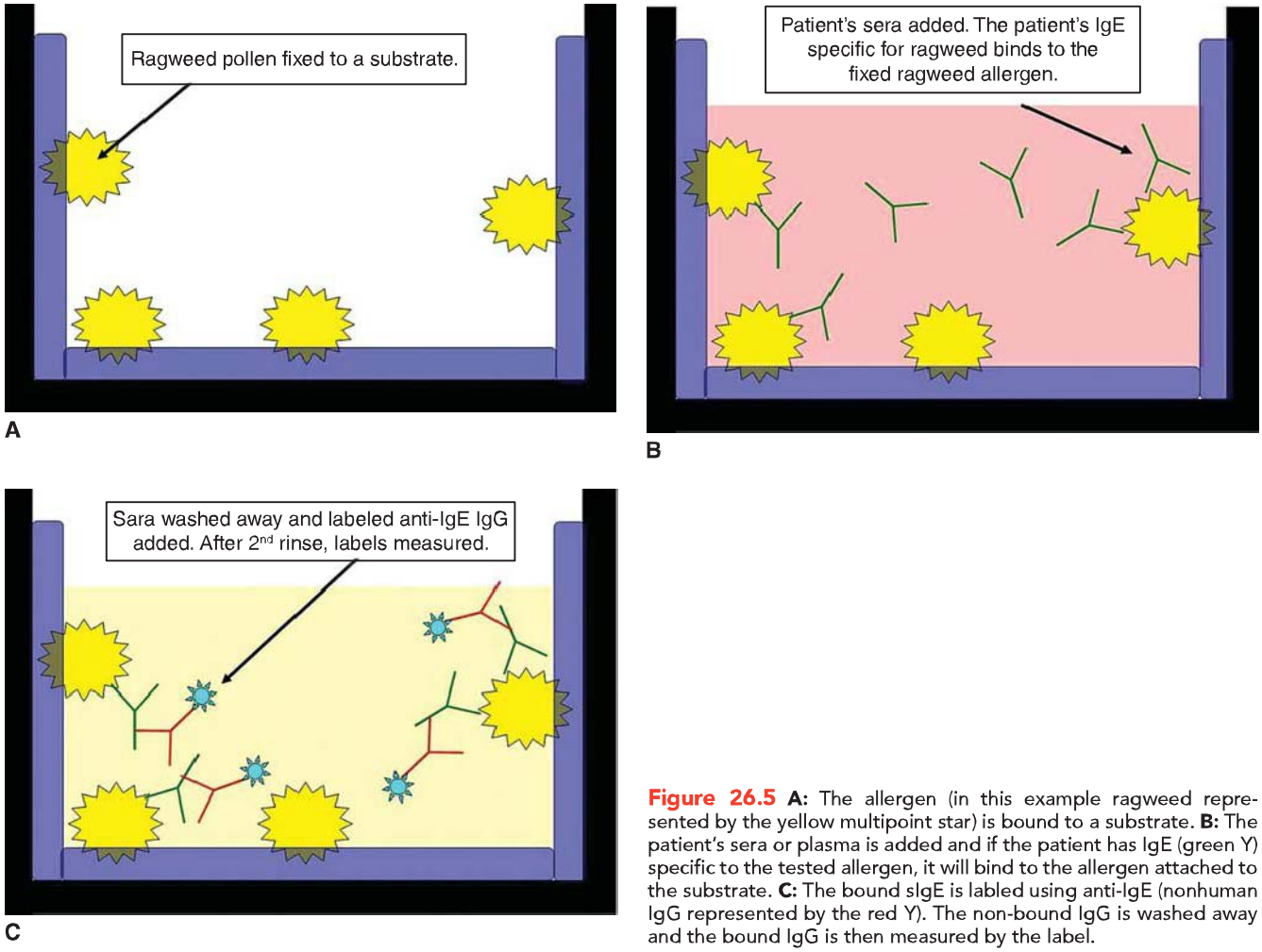


Figure 26.5 **A:** The allergen (in this example ragweed represented by the yellow multipoint star) is bound to a substrate. **B:** The patient's sera or plasma is added and if the patient has IgE (green Y) specific to the tested allergen, it will bind to the allergen attached to the substrate. **C:** The bound sIgE is labled using anti-IgE (nonhuman IgG represented by the red Y). The non-bound IgG is washed away and the bound IgG is then measured by the label.

results than with skin testing. Like skin testing, the clinical signifcance of detectable, but low levels of IgE generates controversy. Also, sIgE testing, as with skin testing, is dependent on the quality of the extracted allergen used.

Another difference between sIgE and skin testing relates to immunotherapy. In skin testing, the same allergen extract is used for skin testing and immunotherapy. In sIge testing, the allergen used in testing and immunotherpy are likely from different manufactures. Especially for nonstandardized allergens, this change of manufacturer is potentially problematic.

Total IgE

IgE crosses the placenta minimally and increases with age in both atopic and nonatopic patients. IgE is scarce and comprises only 0.0005% of the total immunoglobulins of the average adult (57). Total IgE is elevated in atopic conditions such as atopic dermatitis, atopic asthma, allergic fungal sinusitis, and allergic rhinitis. Unfortunately, overlap of atopic and nonatopic total IgE levels limits clinical utility (57). Recently, it has been proposed that the ratio of sIgE to total IgE ratios may be clinically relevant. Higher sIgE/tIgE rations were associated with more severe allergic symptoms. Specifically, high sIgE/tIgE ratios were seen in food and venom allergy where systemic reactions are more common than most inhalant allergy (58). As two sIgE molecules must cross-link to the allergen on the surface of a mast cell to signal degranulation, it is theorized that cross-linking may be more likely as the IgE specific to that allergen constitutes a higher percentage of the total IgE.

INTERPRETING ALLERGY TESTS

Allergy tests should be obtained when a patient's history and physical exam suggest allergic disease and testing results will assist in symptom management. Allergens tested should be reasonable candidates to explain the patient's symptoms. If a patient complained of allergy symptoms only in spring season while living in southeastern United States, testing for ragweed or reindeer may not be sensible.

The degree of testing reactivity is observed by the wheal and flare size in SPTs and quantified in sIgE testing, MQTs, and IDT. It is tempting to correlate higher reactivity with symptom severity; however, multiple studies have not found a correlation (59).

In food allergy, comparisons between the sIgE level and the probability of a reaction on a double-blind

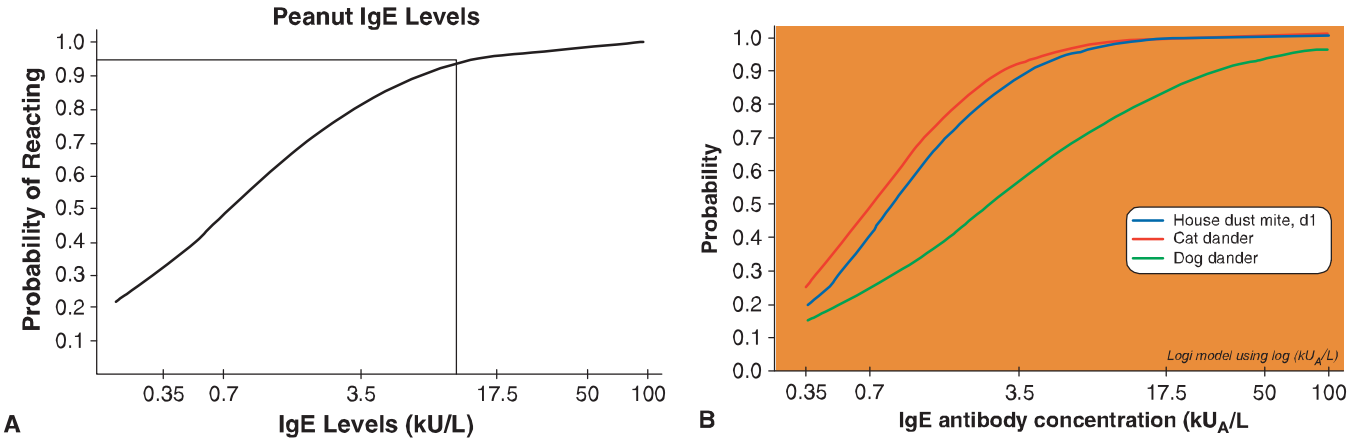


Figure 26.6 Probability of clinical allergy versus sIgE levels (kU/L) **A:** Probability of reacting on a peanut challenge plotted against IgE levels in a population suspected of peanut allergy. A negative IgE test of 0.35 kU/L does not exclude a positive reaction after peanut challenge. Reprinted from Elsevier Limited, License 2677361287765 from Table VI in Sampson H. Update of food allergy. *J Allergy Clin Immunol* 2004;113:805–819, with permission. **B:** Inhalant (Dust mite, Cat, and Dog) Probablity calculated from clinical evaluations plotted against sIgE levels for inhalant allergens. Reprinted from John Wiley and Sons, from Figure 6 in Ahlstedt S. Understanding the usefulness of specific IgE blood tests in allergy. *Clin Exp Allergy* 2002;32:11–16, with permission.

placebo-controlled food challenge do correlate. In food allergy, sIgE levels are more accurate when the sIgE is high. This has led to thresholds of sIgE levels that confer a greater than 95% confidence that a reaction would be seen on a food challenge. If a child with a history suspicious for peanut allergy has a sIgE greater than 15 IU/kL, they have a greater than 95% chance of having a positive reaction during a peanut challenge (6). It is difficult to generate the curves for inhalant allergy because the validity of challenge tests is not as well agreed upon. However, when sIgE levels for inhalant allergens were compared to diagnosis by an allergist based on SPT, history, and physical, a similar probability curve was observed (60) (Fig. 26.6).

HIGHLIGHTS

- Positive allergy tests are more common than clinically symptomatic allergic disease. Because of a significant false positive rate, allergic disease is primarily a clinical diagnosis based on history, physical exam, and knowledge of local allergens.
- Allergens have several properties that affect the symptoms they cause. A clinician's familiarity with the potency, size, abundance, distribution, and cross-reactivity of common allergens is useful in selecting allergens for testing.
- Allergy sensitivity may be assessed by SPT, sIgE tests, IDT, single ITs, and blended tests.
- Allergy testing is necessary to identify individuals who would benefit from allergen-specific immunotherapy. Allergy test results can also guide pharmacologic therapy and environmental control strategies.

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27 Diagnostic Imaging

Jenny K. Hoang *Adam M. Becker*

Computed tomography (CT) and magnetic resonance imaging (MRI) are indispensable radiologic modalities for the evaluation of the paranasal sinuses. These cross-sectional techniques allow for multiplanar visualization, and are superior to plain radiography for resolution of small anatomical structures and lesions. The aim of this chapter is to describe the role of imaging, and the imaging approach to common sinus pathologies.

INDICATIONS FOR SINUS CT AND MRI

Sinonasal imaging is performed for two main indications: inflammatory disease and mass. The choice between use of CT and MRI depends on the clinical scenario. The common indications for CT and MRI of the paranasal sinuses are reviewed in the American College of Radiology Appropriateness Criteria (1). A summary of the indications is found in Table 27.1.

CT has a role in both inflammatory disease and investigation of a mass because of its superior bone resolution. In the case of inflammatory disease, CT is most commonly performed for recurrent acute or chronic rhinosinusitis. There is little yield for imaging in acute and subacute rhinosinusitis since these are clinical diagnoses that are managed nonsurgically (1,2). Exceptions are if complications are suspected, or if the patient has comorbidities that predispose to complications, including diabetes, immune compromised state, or a past history of facial trauma or surgery (2).

MRI is not ideal for visualizing bony structures and generally has no role in uncomplicated inflammatory disease. The strength of MRI is its superior soft tissue resolution, which allows differentiation between three possible causes of sinus opacification on CT: a solid mass, inflammatory mucosa, and an obstructed fluid-filled sinus. Thus, the main roles of MRI are in characterizing suspected masses, staging malignancies, and surveillance of treated neoplasms. MRI is also superior to contrast-enhanced CT for evaluation of the orbit and brain in the setting of complicated rhinosinusitis or invasive fungal sinusitis.

IMAGING TECHNIQUES

Table 27.1 summarizes the physical principles, protocols, and potential risks of CT and MRI. It is important for the clinician to be familiar with these basic concepts and the terminology used to describe imaging findings.

CT Terminology

The shades of grey on CT are described with the terms "density" or "attenuation." High density indicates a "whiter/brighter" appearance on CT, as seen with proteinaceous secretions, allergic mucin, and calcification. The wide range of density values detected by CT (spanning >2,000 Hounsfield units) cannot be displayed on a single set of images; therefore different "CT windows" are used to display a single scan (Fig. 27.1). In the era of electronic picture archiving, CT windows can be changed easily with shortcut buttons. For sinus imaging, "bone windows" are used to display the fine detail of osseous abnormalities or calcifications within a mass. "Soft tissue windows" are also routinely reviewed and have higher contrast to help demonstrate the narrow density differences between soft tissue and fluid.

MRI Terminology

The shades of grey on MRI are described with the term "intensity." The combination of signal intensities on different sequences (e.g., T1 and T2) and the use of intravenous contrast help to infer the tissue properties (Fig. 27.2). For example, simple fluid is hypointense (darker) on T1 sequences, hyperintense (white/brighter) on T2 sequences and does not enhance.

TABLE 27.1 COMPARISON OF CT AND MRI PRINCIPLES, PROTOCOLS, INDICATIONS AND POTENTIAL RISKS

	CT	MRI
Physics Principles	• An x-ray source rotating around the patient emits highly collimated x-ray beams at various angles around the patient. • Detectors opposite the x-ray source register the x-ray beam after it is partly absorbed by the patient. • The x-ray attenuations received by the detectors are converted into images.	• Spinning protons of hydrogen atoms in the body are aligned by a high-strength magnetic field. • A radiofrequency wave is introduced to excite the protons. When the radiofrequency wave is turned off, spinning protons relax and emit a signal. Different tissues have different signals and these signals are converted into images.
Protocol	• Data acquisition in the axial plane. • Multiplanar reconstruction of axial images into sagittal and coronal planes. In many centers this has eliminated the need for direct coronal imaging with the patient in prone position. • No intravenous contrast unless intraorbital or intracranial complications.	• T1-, T2- and postcontrast fat-saturated T1-weighted images in the axial and coronal planes.
Indications	• Acute and subacute sinusitis in immunodeficient patient. • Acute and subacute sinusitis with associated orbital complications and/or neurologic deficit. • Recurrent acute or chronic sinusitis (possible surgical candidate). • Sinonasal polyposis. • Sinonasal obstruction, suspected mass lesion.	MRI and CT are complementary for the following indications: • Acute and subacute sinusitis with associated orbital complications and/or neurologic deficit. • Sinonasal obstruction, suspected mass lesion.
Potential risks	• Uses ionizing radiation. Minimizing use of radiation exposure is especially important in young adults and children. • Iodinated contrast can worsen renal impairment, cause lactic acidosis in diabetic patients on Metformin, and has a very small risk of anaphylactic reaction.	• Implantable devices such as cardiac pacemakers, cochlear implants, metallic intraocular foreign bodies can be preclude MRI scanning. • Use of Gadolinium contrast in patients with renal failure is associated with a risk of nephrogenic sclerosing fibrosis.

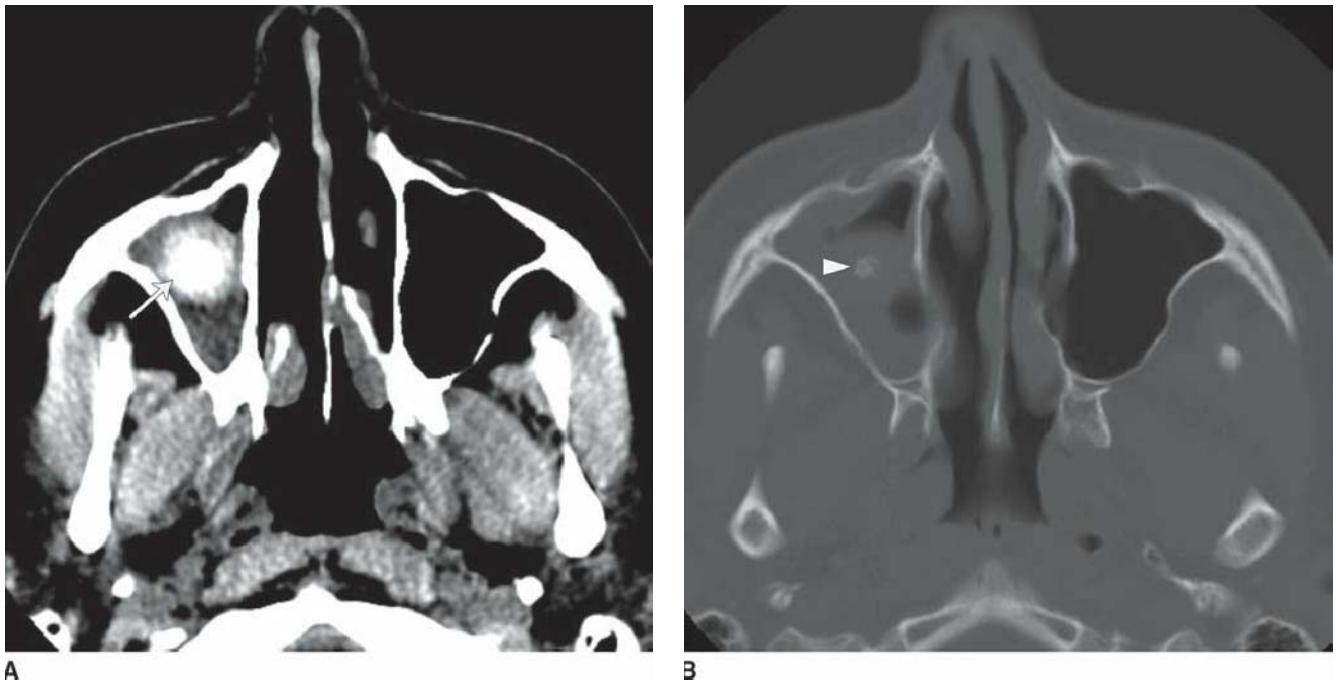


Figure 27.1 Fungus ball in soft tissue and bone windows. **A:** Axial CT image with soft tissue windows shows a right maxillary sinus high-density rounded mass (*arrow*). **B:** Axial CT image with bone windows shows central calcification (*arrowhead*) within the mass. Note that the fungus ball and mucosa have different density appearances on soft tissue window, which cannot be appreciated on bone windows. On bone windows, the calcifications and bony structures are more conspicuous.

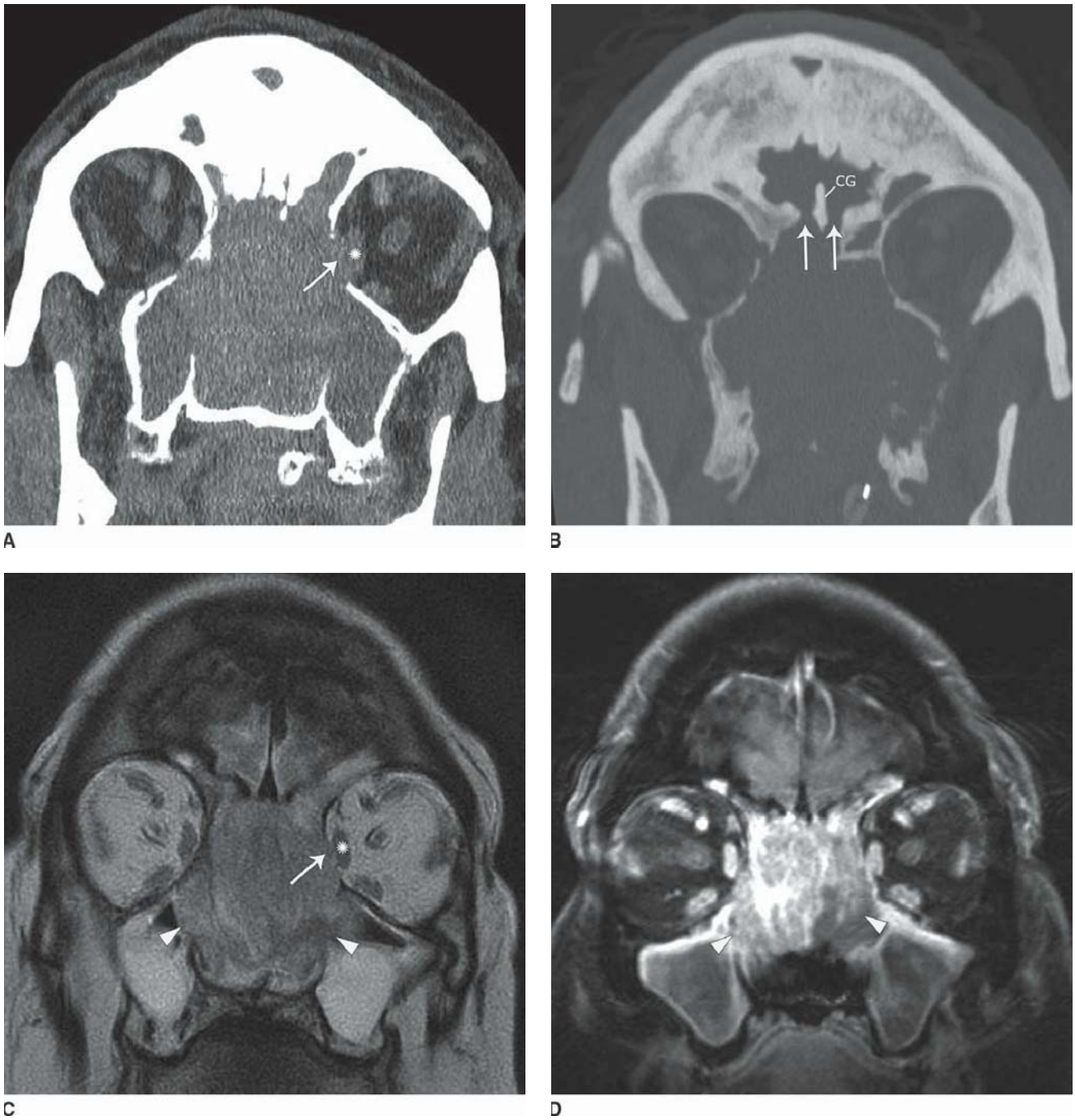


Figure 27.2 Sinonasal carcinoma with invasion of anterior cranial fossa and bony orbit. Differences between CT and MRI. **A:** Coronal CT image shows complete opacification of the bilateral nasal cavity and paranasal sinuses. There is bony destruction at the medial wall of the left orbit (*arrow*) with loss of fat plane around the medial rectus muscle (*asterisk*). **B:** Coronal CT image shows bony destruction at the cribriform plate (*arrows*). CG, crista galli. **C:** Coronal T2-weighted MRI image more clearly depicts the difference between isointense tumor mass (*arrowheads*) filling the nasal cavity and hyperintense inflammatory fluid in the maxillary sinuses. Tumor bows into the orbit (*arrow*), but a smooth contour suggesting that the periorbita is intact. The medial rectus muscle (*asterisk*) has normal signal and size. There is no intracranial mass despite anterior skull base bony destruction. **D:** Coronal enhanced T1-weighted MRI image shows enhancing tumor in the nasal cavity (*arrowheads*) extending into the frontal sinuses. Note that MRI is better than CT in differentiating between tumor and fluid-filled maxillary sinuses, which are T2 hyperintense and nonenhancing.

Other sequences, such those as with fat-saturation or suppression, can help to confirm fat content and make enhancement more conspicuous when the high signal of fat is nulled.

IMAGING APPROACH

Rhinosinusitis

CT is the principal modality used in imaging rhinosinusitis. A systematic approach to interpretation includes evaluation for the following: (a) signs of inflammatory sinus disease, (b) underlying mass or the presence of complications, and (c) anatomical and critical variants that may make future surgery more difficult or hazardous (3).

Imaging Findings of Rhinosinusitis and Sinonasal Polyposis

A mild degree of mucosal thickening is a common, but nonspecific finding on sinus CT. It can be found in acute or chronic rhinosinusitis, but may also be seen in asymptomatic patients. Nasoethmoidal mucosal thickening can also be part of the physiologic nasal cycle (4). Therefore, the presence of mucosal thickening should be interpreted in context with the clinical history and physical examination.

More specific signs of *acute rhinosinusitis* include dependent air–fluid levels and bubbly or strandy secretions (Fig. 27.3). CT cannot differentiate between bacterial and viral sinusitis. An uncommon, but possibly underdiagnosed

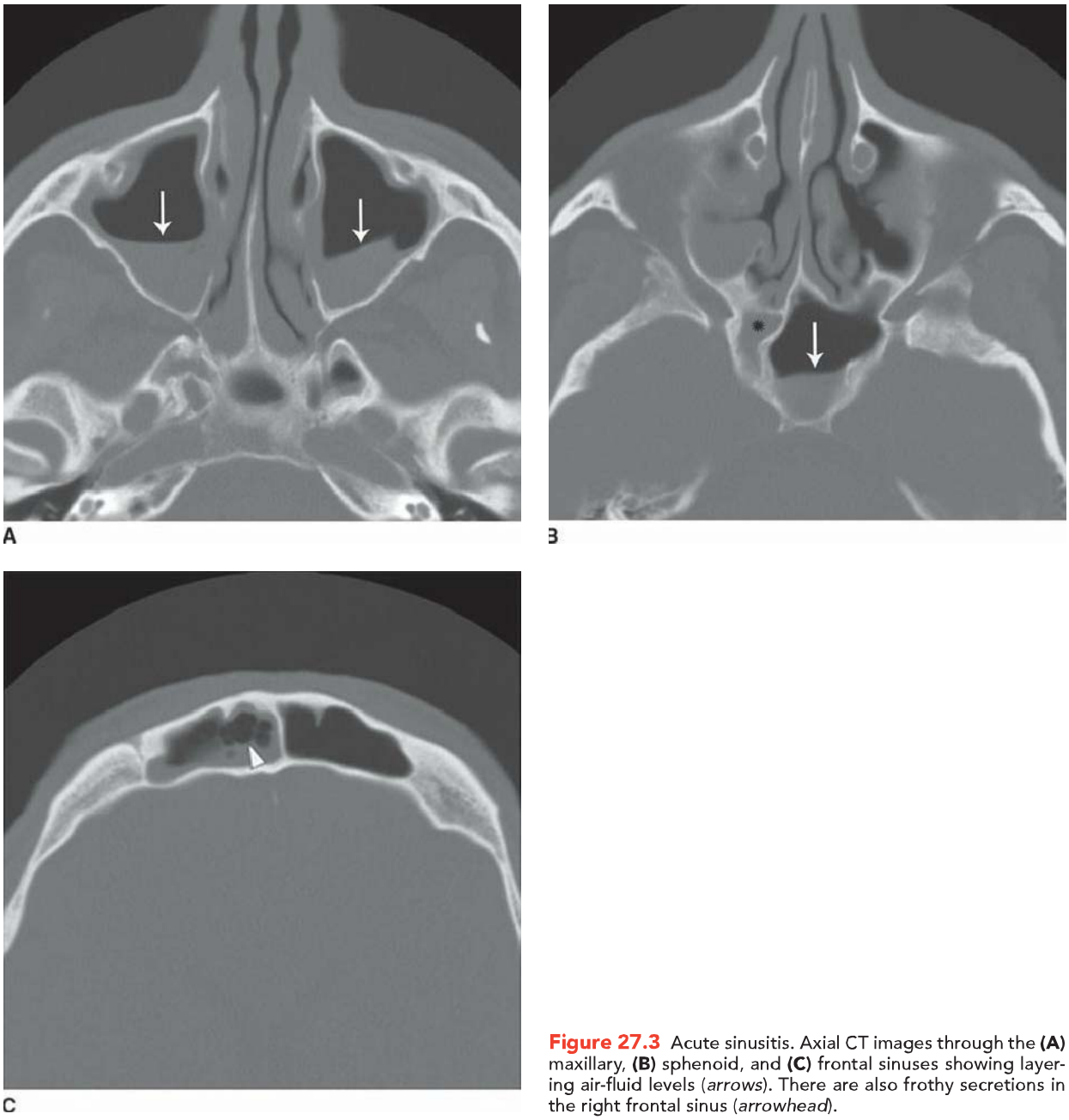


Figure 27.3 Acute sinusitis. Axial CT images through the **(A)** maxillary, **(B)** sphenoid, and **(C)** frontal sinuses showing layering air-fluid levels (*arrows*). There are also frothy secretions in the right frontal sinus (*arrowhead*).



Figure 27.4 Odontogenic maxillary sinusitis. Coronal CT image shows a left molar periapical abscess (*arrowheads*) contiguous with the left maxillary sinus in keeping with an oroantral fistula. There is mucosal thickening and possibly fluid in the left maxillary sinus. Other paranasal sinuses are normal.

cause of acute maxillary sinusitis is odontogenic infection. This should be suspected if the CT findings of sinusitis are severe in the presence of an oroantral fistula, periodontal lucency (abscess), or a tooth root projecting into the maxillary sinus (Fig. 27.4) (5). The typical finding in *chronic rhinosinusitis* is significant mucosal thickening or opacification in a nonexpanded sinus, often with ostial obstruction. A characteristic, but less common sign of chronic rhinosinusitis is sclerosis and thickening of bony sinus walls, particularly seen in the sphenoid and maxillary sinuses (Fig. 27.5). Chronic rhinosinusitis may also be associated with high-density opacification that often represents viscous or desiccated secretions, but can also be a sign of coexisting allergic fungal rhinosinusitis or fungus ball.

In correlating clinical symptoms with the pattern of disease on imaging, the sites of drainage pathway obstruction are of particular interest when planning endoscopic sinus surgery (ESS). There are three paranasal drainage pathways on each side that need to be evaluated for obstruction and the cause of obstruction: the ostiomeatal complex (OMC), frontal recess, and sphenoethmoidal recess (SER). The coronal plane is most similar to the endoscopic view and enables excellent visualization of the OMC (Fig. 27.6). The SER is best viewed in the axial and sagittal plane, and the frontal recess is best evaluated with a combination of coronal and sagittal imaging (Fig. 27.6).

Sinonasal polyposis is characterized by low-density polypoid lesions that fill the bilateral nasal cavity and the sinuses (Fig. 27.7). The polyps can obstruct the drainage pathways at multiple sites, resulting in retained secretions and opacification of sinuses. In neglected cases, they can exert pressure on bony structures leading to expansion of the sinonasal cavity and bony remodeling rather than focal bony destruction.

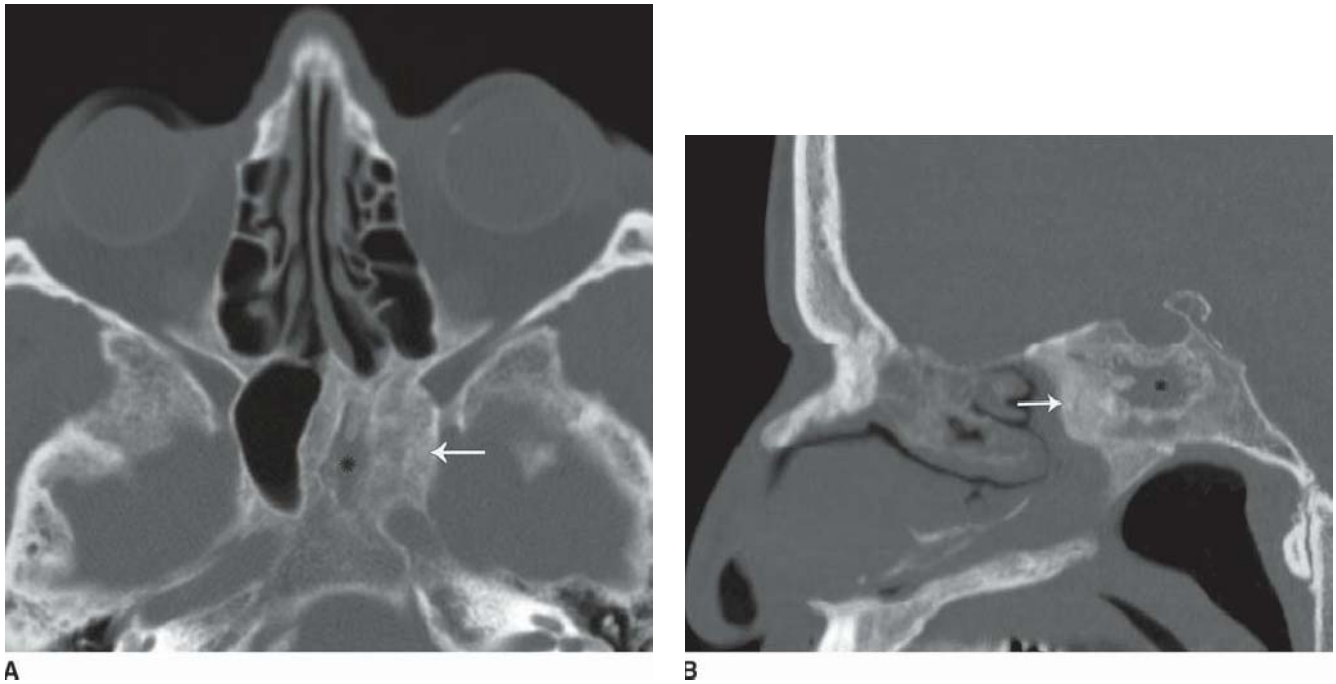


Figure 27.5 Chronic sinusitis. **A:** Axial and **B:** sagittal CT images show opacification of the left sphenoid sinus (asterisks) with bony sclerosis and wall thickening (*arrows*).

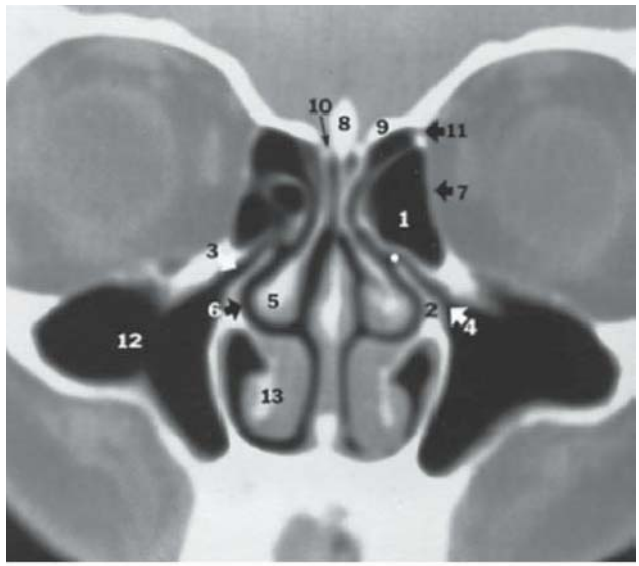
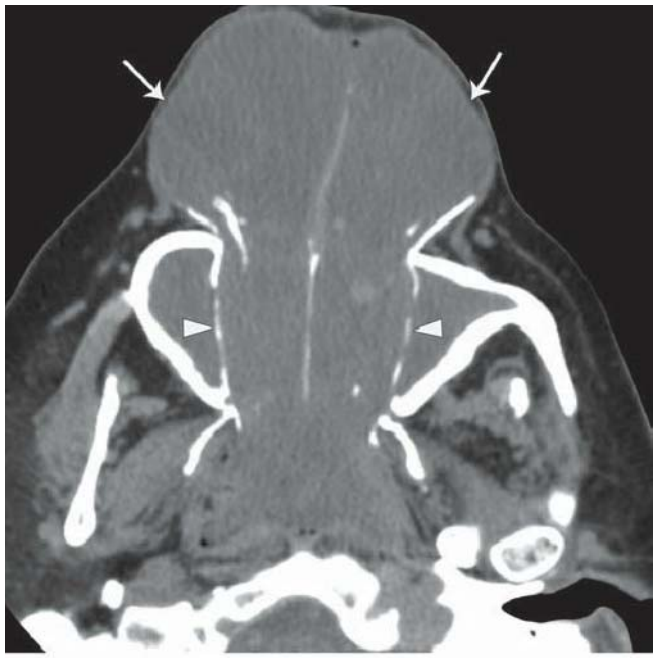
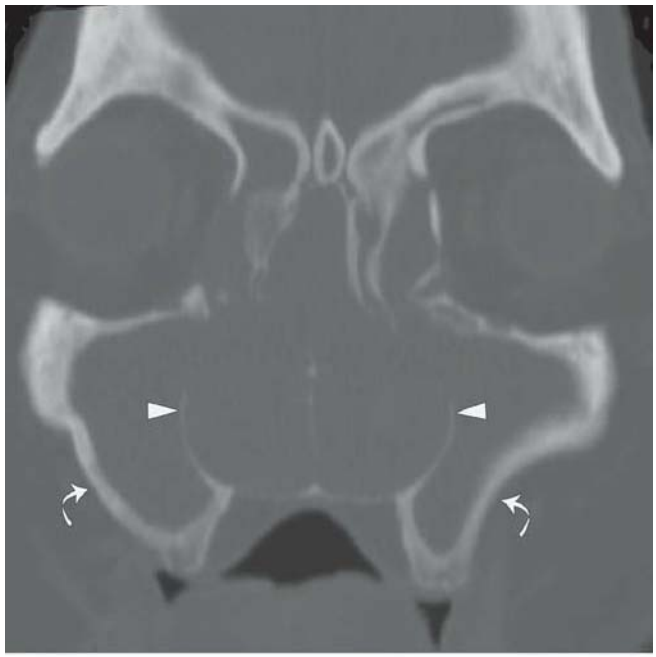


Figure 27.6 Normal paranasal sinus anatomy. **A:** Coronal CT image shows the normal OMC. Components of the ostiomeatal complex (OMC) are as follows: *1*, bulla ethmoidalis; *2*, uncinate plate; *3*, infundibulum; *4*, inner maxillary sinus ostium; *5*, middle turbinate; *6*, middle nasal meatus; *, hiatus semilunaris. The following are other important landmarks on this image: *7*, lamina papyracea; *8*, crista galli; *9*, fovea ethmoidalis; *10*, medial lamella; *11*, anterior ethmoidal foramen; *12*, maxillary antrum; *13*, inferior turbinate. **B:** Sagittal CT image shows the frontal recess. The frontal ostium (*arrows*) produces the waist of the classic hourglass configuration. Inferiorly, a large agger nasi cell bulges posteriorly to severely narrow and distort the recess. FS, frontal sinus; FR, frontal recess; AN, agger nasi; L, lacrimal bone; CB, concha bullosa; m, middle nasal meatus. **C:** Sagittal CT image shows the sphenoethmoidal recess (SER) (*arrowheads*). S, sphenoid sinus; PE, posterior ethmoidal sinus; A, anterior ethmoidal sinus; *arrowheads*, SER; *1*, inferior turbinate; *2*, middle turbinate; *3*, superior turbinate; *arrows*, basal lamella.



A



B



C

Figure 27.7 Sinonasal polyposis. **A:** Axial CT image shows complete opacification of the nasal cavity with soft tissue density masses projecting through the nostrils (*arrows*). There is bony thinning of the walls of the nasal cavity (*arrowheads*). **B:** Coronal CT image show nasal cavity opacification with thinning of the walls of the nasal cavity (*arrowheads*). There is also opacification of the maxillary sinuses with bony sclerosis and thickening (*curved arrows*). **C:** Photograph of polyps causing cosmetic deformity of the nose.

Other Inflammatory Sinus Lesions

Mucoceles are cysts lined by pseudostratified ciliated columnar epithelium (Fig. 27.8) and are most frequently observed in the frontal sinus followed by the ethmoidal, maxillary, and sphenoid sinuses. They are believed to form because of chronic obstruction of a sinus ostium, leading to accumulation of fluid within the sinus cavity and slow asymptomatic expansion of the sinus. Imaging typically demonstrates an enlarged completely opacified sinus with rounded contours and thinning of sinus walls. The density of the opacified sinus is usually low, representing fluid, but the sinus density can also be high as mucus becomes inspissated. Large mucoceles can lead to cosmetic deformities such as orbital proptosis and obstruct adjacent drainage pathways.

The less common complication of a chronically obstructed sinus is involution of the sinus, known as *atelectatic sinus* or silent sinus syndrome (Fig. 27.9). This forms because of negative intrasinus pressure and is most commonly seen in the maxillary sinus. The imaging findings are thinner sinus walls that are bowed or pulled inward to the center of the sinus. There may be cosmetic deformity or enophthalmos as the orbital floor bows down.

Retention cysts are common incidental findings in the maxillary and sphenoid sinuses. They are submucosal

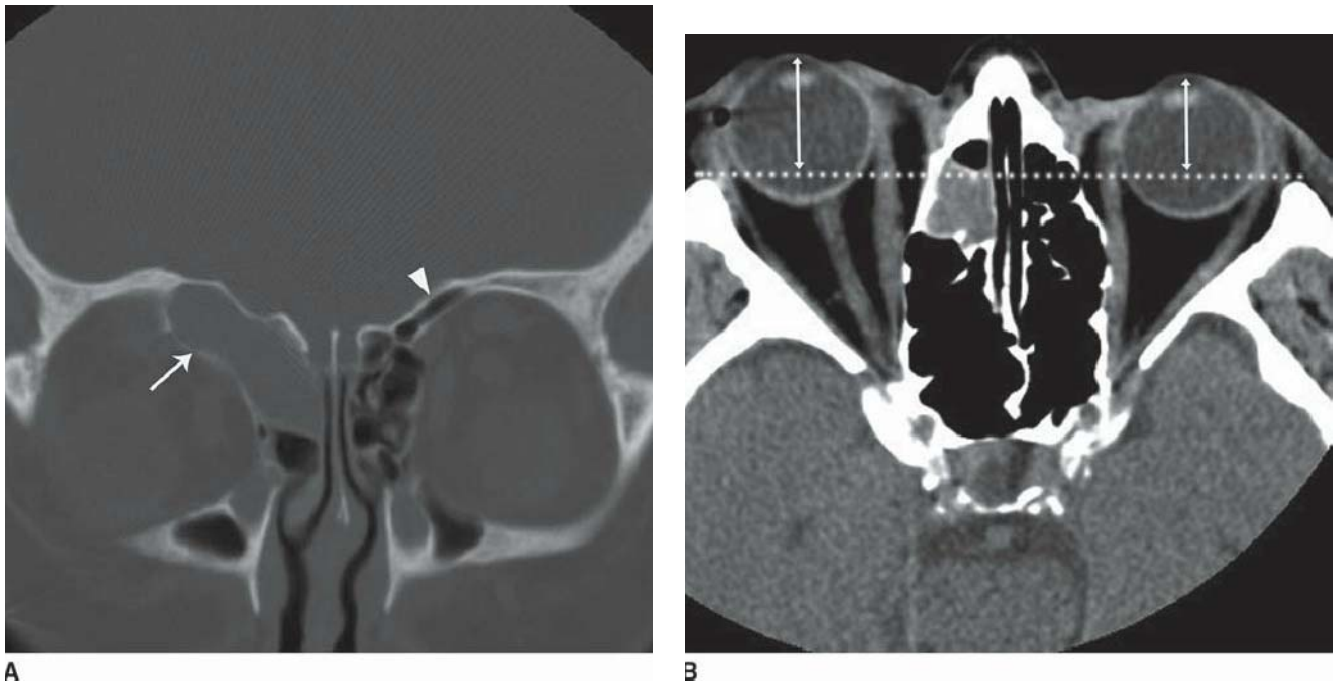


Figure 27.8 Frontal sinus mucocele with proptosis. **A:** Coronal CT image shows rounded expansion of the right frontal sinus with bony thinning (*arrow*) compared to the normal left frontal sinus (*arrowhead*). **B:** Axial CT image shows right proptosis due to mass effect from the mucocele. The dotted line is the interzygomatic line and allows comparison of the position of the right and left globe (*double arrowed lines*).

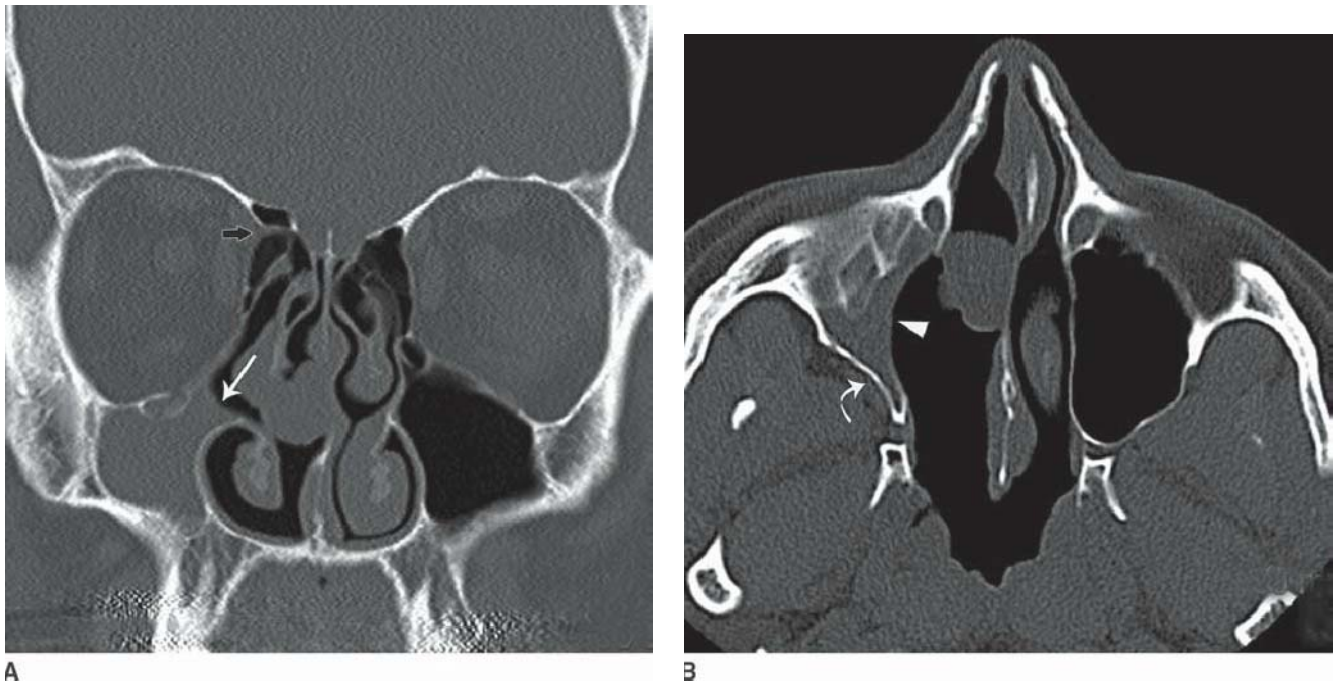


Figure 27.9 Atelectatic sinus. **A:** Coronal CT image shows a smaller right maxillary sinus. There is lateral rotation of the uncinate process (*white arrow*) that widens the space between the uncinate process and the middle turbinate. Note also the normal "nipple sign" indicating the anterior ethmoidal foramen (*black arrow*). **B:** Axial CT image shows smaller right maxillary sinus with inward bowing of the posterior (*curved arrow*) and medial walls (*arrowhead*) of the maxillary sinus. The atelectatic sinus predisposed the patient to complications during endoscopic sinus surgery (ESS).



C

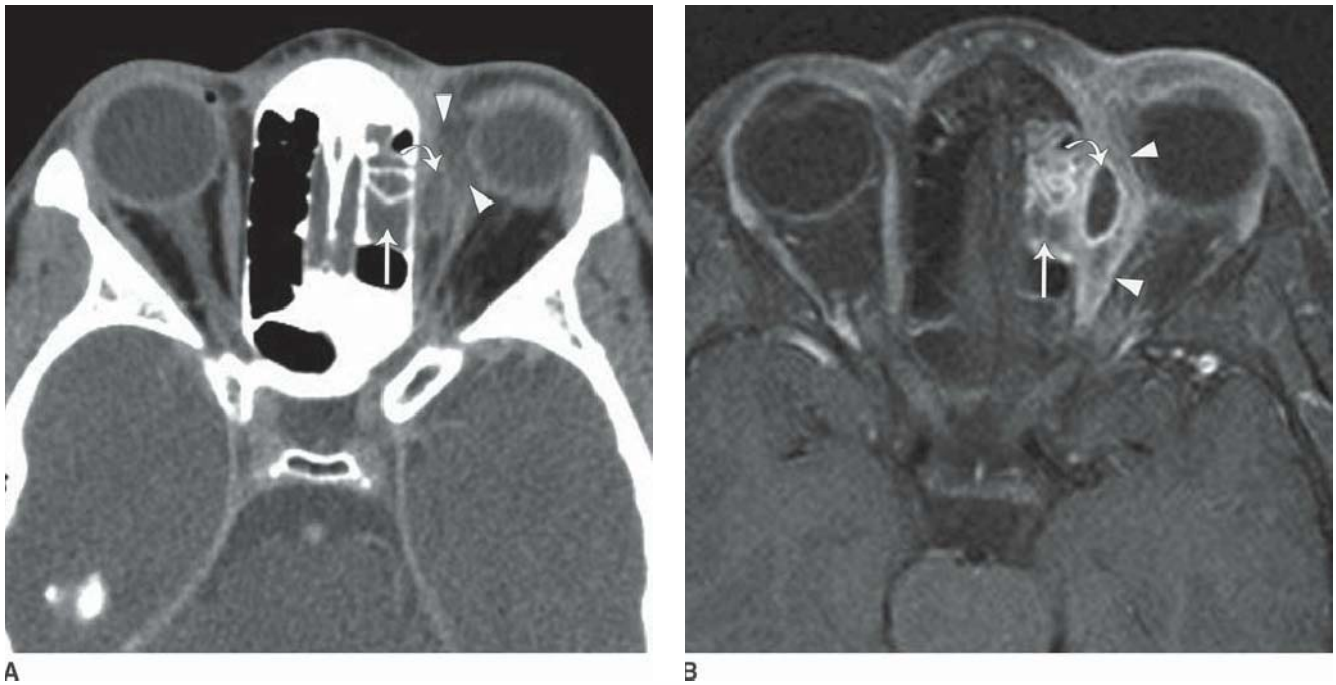
Figure 27.9 *(Continued)* **C:** Postoperative coronal CT image of patient in A and B demonstrating the ESS complication of a fracture to the floor of the orbit (*arrowhead*) and injury to the inferior rectus muscle with enlargement and fat stranding (*arrow*). Courtesy of MT Bhatti, MD, Duke University Medical Center.

collections of fluid (serous retention cysts) or collections from an obstructed seromucinous gland (mucous retention cysts). They most frequently occur in the maxillary antrum and appear as smooth, outwardly convex soft tissue density masses. On CT, it is difficult to differentiate a cyst from a polyp since both have soft tissue density. On MRI, a cyst does not enhance except for its mucosal surface. A polyp represents hyperplastic mucosa and will solidly enhance.

Evaluating Imaging for Complications and Obstructive Masses

Complications of sinusitis include spread of infection to the orbits, bone, and brain. CT or MRI can readily demonstrate an orbital subperiosteal abscess (Fig. 27.10) and deep extent of infection when there is clinically apparent periorbital cellulitis. Infection of the frontal bone can lead to a subperiosteal abscess known as *Pott puffy tumor* (6). If this is present, it is important to evaluate for intracranial complications (Fig. 27.11), which can occur with or without bony changes. MRI is more sensitive than CT for intracranial complications such as meningitis, subdural or epidural empyema (Fig. 27.12), brain abscess, and cavernous sinus thrombosis.

The most common cause of sinus drainage pathway obstruction is mucosal thickening, but occasionally the cause for obstruction may be due to anatomic variations and rarely there is an obstructing mass. The best sign of an underlying mass on CT is a soft tissue opacity with bony destruction (Fig. 27.13). In such cases, direct endoscopy and biopsy with or without preoperative MRI is the key to making a diagnosis. Prior to biopsy, it is important to consider whether the mass could be due to herniation of



A B

Figure 27.10 Orbital subperiosteal abscess complicating ethmoid sinusitis. **A:** Axial-enhanced CT image shows left ethmoid sinus opacification from acute sinusitis (*arrow*) and left orbit extraconal fat stranding (*arrowheads*). There is a small low attenuation collection (*curved arrow*) that is better seen on MRI. **B:** Axial-enhanced fat-saturated T1-weighted image shows left ethmoid sinus mucosal enhancement from acute sinusitis (*arrow*) and left orbit extraconal fat enhancement (*arrowheads*). There is a small ring-enhancing collection (*curved arrow*) representing an abscess.

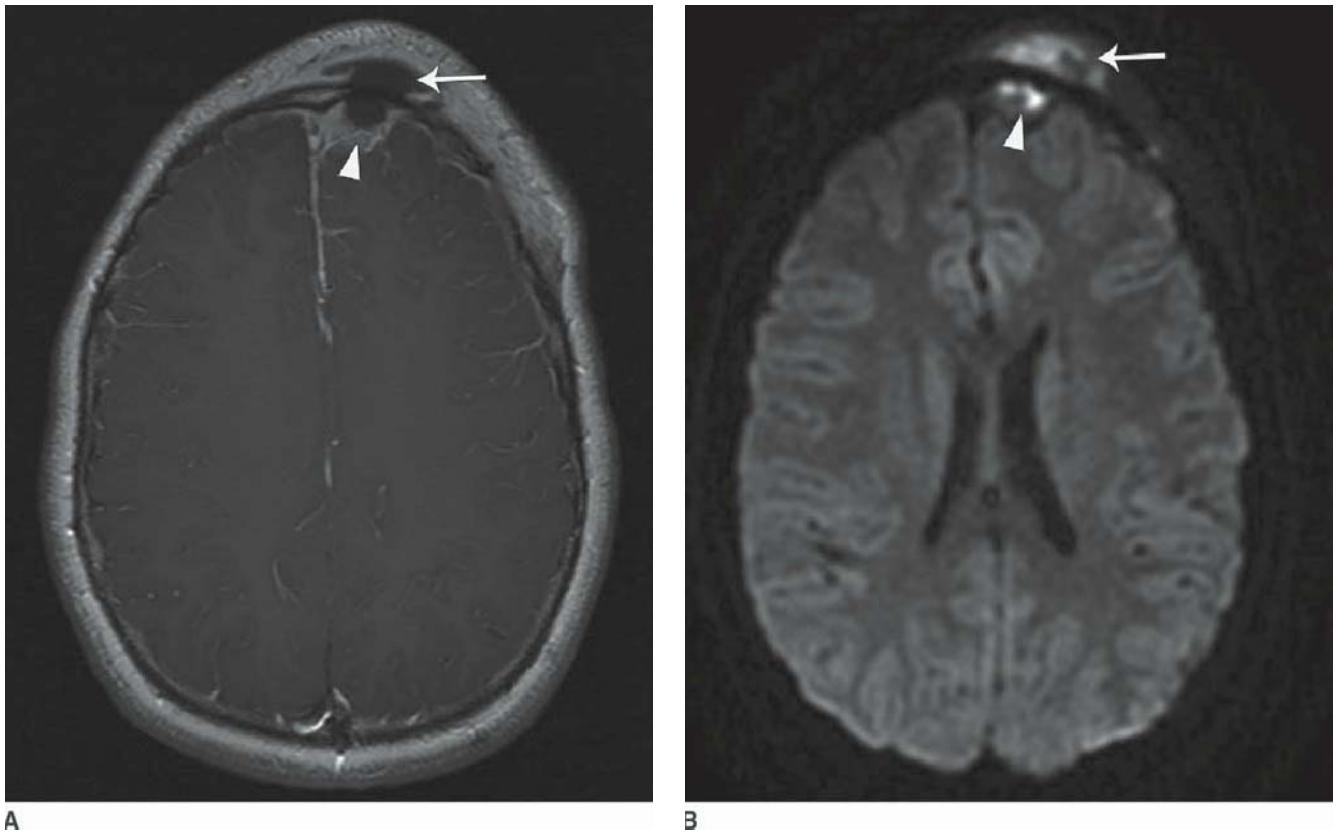


Figure 27.11 Pott puffy tumor with epidural empyema. **A:** Axial-enhanced T1-weighted image shows a hypointense collection overlying the left frontal bone (*arrow*) that is continuous with a rim enhancing extraaxial (outside brain parenchyma) collection overlying the left frontal lobe (*arrowhead*). **B:** Axial diffusion-weighted image shows bright signal in the collections indicating restricted diffusion. This supports the diagnosis of abscess.

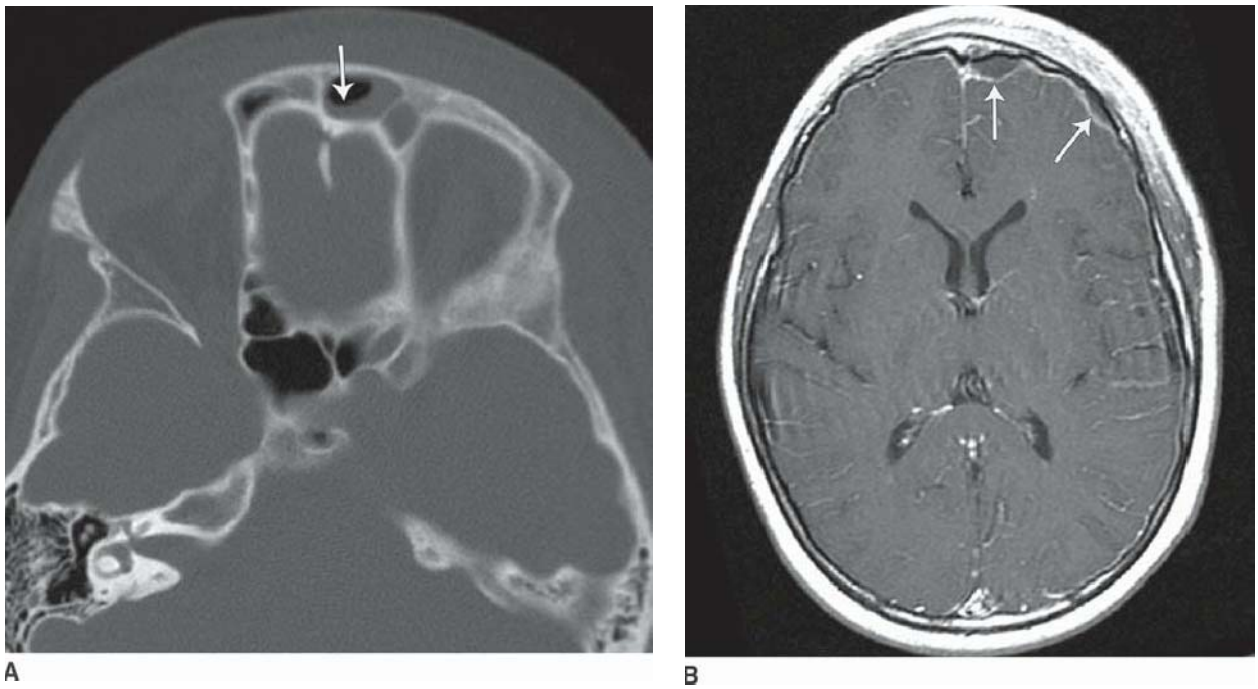


Figure 27.12 Subdural empyema complicating frontal sinusitis. **A:** Axial CT image shows left frontal sinus opacification with an air-fluid level (*arrow*) suggestive of acute sinusitis. **B:** Axial-enhanced T1-weighted MRI image of the brain shows a rim-enhancing crescentic extraaxial collection overlying the left frontal lobe consistent with a subdural empyema secondary to acute sinusitis.

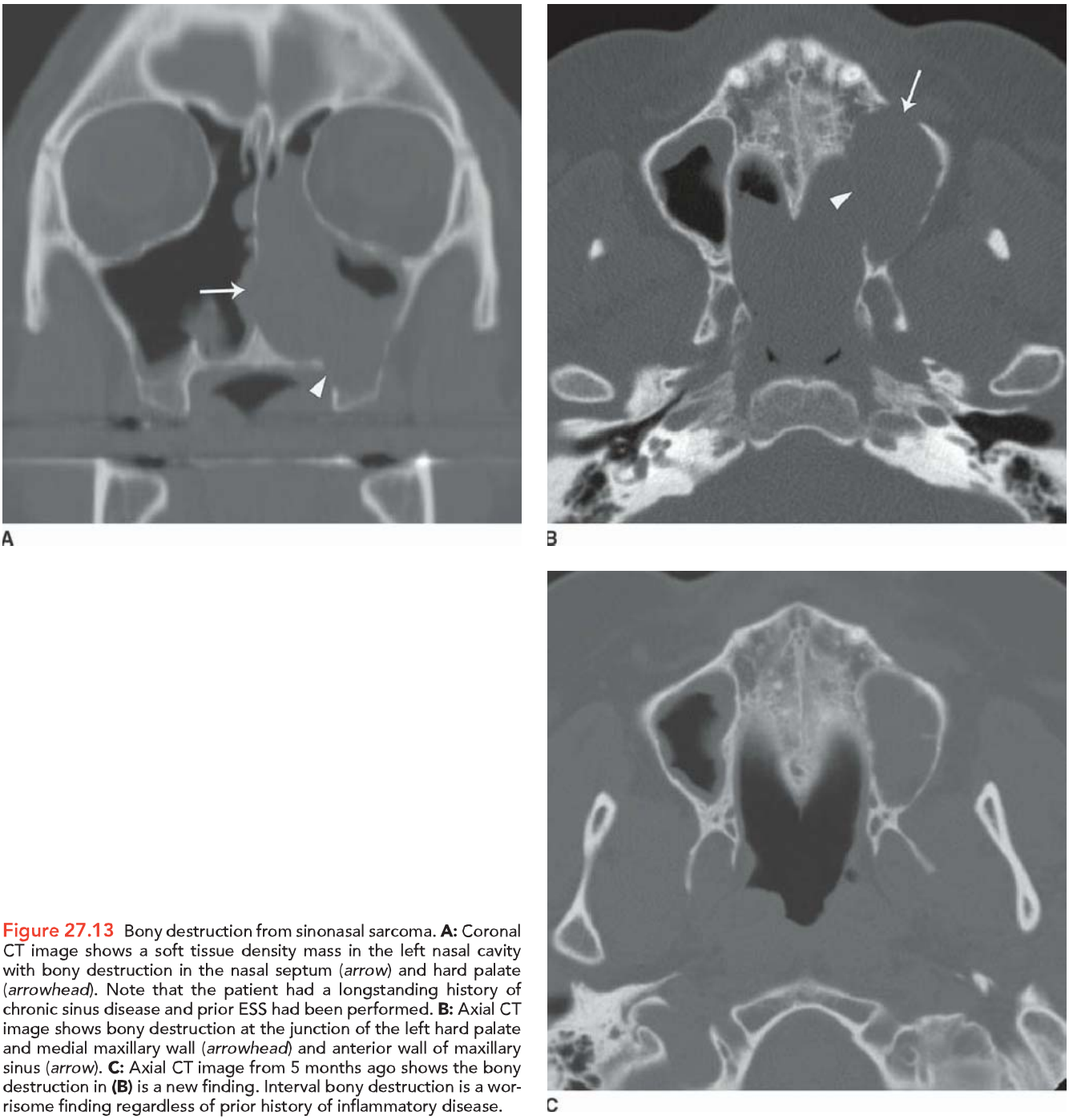


Figure 27.13 Bony destruction from sinonasal sarcoma. **A:** Coronal CT image shows a soft tissue density mass in the left nasal cavity with bony destruction in the nasal septum (*arrow*) and hard palate (*arrowhead*). Note that the patient had a longstanding history of chronic sinus disease and prior ESS had been performed. **B:** Axial CT image shows bony destruction at the junction of the left hard palate and medial maxillary wall (*arrowhead*) and anterior wall of maxillary sinus (*arrow*). **C:** Axial CT image from 5 months ago shows the bony destruction in **(B)** is a new finding. Interval bony destruction is a worrisome finding regardless of prior history of inflammatory disease.

intracranial contents. Meningoceles and encephaloceles appear on CT as a soft tissue mass abutting the skull base with focal bony dehiscence. The diagnosis is best confirmed with MRI. Meningoceles show T2 hyperintensity due to the presence of cerebrospinal fluid (CSF). Encephaloceles are characterized by a soft tissue mass with signal isointense to gray matter and contiguity to intracranial parenchyma (Fig. 27.14).

Finally, the sinus CT provides views of the brain, nasopharynx, and orbit which should be reviewed for incidental but significant findings or alternate nonsinus pathologies causing symptoms, such as mass or aneurysm.

Important Variants to Consider for Endoscopic Sinus Surgery

An important role of sinus CT prior to ESS is to detect anatomical variants that predispose to recurrent disease and affect operative technique, and critical variants that make surgery hazardous. The incidence of major ESS complications is 0.4% to 1.3% (7–9). Major complications include damage to the optic nerve, extraocular muscles, CSF leak,

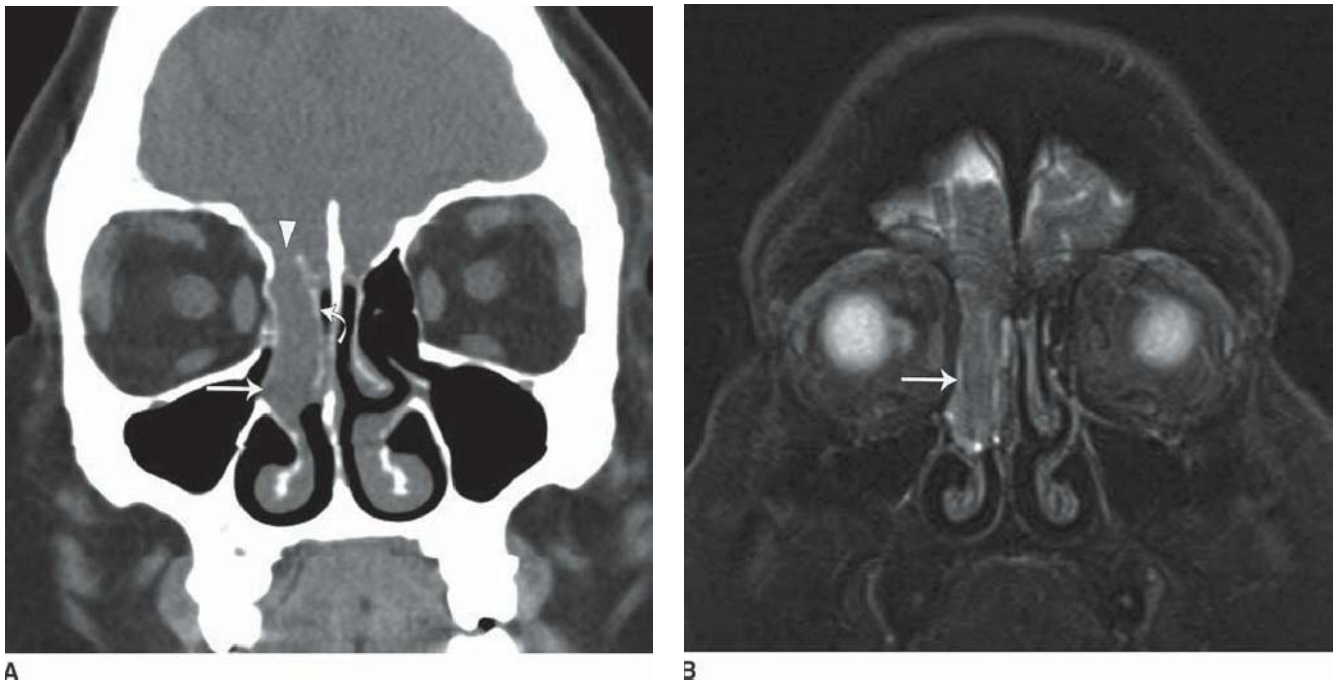


Figure 27.14 Encephalocele mimics a mass. **A:** Coronal CT image shows a soft tissue density mass in the right nasal cavity (*arrow*). There is a bony defect in the fovea ethmoidalis of the right cribriform plate (*arrowhead*) with widening of the space between the vertical lamella (*curved arrow*) and the roof of the orbit. **B:** Coronal T2-weighted MRI image shows the mass to be continuous with the right frontal lobe and to have the same signal characteristics.

meningitis, carotid vascular injury, orbital hematoma, and nasolacrimal duct stenosis.

Anatomical Variants

Nasal septal deflections and spurs are best visualized in the coronal plane (Fig. 27.15). Noting the direction of septal deviation is helpful for surgical planning as the patient may require septoplasty to facilitate ESS. Similarly, nasal turbinate reduction could be performed for an obstructing edematous inferior nasal turbinate. Another important variant is a laterally deviated uncinate process, with or without atelectatic sinus, which can increase the risk of medial orbital wall injury during uncinectomy (Fig. 27.9, see above text on *Other Inflammatory Sinus Lesions*).

Middle turbinate variations include paradoxical middle turbinates and concha bullosa. Paradoxical middle turbinates occur when the normal medial convex curvature is reversed. In some cases, this can lead to narrowing of the middle meatus and may contribute to the development of chronic rhinosinusitis. Concha bullosa occurs when there is pneumatization of the middle turbinate (Fig. 27.15). This may result in a very large turbinate that can compress the uncinate process laterally. The role of the concha bullosa in sinus disease is controversial when viewed across studies, with its size being more important than its mere presence with regard to sinus disease (10).

The Haller cell, or infraorbital ethmoid air cell, represents the most common variation in the maxillary sinus

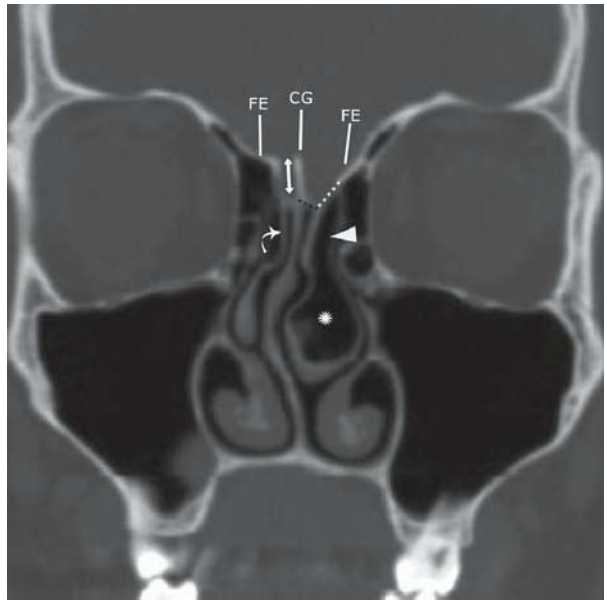


Figure 27.15 Anatomical and critical variants important for ESS. Coronal CT image shows anatomical variants of concha bullosa (*asterisk*) and concha lamella (*arrowhead*). The nasal septum is deviated to the right. There is a critical variant of asymmetry in the olfactory fossa, deeper on the right. The olfactory fossa (*double-headed arrow*) is formed by crista galli (CG) in midline, medial lamella (*black dotted line*) in the inferior aspect, and lateral lamella (*white dotted line*) in the lateral aspect. A deep olfactory fossa with long lateral lamellae as shown on the right can be complicated by fractures during ESS. Medial and lateral lamellae are separated by vertical lamella (*curved arrow*) of the middle turbinate. Fovea ethmoidalis (FE) is continuation of superior orbital roof to cribriform plate.

region. This is an ethmoidal cell that pneumatizes along the medial roof of the maxillary sinus and inferomedial portion of the lamina papyracea. It is present in up to 34% of patients and frequently encroaches on the infundibulum (10).

Anatomical variants of the frontal recess are best appreciated on coronal and sagittal imaging. The frontal recess can be narrowed by enlargement of the bordering agger nasi cell (anteriorly) (Fig. 27.6) and ethmoid bulla (posteriorly), or the presence of variant anterior ethmoid air cells in the frontal recess. Failure to resect these cells during frontal sinus endoscopic surgery can lead to recurrent disease (11).

Critical Variants

The lateral lamella is the thinnest part of the cribriform plate and at risk of fracture during ESS, especially when the olfactory fossae are deep or asymmetrical (Fig. 27.15). Fractures in the cribriform plate can result in defects in the bone and dura, leading to early complications of ascending meningitis and late complications of intracranial hypotension from CSF leaks, meningoceles, and meningoencephaloceles. In a classic study, Keros proposed a classification based upon the position of the cribriform plate in relation to the ethmoid roof. In type I olfactory fossa, the olfactory sulcus is 1 to 3 mm deep, and the corresponding lateral lamella is short. In type II olfactory fossa, the olfactory sulcus is 3 to 7 mm deep, and the corresponding lateral lamella forms a considerable portion of the medial ethmoid wall. In type III olfactory fossa, the olfactory sulcus is 7 to 16 mm deep and the ethmoid roof lies at a significant level above the cribriform plate.

Unrecognized congenital or posttraumatic dehiscence of the lamina papyracea may predispose to orbital injury (Fig. 27.16). The most common injuries are medial and inferior rectus muscle laceration that can lead to focal or global scarring and gaze dysfunction (12).

The anterior ethmoidal artery travels through a bony canal called the anterior ethmoidal foramen in the superior lamina papyracea and serves as a surgical landmark. Anatomic studies have shown that the anterior ethmoid artery is dehiscent in the nasal cavity between 16% and 30% of cases (13,14). When the artery courses below the skull base through the ethmoid air cells it can be inadvertently injured. Retraction of a severed artery into the orbit may produce an orbital hematoma, requiring urgent decompression. The anterior ethmoidal foramen is best visualized in the coronal section by identifying the so-called nipple sign, representing the site where the artery exits the orbit and traverses the skull base (Figs. 27.6 and 27.9).

Focal bony dehiscence of the sphenoid sinus in areas overlying the optic nerve, internal carotid artery, and the second (maxillary) division of the trigeminal nerve can result in injury to these neural and vascular structures. The optic nerve and internal carotid artery may also be at risk when there are Onodi cells, which occur when a posterior ethmoid air cell pneumatizes over the top of the sphenoid.

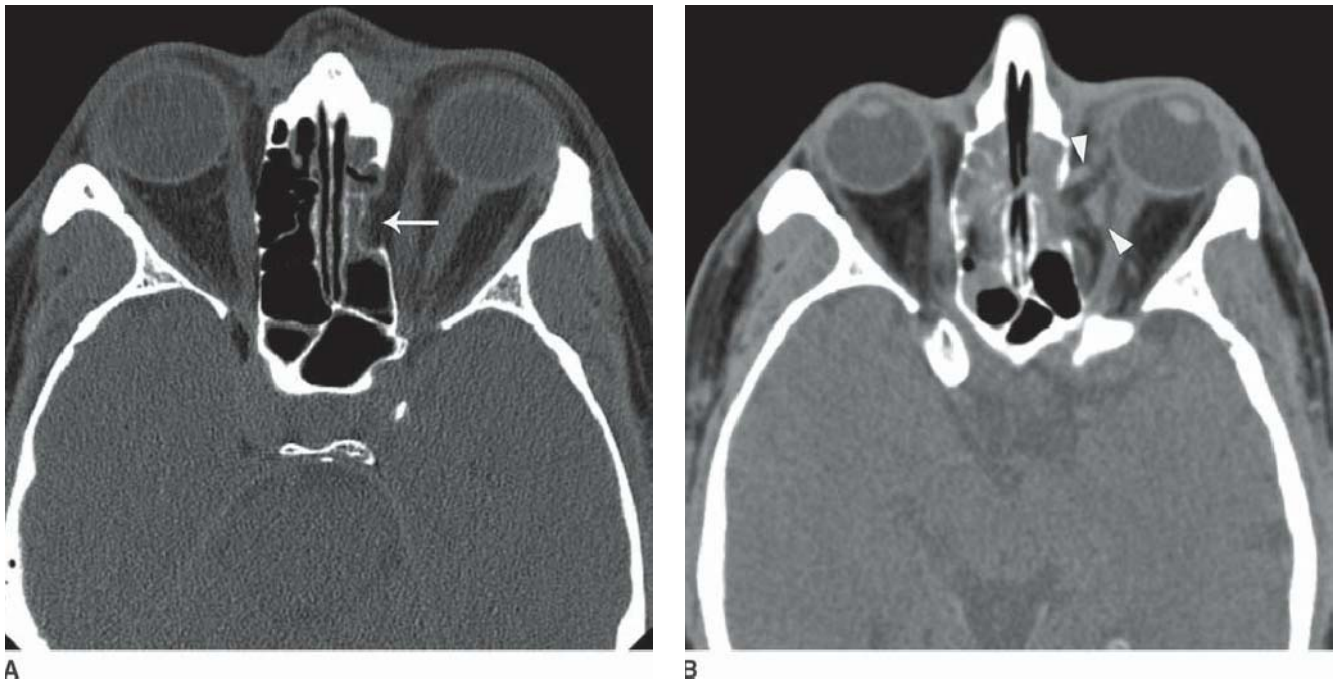


Figure 27.16 Orbital injury from lamina papyracea defect. **A:** Preoperative axial CT shows a defect in the left lamina papyracea (*arrow*) from an old orbital blow-out fracture. **B:** Postoperative axial CT shows loss of the normal left medial rectus muscle. Fat stranding and high-density blood products are present in the intraconal space (*arrowheads*). Courtesy of MT Bhatti, MD, Duke University Medical Center.

This places the optico–carotid recess within the posterior ethmoid cavity.

If technical difficulties are anticipated or if surgery involves the sphenoid sinus, the surgeon may choose to perform endoscopic surgery with a stereotactic CT image guidance system (6). This requires preoperative CT imaging with thin slice images.

FUNGAL AND GRANULOMATOUS SINUSITIS

Fungal sinusitis encompasses a wide variety of manifestations, from relatively innocuous to rapidly fatal. Invasive fungal infection should be considered in any patient with chronic rhinosinusitis, particularly when the patient is immunocompromised or has intractable symptoms despite adequate bacterial therapy. There are five forms of fungal sinusitis. Immunocompetent patients may develop allergic fungal sinusitis or a fungus ball. Invasive fungal sinusitis, which can be acute or chronic, most commonly occurs in immunocompromised patients but may also rarely develop in the immunocompetent population (15,16). The final form of fungal sinusitis is granulomatous invasive fungal sinusitis, a rare condition seen almost exclusively in northern Africa and which occurs in immunocompetent patients.

CT is the main imaging modality for evaluating fungal sinusitis with the exception of invasive fungal sinusitis where MRI can be more accurate in defining the presence and extent of orbital or intracranial involvement.

Imaging Findings of Noninvasive Fungal Sinusitis

Allergic fungal sinusitis typically presents with involvement of multiple sinuses and the nasal cavity, but can be present with incomplete opacification of sinuses, especially in postoperative recurrences (17). It is also possible for allergic fungal sinusitis to occur in just one sinus and even to occur in a sinus without nasal involvement. On CT, the sinuses are opacified by high-density allergic mucin. Characteristic bony changes are bony sinus expansion, remodeling, and thinning (Fig. 27.17). On MRI, there is low signal intensity or signal void on T2-weighted sequences.

Fungus ball is usually limited to one sinus, and most commonly the maxillary sinus. On CT, it appears as a high-density mass within the lumen of the sinus with or without punctate calcifications (Fig. 27.1). Associated bony changes can range from sclerotic thickening due to chronic obstruction to expansion and thinning from pressure necrosis. On MRI, the fungus ball is hypointense on T1- and T2-weighted sequences.

Imaging Findings of Invasive Fungal Sinusitis

Acute invasive fungal infection is due to organisms such as *Aspergillus* or Zygomycetes. In contrast to noninvasive fungal sinusitis that is limited to the lumen of the sinus, invasive fungal infection invades the mucosa to involve bone, blood vessels, and adjacent soft tissue. Invasive disease tends to be unilateral and most commonly beginning

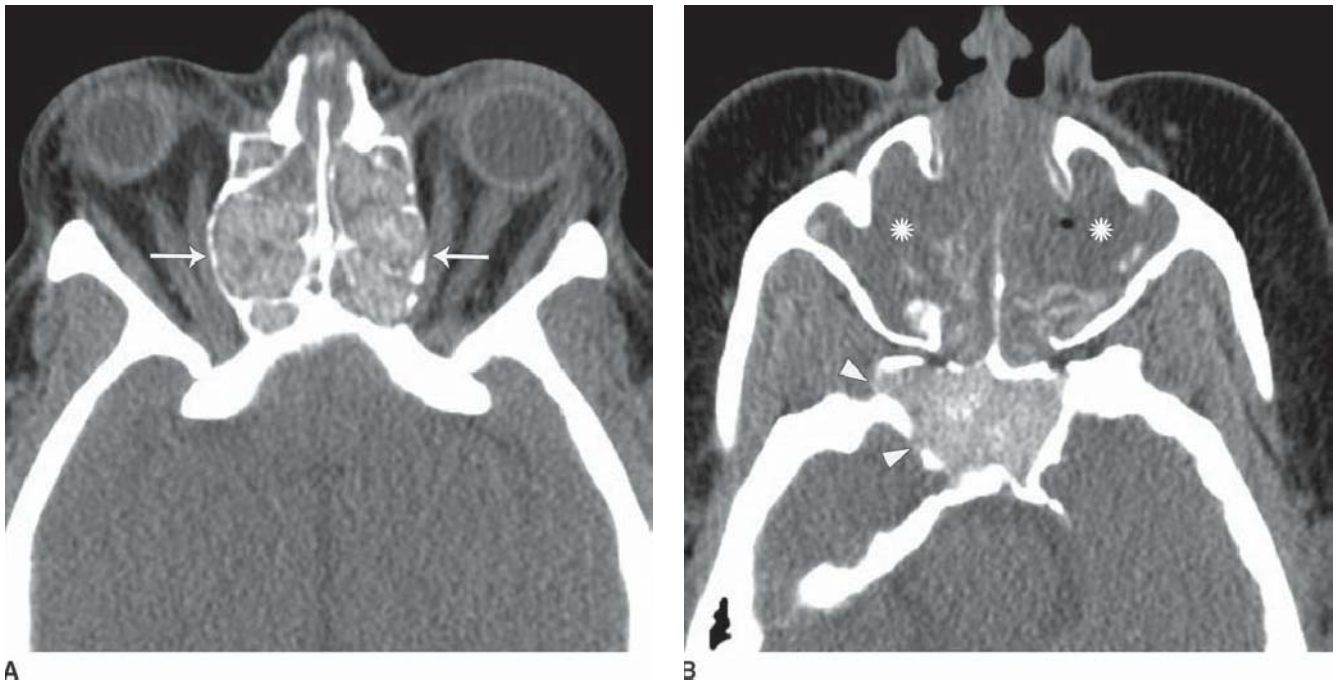


Figure 27.17 Allergic fungal sinusitis. **A:** Axial CT image shows bilateral ethmoid (*arrows*) opacification with high-density secretions and expansion. **B:** Axial CT image shows bilateral sphenoid sinus opacification with high-density secretions and focal areas of bony dehiscence (*arrowheads*). The high-density secretions in this case represent allergic mucin. A differential is inspissated secretions.

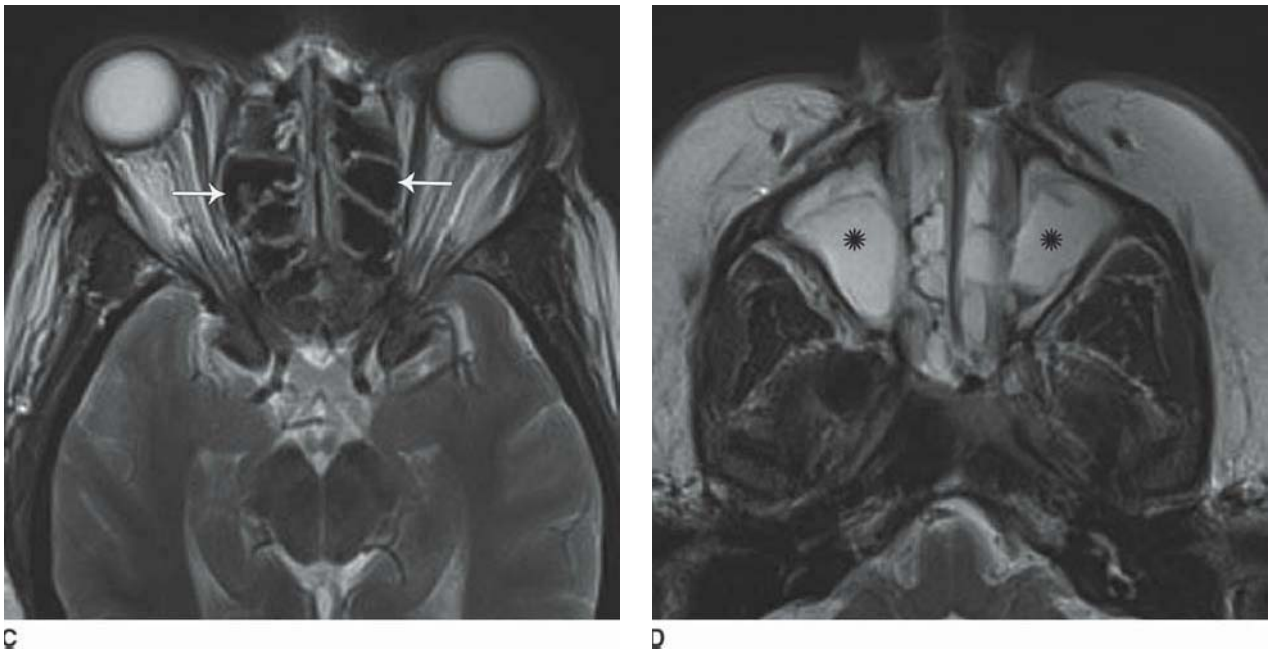


Figure 27.17 *(Continued)* **C:** Axial T2-weighted MRI image shows a signal void in the ethmoid sinuses also in keeping with allergic mucin. A pitfall is to mistake the signal void for air. **D:** Axial T2-weighted MRI image shows T2 hyperintense maxillary sinus opacification (*asterisk*) while on CT this is a soft tissue density (**B**, *asterisk*). This represents inflammatory fluid.

in the nasal cavity (18,19). Findings on CT are low attenuation or soft tissue density thickening in the sinus. On MRI, fungal elements can cause T2 hypointense signal. Spread of infection outside the sinus appears as T2 hyperintense signal and enhancement in the soft tissues (Fig. 27.18). Nonenhancement due to infarction of soft tissues may also be seen. Extension beyond the sinonasal cavity, orbital involvement, and bony erosion are signs of advanced

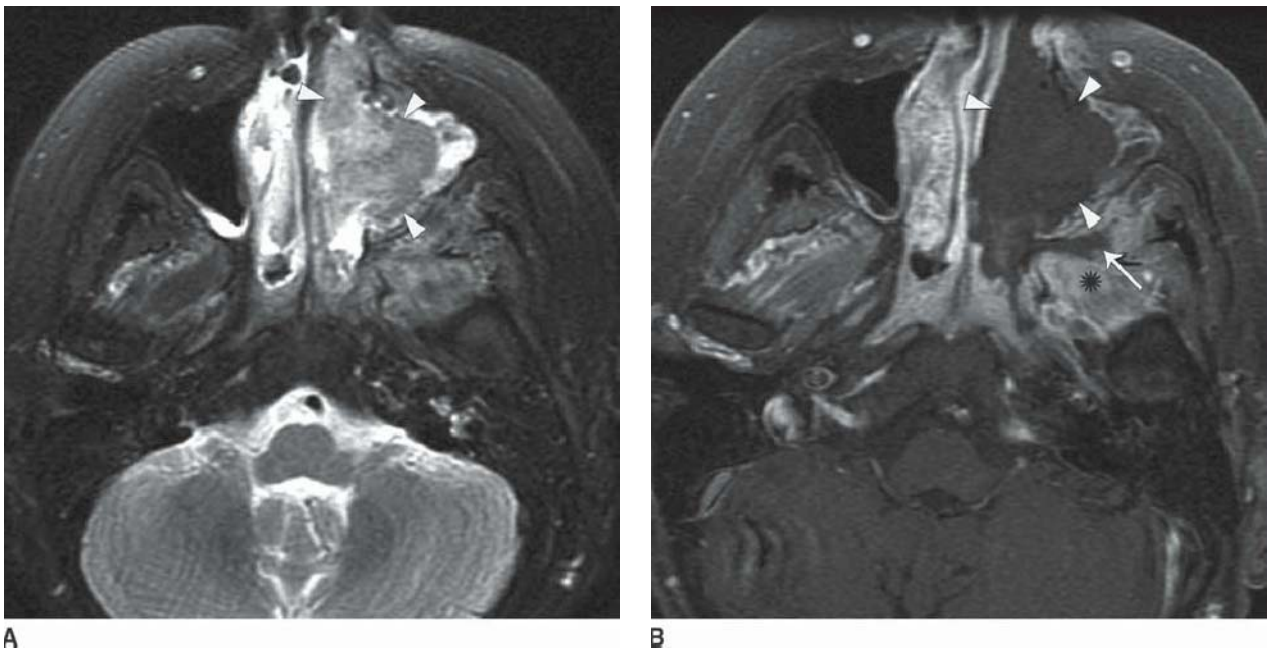


Figure 27.18 Invasive fungal sinusitis. **A:** Axial fat-saturated T2-weighted MRI image shows an isointense mass (*arrowheads*) in the left maxillary sinus and nasal cavity. There is also T2 hyperintense signal in left masticator space (infratemporal fossa). **B:** Axial-enhanced fat-saturated T1-weighted MRI image shows the maxillary sinus mass to have no enhancement (*arrowheads*). This is in keeping with necrotic eschar associated with invasive fungal infection. Note that similar nonenhancing tissue extends beyond the sinus to the masticator space (*arrow*). There is also enhancing tissue in the left masticator space (*asterisk*) in keeping with local fungal invasion.

disease that may be difficult to cure (19). In the absence of deep extension and bony changes, early findings in invasive fungal sinusitis are nonspecific and do not correlate well with surgical and pathologic findings.

Of note, orbital and intracranial fungal extension can occur even without bony destruction because of vascular invasion. Intraorbital invasion may appear as orbital fat stranding, extraocular muscle enlargement, and proptosis. Frank signs of intracranial invasion include the following: cavernous sinus thrombosis, carotid artery invasion leading to pseudoaneurysm or occlusion, leptomeningeal enhancement (meningitis), and brain parenchymal lesions from cerebritis, abscess, or granulomas.

Chronic invasive fungal sinusitis is also characterized by fungal hyphae in the mucosa and beyond, but the course of disease occurs over months and years and patients are usually immunocompetent. On CT, this entity can mimic tumor because of its mass-like appearance and extension outside the sinus. On MRI, the signal is most commonly T1 and T2 hypointense.

Imaging Findings of Granulomatous Sinusitis

The most common cause of granulomatous sinusitis is Wegener granulomatosis. On CT, early findings are nonspecific soft tissue nodules along the nasal septum with marked mucosal thickening. Later, there may be perforation of the cartilaginous nasal septum followed by destruction of the bony nasal septum and sinus walls as the disease progresses.

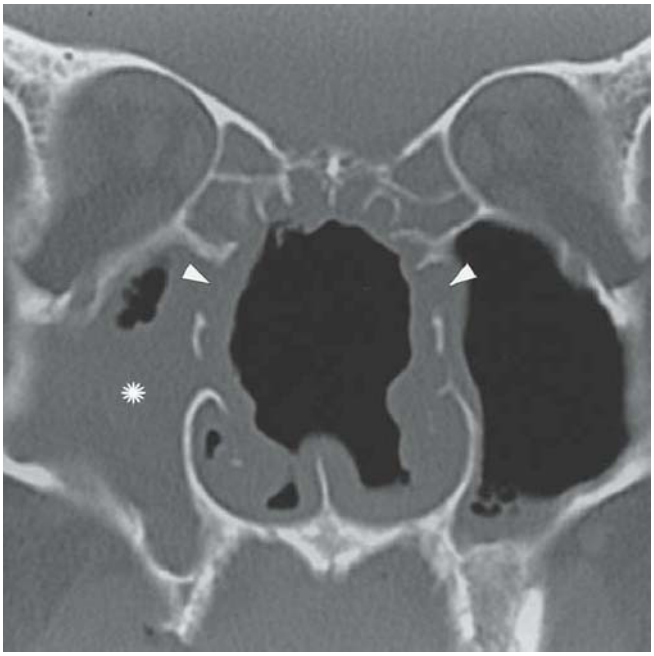


Figure 27.19 Granulomatous disease in cocaine user. Coronal CT image shows a large septal perforation that involves both bone and cartilage. The middle turbinates are eroded and there is circumferential soft tissue thickening throughout the nasal cavity. There is secondary obstruction of the OMCs bilaterally, with ethmoid opacification and right maxillary sinus fluid (*asterisk*).

Other causes of granulomatous sinusitis have the similar imaging findings and are classified as infectious or noninfectious. Noninfectious etiologies include sarcoidosis and foreign body reaction from beryllium, chromate salts, and cocaine (Fig. 27.19). Infectious diseases are uncommon in developed countries and include actinomycosis, nocardiosis, blastomycosis, tuberculosis, syphilis, rhinoscleroma, and leprosy. Histopathology is necessary to differentiate granulomatous invasive fungal sinusitis from chronic invasive fungal sinusitis, as there are no differences in radiologic features (20).

SINONASAL NEOPLASM

A variety of neoplasms can develop in the paranasal sinuses. The most common sinonasal tumor is squamous cell carcinoma (SCC), which accounts for nearly 80% of malignant tumors in the paranasal sinuses (21). Other neoplasms are classified as epithelial or nonepithelial. Epithelial tumors occur in the epithelial lining of the sinonasal cavities (adenocarcinoma, melanoma), accessory salivary tissue (adenoid cystic carcinoma, mucoepidermoid carcinoma), neuroendocrine tissue (sinonasal undifferentiated carcinoma, small cell carcinoma), and the olfactory mucosa (esthesioneuroblastoma) (22). Nonepithelial tumors include non-Hodgkin lymphoma and sarcomas.

CT and MRI are complementary in the diagnosis and workup of sinonasal neoplasm. A systematic approach to interpretation includes the following steps: (a) confirmation that a lesion is a mass, (b) identification of specific features suggestive of neoplasm, and (c) tumor staging for malignant disease.

Is It a Mass or Inflammation?

CT better demonstrates bony destruction, but MRI is extremely valuable for tumor imaging as it can distinguish mass from secretions and inflammatory mucosa. On MRI, the T2-weighted sequences are key: most sinonasal tumors have isointense to hypointense T2 signal while inflammatory secretions and mucosa are T2 hyperintense (Figs. 27.1, 27.20 and 27.21). Both tumors and inflammatory mucosal disease enhance with contrast, but fluid does not enhance. Being familiar with the characteristics of a mass helps to define the size and extent of tumor for biopsy and treatment planning.

Characterizing the Mass

CT imaging cannot reliably determine the histologic diagnosis of a tumor, but it does provide clues to whether the mass may be benign or malignant. Malignant tumors, such as SCC, lymphoma, and metastases, have focal and irregular bony destruction on CT (Figs. 27.1 and 27.21). In contrast, benign slow-growing tumors tend to cause sinus

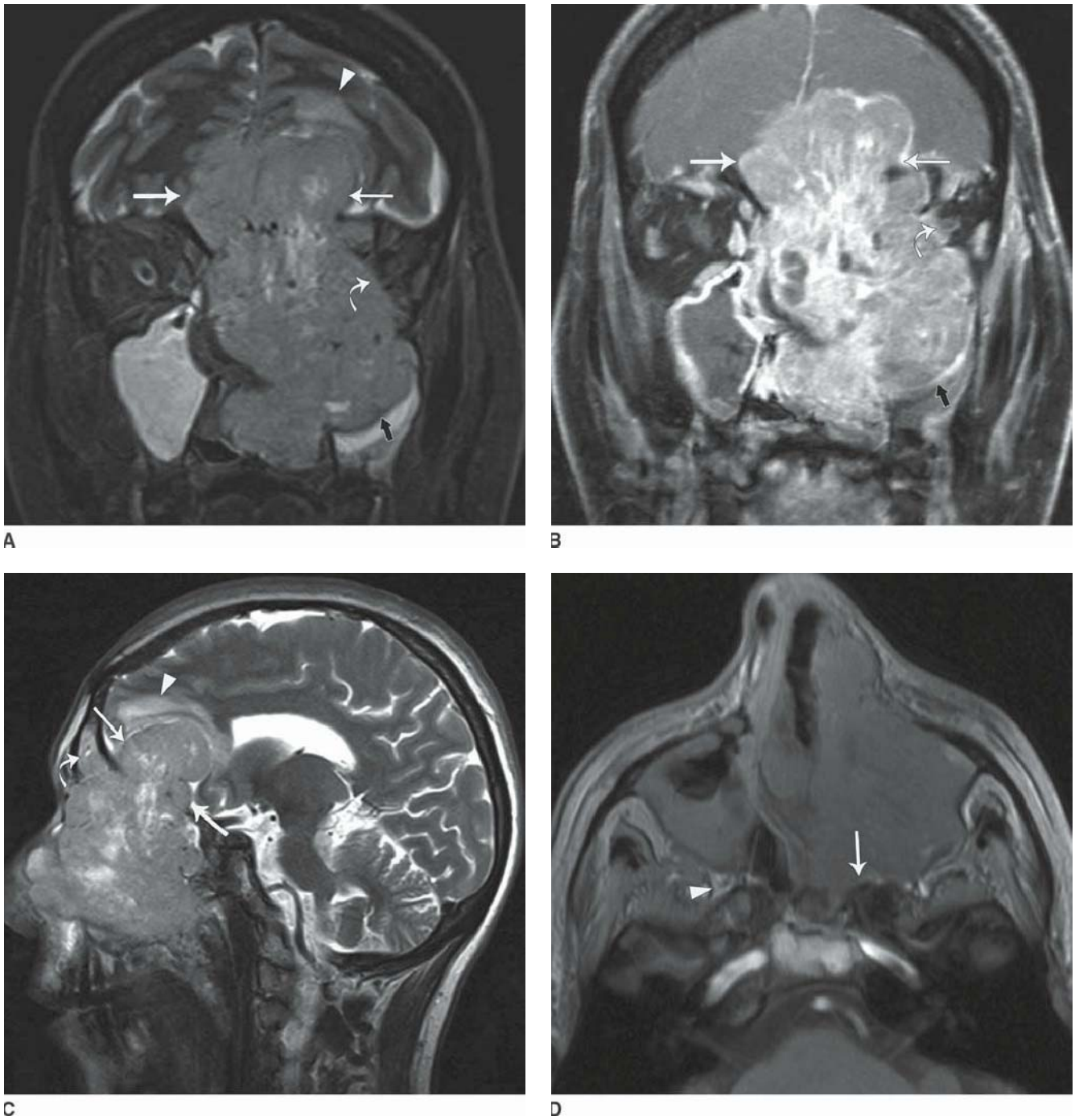


Figure 27.20 Sinonasal carcinoma with intracranial and orbital invasion. **A:** Coronal T2-weighted and **B:** enhanced T1-weighted fat-saturated MRI images show an isointense mass in the nasal cavity with intracranial extension (*arrows*). There is intraorbital tumor with irregular nodular contours suggestive of invasion through the periorbita (*curved arrows*). On the enhanced images **(B)**, there is also loss of normal appearance of the medial rectus, inferior rectus, and superior oblique muscles and tumor abutting the optic nerve (*curved arrow*). There is associated edema in the left frontal lobe from mass effect (*arrowhead*) and invasion into the left maxillary sinus (*black arrows*). **C:** Sagittal T2-weighted MRI image shows intracranial extension (*arrows*) and brain edema (*arrowhead*). There is also extension into the frontal sinus (*curved arrow*). **D:** Axial T1 MRI image shows tumor extension from the left maxillary sinus into the pterygopalatine fossa (*arrow*). Note the right pterygopalatine fossa containing normal fat (*arrowhead*).

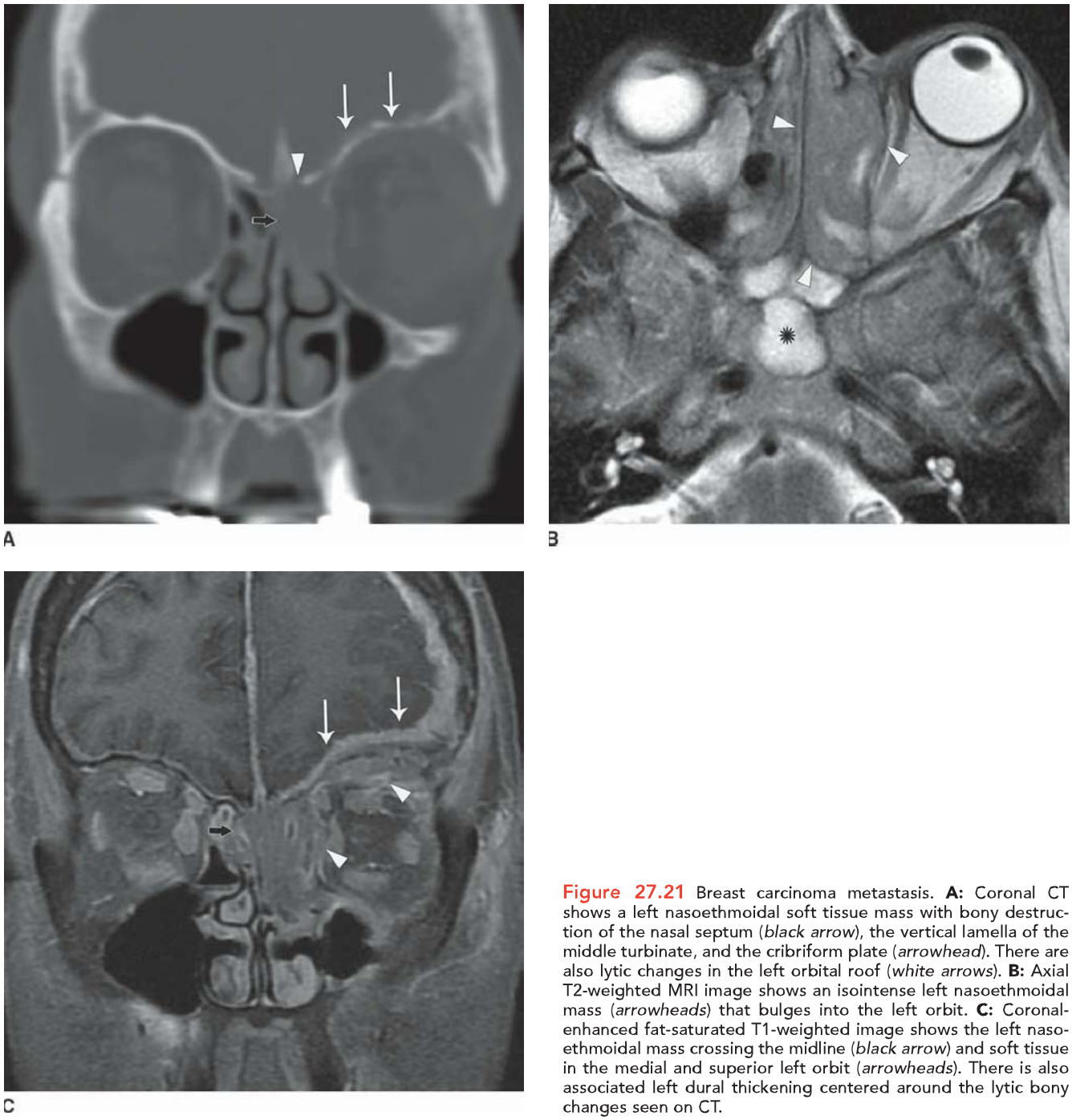


Figure 27.21 Breast carcinoma metastasis. **A:** Coronal CT shows a left nasoethmoidal soft tissue mass with bony destruction of the nasal septum (*black arrow*), the vertical lamella of the middle turbinate, and the cribriform plate (*arrowhead*). There are also lytic changes in the left orbital roof (*white arrows*). **B:** Axial T2-weighted MRI image shows an isointense left nasoethmoidal mass (*arrowheads*) that bulges into the left orbit. **C:** Coronal-enhanced fat-saturated T1-weighted image shows the left nasoethmoidal mass crossing the midline (*black arrow*) and soft tissue in the medial and superior left orbit (*arrowheads*). There is also associated left dural thickening centered around the lytic bony changes seen on CT.

expansion and bony remodeling (Fig. 27.22). Of note, an imaging trap is that bony remodeling and smooth expansion can be present in some malignant tumors, including adenoid cystic carcinoma, melanoma, and esthesioneuroblastoma. CT can also detect tumoral calcifications, but this is also not a specific sign. Intralesional calcifications can be present in SCC, adenocarcinoma, inverted papilloma, esthesioneuroblastoma, and mesenchymal tumors of bone or cartilaginous origin.

MRI is no better than CT for precise histologic diagnosis. Most malignant tumors have similar characteristics showing T1 and T2 isointense to hypointense signal. The exception is mucosal melanoma, which can be T1 hyperintense if it contains paramagnetic melanin or hemorrhage (23). There can also be distinguishing findings for esthesioneuroblastoma when there is intracranial invasion. This tumor can have cysts at the tumor interface with brain parenchyma (Fig. 27.23), and a dumbbell shape with a waist at the cribriform plate (24,25).

A notable benign tumor is the inverted papilloma. This epithelial tumor of the sinonasal cavity can mimic a malignant neoplasm with invasion into surrounding structures and recurrence after resection (26). Additionally, inverted papillomas can degenerate into or coexist with malignancy:

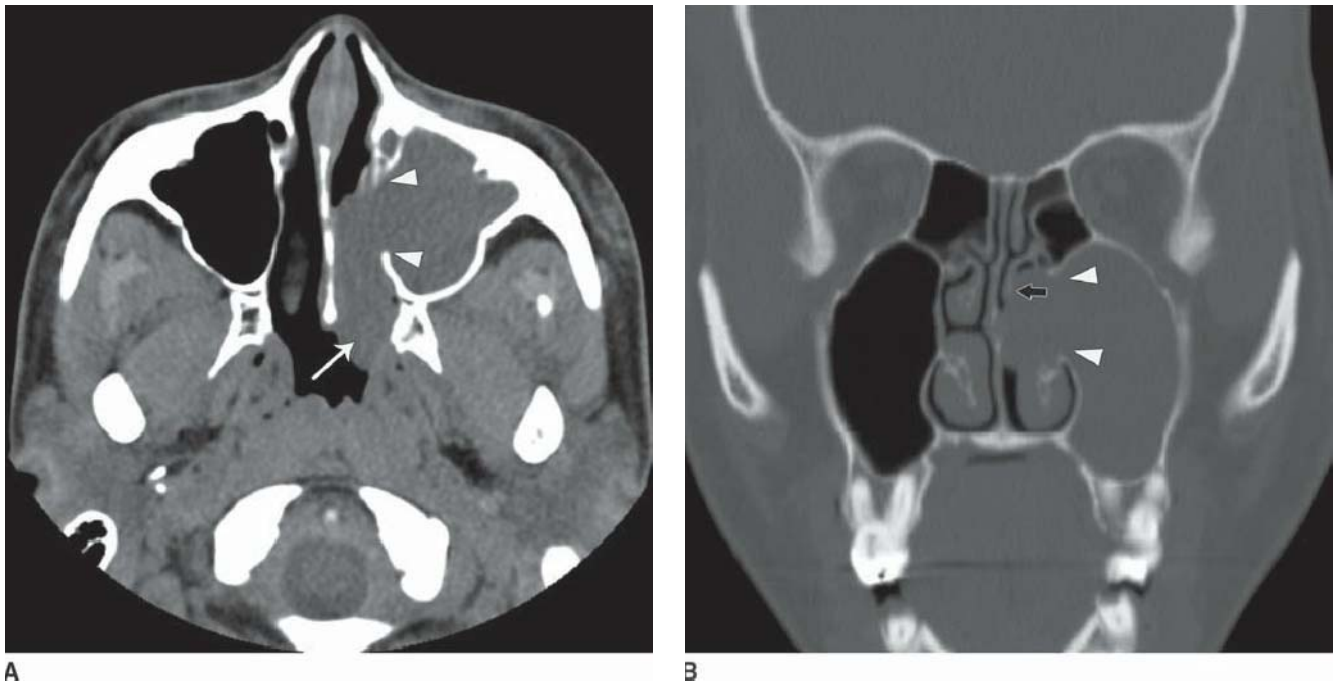


Figure 27.22 Antrochoanal polyp. **A:** Axial CT shows a mass in the left nasal cavity and maxillary sinus extending past the left nasal choana to the nasopharynx (*arrow*). There is bony remodeling with widening of the maxillary ostium (*arrowheads*). **B:** Coronal CT shows a mass in the left nasal cavity and maxillary sinus. Again there is bony remodeling with widening of the maxillary ostium (*arrowheads*) and truncation of the medial turbinate (*black arrow*).

up to 5% to 15% of resected cases are associated with SCC (26,27). Inverted papillomas typically arise from the lateral nasal wall at the level of the middle turbinate or less commonly within the maxillary sinus. On CT, they can have an aggressive appearance with bony destruction of the lateral nasal wall and extension into the maxillary antrum (Fig. 27.24). Alternatively, the adjacent bone can be sclerotic and mimic chronic sinusitis (28). There may also be curvilinear or irregular calcifications giving the tumor a cerebriform appearance. Other benign soft tissue tumors that occur around the paranasal sinuses are juvenile angiofibroma (Fig. 27.25) and neurogenic tumors.



Figure 27.23 Esthesioneuroblastoma. Coronal-enhanced fat-saturated T1-weighted image shows a bilateral nasoethmoidal mass (*arrowheads*) with intracranial extension. Peritumoral cysts (*arrows*) are noted at the junction of the tumor and brain parenchyma.

Since the sinus walls are bony, fibroosseous lesions can also involve the sinus and include osteomas, fibrous dysplasia, ossifying or nonossifying fibroma, chondromas, and malignant chondroid lesions. Another bony lesion that can mimic tumor is arrested skull base pneumatization (Fig. 27.26). This is a developmental variant that arises when early fatty marrow conversion occurs in preparation for sinus pneumatization, but pneumatization fails to occur. It is most commonly seen around the basisphenoid bone and is characterized on CT as a nonexpansile lesion with osteosclerotic borders and curvilinear calcifications (29). On MRI, the internal fat gives a characteristic pattern of T1 and T2 hyperintense signal.

Tumor Staging with Imaging

The most important role of imaging for malignancy is to define the extent of tumor for staging and treatment planning. The staging system for carcinoma is the American Joint Cancer Committee (AJCC) tumor, nodes, metastasis (TNM) classification (30). It applies only to the two most

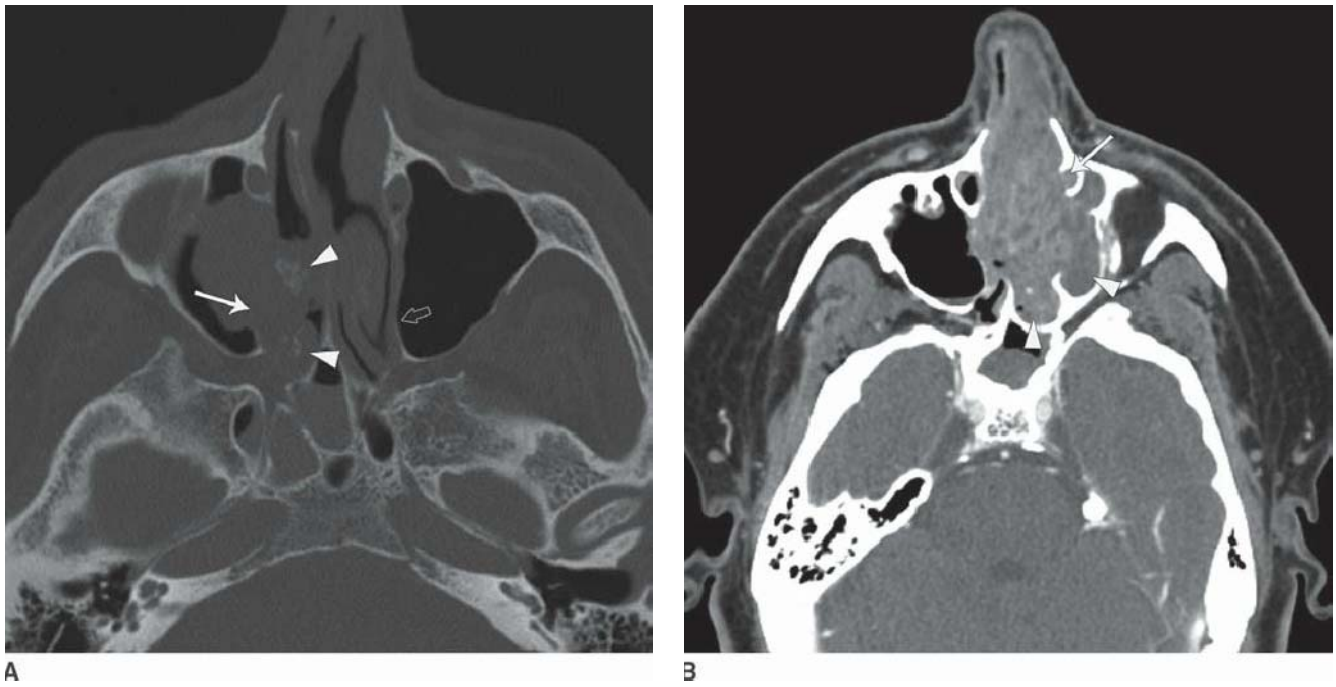


Figure 27.24 Inverted papilloma. **A:** Axial CT image shows a soft tissue mass in the right nasal cavity and maxillary antrum. There is bony erosion of the medial maxillary wall (*white arrow*) when compared to the left (*black arrow*). Intralesional calcifications are also seen (*arrowhead*). **B:** Axial CT image in a different patient shows a soft tissue mass in the left nasal cavity and maxillary antrum with scalloping of the maxillary sinus walls (*arrowhead*). This is characteristic of longstanding or recurrent inverted papilloma. There is also bony destruction of the nasal septum and possible invasion into the nasolacrimal duct (*arrow*). The surgical specimen in this case showed associated SCC.



Figure 27.25 Juvenile nasopharyngeal angiofibroma. Enhanced axial CT shows a large enhancing mass in the nasopharynx (*asterisk*), left nasal cavity (*arrow*), left maxillary sinus, and infratemporal fossa/masticator space (*arrowhead*). There is widening of the pterygomaxillary fissure (*double headed arrow*).

common sites for sinonasal tumors: the nasoethmoid complex and the maxillary antrum (Table 27.2). The components of the staging system are intrasinus tumor extent as defined by subsites, and deep invasion of critical structures such as the skull base, pterygopalatine fossae, orbits, and palate. CT and MRI have a complementary role. CT is preferred for evaluating bony invasion while MRI best delineates intracranial, perineural, and intraorbital disease.

Carcinoma, lymphoma, and esthesioneuroblastoma frequently invade the skull base. Early skull base invasion is best seen on coronal CT images (Fig. 27.21), but MRI surpasses CT in identifying dural enhancement (Fig. 27.21), and parenchymal edema and enhancement. Linear dural enhancement has lower specificity for dural invasion since reactive changes from adjacent tumor could also have this appearance. More specific signs for dural invasion are nodular dural enhancement, dural thickening greater than 5 mm, or associated leptomeningeal enhancement (31). Brain parenchymal invasion is characterized by intraparenchymal enhancement with edema. Brain edema may also be seen if there is mass effect from the tumor without parenchymal invasion (Fig. 27.20).

Orbital invasion can occur when tumor abuts the medial or inferior orbital wall and is best depicted on coronal imaging. CT shows bony invasion, which indicates a tumor stage of

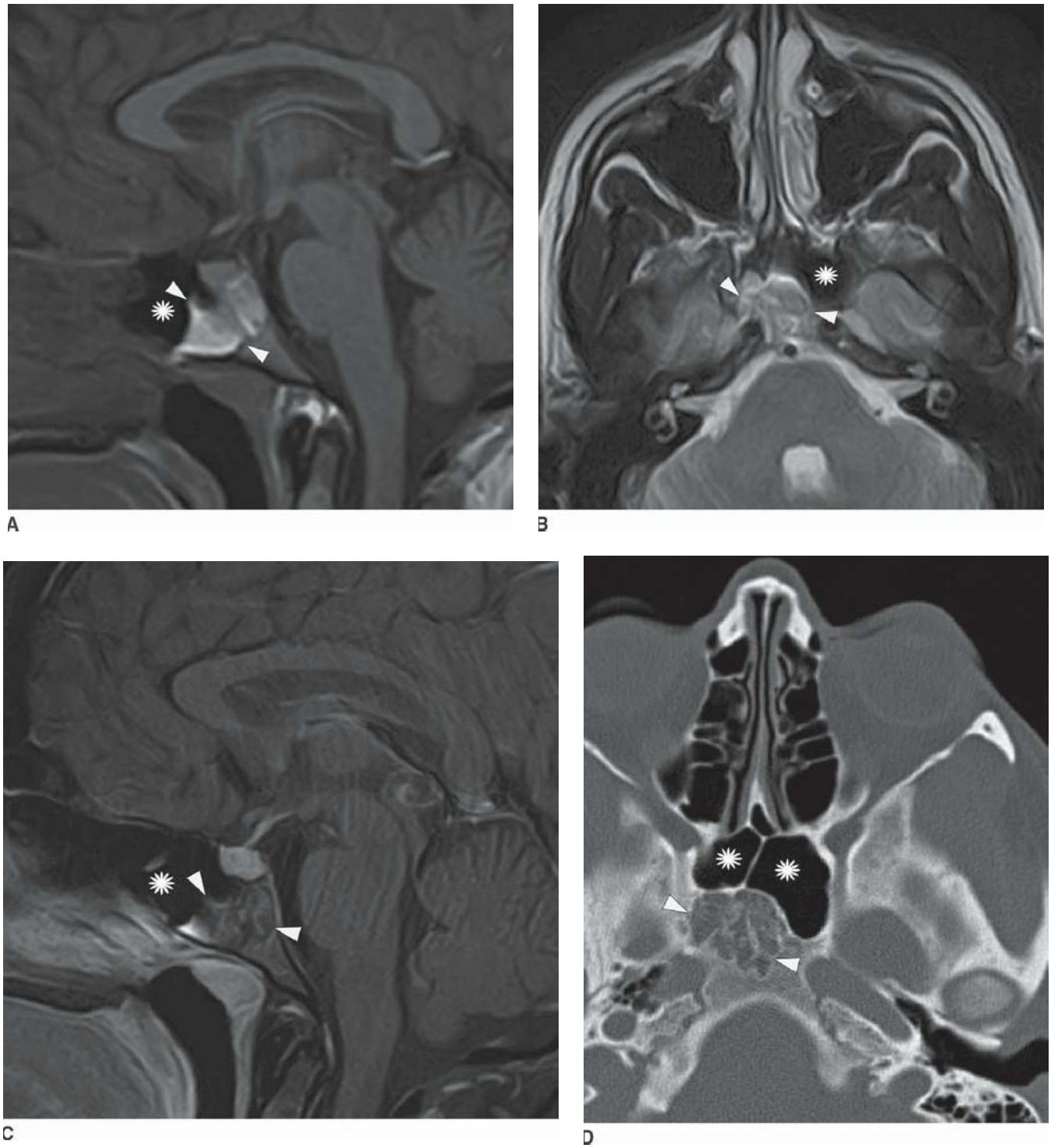


Figure 27.26 Arrested pneumatization of the basisphenoid, a developmental variant. **A:** Sagittal T1-weighted and **B:** axial T2-weighted images show a T1 and T2 hyperintense lesion in the basisphenoid bone (*arrowheads*). There is pneumatization of the sphenoid sinuses (*asterisk*), but the right sphenoid sinus is small. **C:** Sagittal-enhanced fat-saturated T1-weighted image shows that the lesion (*arrowhead*) does not enhance and signal suppresses in keeping with fat. **D:** Axial CT image shows a well-defined lesion (*arrowhead*) in the basisphenoid with sclerotic margins and central calcifications.

T3 (Fig. 27.2). Bone can be resected and this sign alone does not determine the need for orbital exenteration. Invasion of the periorbita, the orbital aspect of the periosteum, indicates stage T4 disease and is a crucial finding as this is a criterion for orbital exenteration. Signs of invasion through the periorbita are best seen on MRI with intraorbital fat stranding, a nodular interface with the orbit, and loss of the fat plane between the tumor and rectus muscles (Fig. 27.20) (32).

TABLE 27.2 AJCC 7TH EDITION NASAL CAVITY AND PARANASAL SINUS STAGING SYSTEM

	Maxillary Sinus	Nasal Cavity and Ethmoid Sinus
Primary tumor staging		
T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone.	Tumor restricted to any 1 subsite[a] +/− bony invasion.
T2	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus (except extension into the posterior wall of the maxillary sinus and pterygoid plates).	Tumor invading two subsites[a] in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion.
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate.	
T4a (resectable)	Tumor invades any of the following: anterior orbital contents, skin of nose/cheek, minimal extension to anterior fossa, pterygoid plates, sphenoid or frontal sinuses.	
T4b (unresectable)	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus.	
Regional lymph node staging		
N0	No evidence of cancer in the regional lymph nodes.	
N1	Metastasis to a single ipsilateral lymph node measuring ≤3 centimeters (cm).	
N2	**N2a:** Metastasis to a single ipsilateral lymph node measuring >3 cm, but ≤6 cm. **N2b:** Metastasis to multiple ipsilateral lymph nodes measuring ≤6 cm. **N2c:** Metastasis to bilateral or contralateral lymph nodes, which are ≤6 cm.	
N3	Nodal metastases >6 cm	

[a]The subsites of the nasal cavity are septum, floor, lateral wall, and vestibule. The subsites of the ethmoid sinus region are right ethmoid sinus and left ethmoid sinus.

MRI is also valuable for showing perineural spread of tumor. Signs of perineural tumor spread are nerve enhancement or thickening. Advanced cases may show widening or destruction of the neural foramen or canal at the skull base. The most commonly involved nerve in sinonasal carcinoma is the second division (V2) of the trigeminal nerve. Tumor can spread via small peripheral branches of V2 or there may be direct invasion of V2 via the pterygopalatine fossa that lies posterior to the maxillary sinus (Fig. 27.20). From the pterygopalatine fossa, tumor can spread in several directions: superiorly toward the superior or inferior orbital fissures, or posteriorly into the foramen rotundum. Perineural tumor spread is more common in cases of tumor recurrence and is associated with a decreased survival rate.

Correct preoperative evaluation of nodal disease with imaging provides important prognostic information (33). The nodal staging system comprises N0 to N3 and is shown on Table 27.2 (30). Nodal metastases occur in approximately 9% to 15% of patients with sinonasal malignancy and should be suspected if there is extension of tumor to involve the skin, gingivobuccal sulcus, or the pterygoid musculature (32,33). Levels I and II are the most frequently involved groups, and the signs worrisome for nodal metastases are size greater than 10 mm, central low attenuation regions representing necrosis, hyperenhancement, and loss of well-defined margins suggesting extracapsular spread. Of note, size is not the best criterion for malignancy as metastases can exist is subcentimeter lymph nodes, and enlarged hyperplastic benign nodes can also occur in the neck. Use of fluorodeoxyglucose positron emission tomography (FDG-PET) or diffusion-weighted MRI for nodal assessment may increase sensitivity and specificity.

CONCLUSION

CT and MRI are the main modalities for evaluating paranasal sinus diseases. Imaging of rhinosinusitis is dominated by CT. MRI is complementary to CT for complicated inflammatory disease and neoplasia. Evaluation of sinonasal disease with these modalities should be approached systematically in the context of the clinical scenario. One of the major roles of imaging is for preoperative planning

to evaluate extent of inflammatory and neoplastic disease and to identify anatomy that may make surgery more challenging or hazardous.

HIGHLIGHTS

- CT is valuable for evaluating all pathologies of the paranasal sinuses because of its high resolution of bony structures and the ability to reconstruct axially acquired images in coronal and sagittal planes.
- MRI is superior to CT for soft tissue characterization, and is thus complementary to CT when there is a sinonasal mass, and intracranial or orbital complications of inflammatory sinus disease.
- T2-weighted sequences are key for delineating sinonasal tumor. Most tumors have isointense to hypointense T2 signal while inflammatory secretions and mucosa are T2 hyperintense. Both tumors and inflammatory mucosal disease enhance with contrast, but fluid does not enhance.
- The presence of a fluid level and frothy or strandy secretions suggests acute sinusitis. Sclerosis of sinus walls indicates chronic sinusitis. In the absence of these findings, mucosal thickening is nonspecific and acute and chronic sinusitis cannot be differentiated on imaging.
- Identification of anatomical and critical variants on preoperative CT imaging is crucial to performing safe sinus surgery.
- Review of axial, coronal, and sagittal images is necessary to identify the natural sinus drainage pathways.
- High-density secretions on CT can represent inspissated secretions or allergic mucin. Allergic fungal sinusitis can be associated with sinus cavity expansion and thinning of the bony walls.
- In complicated bacterial sinusitis and invasive fungal sinusitis, bony destruction may be absent despite intracranial and intraorbital invasion if the route of spread is vascular.
- Imaging cannot reliably characterize the histology of tumor because of overlapping findings. The most important role of imaging malignancy is to define the extent of tumor for staging and treatment planning.

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28 Diagnostic Tools for Sinonasal Disease and Role of Office Imaging

Luke Rudmik *Timothy L. Smith*

Due to the breadth of sinonasal pathologies, several diagnostic tools are available during rhinologic evaluation. Diagnostic evaluation always begins with a thorough history and physical exam. The importance of a complete history and physical cannot be over emphasized, as it narrows the differential diagnosis and focuses subsequent diagnostic tests. An incomplete history and exam may result in needless investigations and, worst-case scenario, lead to a misdiagnosis with a delay in treatment. A formal discussion on the rhinologic history and physical exam is beyond the scope of this chapter but should be performed on all patients. This chapter discusses the various rhinologic investigations used to evaluate patients with sinonasal pathology.

RIGID SINONASAL ENDOSCOPY

Rigid sinonasal endoscopy remains one of the most useful diagnostic tools used during the evaluation of sinonasal disease. Recent advancements in endoscopic technology have provided high-definition image detail with improved magnification. Most otolaryngologists will perform in-office rigid sinonasal endoscopy using a 4 mm 30-degree endoscope; however, a smaller 2.7 mm diameter endoscope and 0, 45, and 70-degree scopes are available, depending on surgeon preference. Utilizing a rigid, rather than flexible, endoscope enables the physician to scope with one hand and perform procedures, such as suctioning or debriding, with the other hand.

To improve patient comfort and optimize visualization, the procedure often begins with the application of a topical anesthetic and decongestant. Application can be achieved with either cotton pledgets or nebulized spray and commonly involves a mixture of 4% Xylocaine and xylometazoline.

A systematic approach to the endoscopic exam will provide a thorough evaluation and minimize missed information. A common approach to rigid sinonasal endoscopy involves a three-pass technique (Table 28.1). The first pass involves passing the scope medial to the inferior turbinate, along the floor of nose. Structures visualized include the inferior turbinate, inferior portion of the middle turbinate, nasopharynx, and eustachian tube. The second pass places the scope medial to the middle turbinate to visualize the sphenoethmoidal recess. The relationship of the septum to the middle turbinate may impair this step. A classification by Schaitkin et al. (1) describes the endoscopic turbinoseptal (TS) relationship following nasal decongesting: TS1—medial and lateral aspect of middle turbinate is visualized; TS2—anterior attachment of middle turbinate partially obscured by septum; TS3—anterior attachment of middle turbinate completely obscured by septum; and TS4—septum contacting the lateral nasal wall (Fig. 28.1). Patients with TS2, 3, and 4 often require a septoplasty for access during endoscopic sinus surgery (ESS). The third pass visualizes lateral to the middle turbinate, within the middle meatus. Anatomic abnormalities such as choncha bullosa and accessory fontanelles can be visualized. Noting the presence of the mucosal inflammation, mucopurulence, mucus recirculation, crusting, masses, or polyps are important information, which can guide the ordering of subsequent diagnostic tests (Fig. 28.2).

A thorough and complete endoscopic exam is critical in the evaluation of a patient with sinonasal disease. The objective information provided can improve diagnosis, guide therapy, and monitor therapeutic response during follow-up. A systematic approach, as mentioned above, can improve diagnostic yield and consistency.

RADIOLOGIC INVESTIGATIONS

Radiographic imaging of the paranasal sinuses has evolved over the last century. Early options were limited to plain films (roentgenographs), which were fraught with inaccuracy and provided minimal diagnostic yield. Several

TABLE 28.1 RIGID SINONASAL ENDOSCOPY 3-PASS TECHNIQUE

Endoscopic Pass	Structures Visualized
1st Pass Medial to the inferior turbinate (along floor of nose)	Inferior Turbinate Inferior aspect of Middle turbinate Nasopharynx Eustachian tube torus
2nd Pass Medial to the middle turbinate	Septal relationship with middle turbinate (TS1-4) Superior turbinate Sphenoethmoidal recess / sphenoid os
3rd Pass Medial to the middle turbinate (within the middle meatus)	Lateral portion of middle turbinate Accessory fontanelles

technologic innovations over the last 15 to 20 years have given otolaryngologists several new imaging modalities, which have subsequently advanced our understanding of sinonasal disease and improved patient care. Current options primarily include high-resolution computed tomography (CT) and magnetic resonance imaging (MRI). Although the majority of sinonasal pathology can be diagnosed with a thorough history, physical exam, and rigid sinonasal endoscopy, radiographic imaging has become a standard adjunct in the workup of sinonasal disease. The primary role of radiologic imaging is to improve the diagnosis, define extent of regional disease, and aid in surgical planning.

Plain Films (Roentgenographs)

Plain films have been the traditional sinus imaging modality; however, they have been made obsolete with the emergence of CT and MRI. The four most common sinus plain film views include: Waters', Caldwell, Lateral, and Submentovertex. The radiation exposure from these four views is 40 to 60 mSv (2). Although limited, these views were able to assess the size and opacification of the sinuses, as well as identify septal deviations (3).

The major limitations of plain films are their inability to provide accurate diagnostic information pertaining to the status of the ostiomeatal complex (OMC), surrounding soft tissue, and anatomic variations of the sinuses. Although demonstration of an air-fluid level may be helpful during the workup of acute rhinosinusitis, several studies have demonstrated limited accuracy rates (70% and 75%) (4,5)

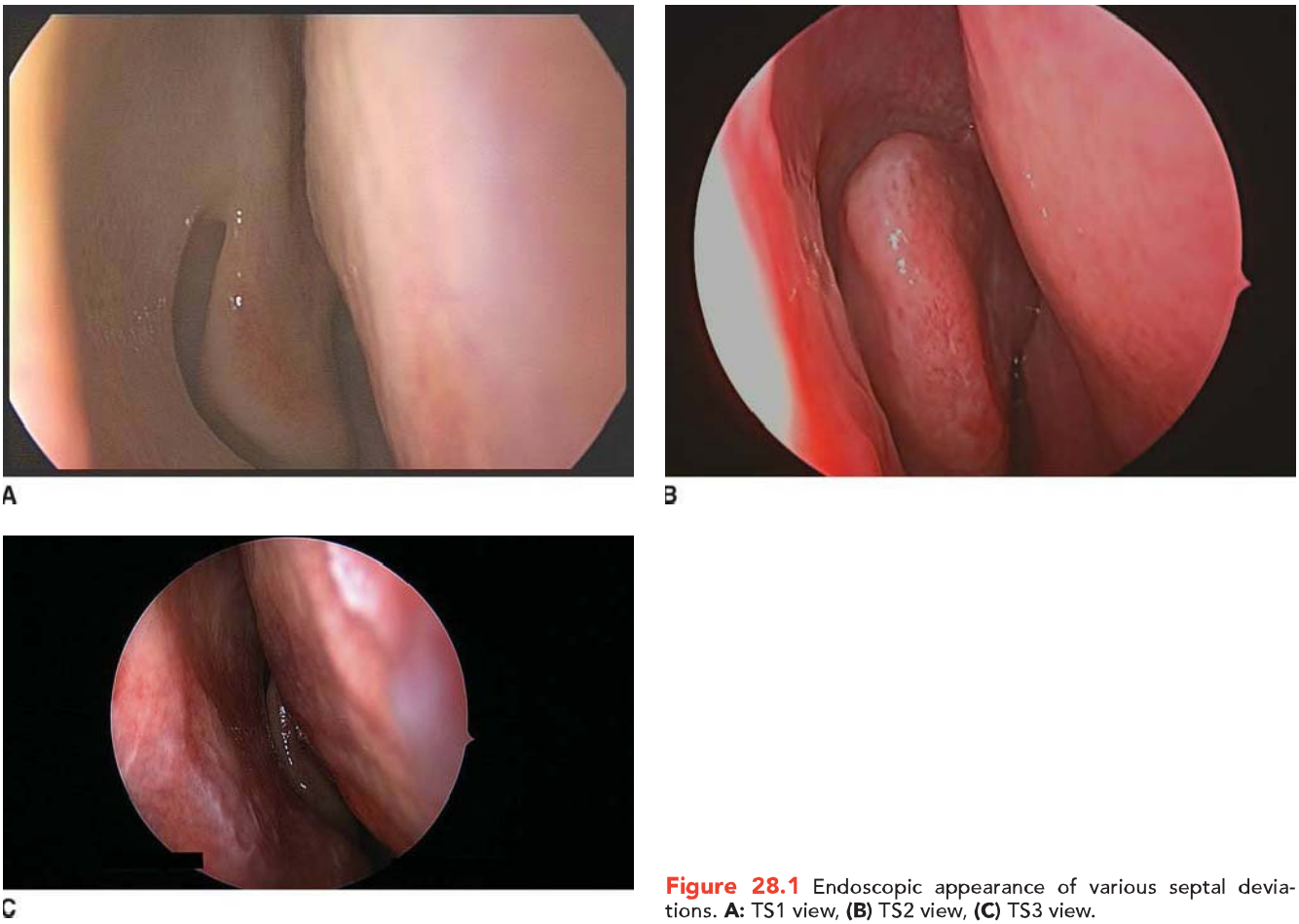
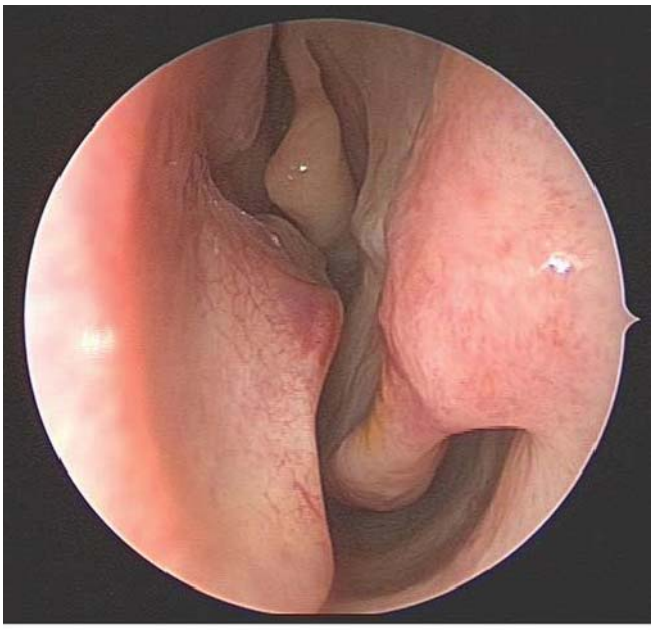


Figure 28.1 Endoscopic appearance of various septal deviations. **A:** TS1 view, **(B)** TS2 view, **(C)** TS3 view.



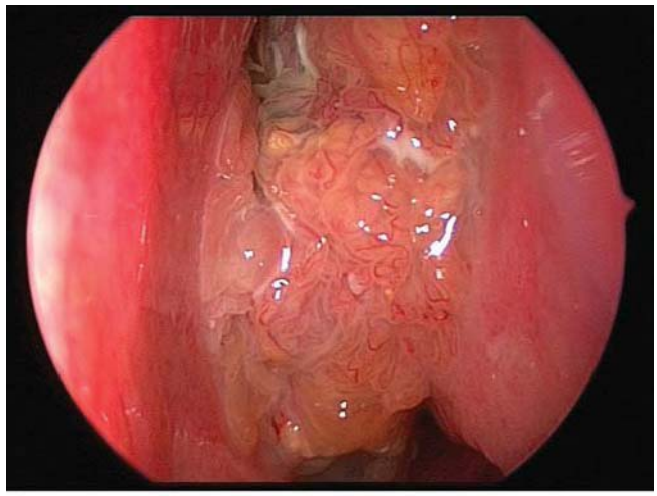
A



B



C



D



E

Figure 28.2 Endoscopic appearance of sinonasal pathology. **A:** Left septal spur, **(B)** acute bacterial rhinosinusitis, **(C)** missed ostium sequence, **(D)** inverting Papilloma, **(E)** choncha bullosa.

when compared to a CT scan. With the advent of ESS, detailed preoperative anatomic assessment is necessary to optimize surgical dissection and minimize complications. Due to significant tissue and bony overlap, plain films cannot provide detailed anatomic information. Currently, the only indication for plain films of the sinuses is the inability to obtain other imaging modalities such as CT or MRI.

Computed Tomography

The emergence of high-resolution CT imaging has advanced our understanding of sinonasal anatomy and physiology, and was fundamental to the rise of ESS (6). The major advantage of CT imaging is the excellent anatomic bony detail it provides. As a result, it has become the gold standard imaging modality for inflammatory diseases of the paranasal sinuses and is essential for preoperative planning.

Imaging the sinuses in the coronal plane is preferred since it provides excellent detail of the OMC; however, significant neck extension during image acquisition makes this position difficult. Therefore, current sinus CT protocols acquire thin axial slice thicknesses, usually less than 3 mm (ideally 1 mm), which permits high-resolution multiplanar reconstruction in the coronal and sagittal planes. Slice thickness of 1 mm is often required for accurate image-guidance compatibility. Intravenous contrast is not used in standard sinus CT protocols; however, it may be utilized during cases when there is a suspected complication of inflammatory disease (such as abscess or thrombosis) or during the evaluation of a sinonasal neoplasm. New multidetector CT scanners allow for acquisition of up to 64 slices with one rotation of the tube. This significantly reduces acquisition times and minimizes motion artifact. Although the radiation dose from a high-resolution CT scan of the sinuses may vary depending on scanning protocol, most yield a dose of 0.96 mSv (7).

A sinus CT can provide helpful diagnostic information in a variety of sinonasal pathologies (Table 28.2). In order to optimize diagnostic yield, it is important to develop a systemic approach to the interpretation of a sinus CT. Although most information is obtained from the coronal plane, helpful information can be obtained from the axial and sagittal images (Table 28.3). Interpretation incorporates a combination of defining the extent of local disease, identifying anatomic variations, and when indicated, surgical planning (8). To optimize bony detail while preserving soft tissue definition, some authors have suggested viewing CT images on a width-level ratio of 2,000/200 (9). The bony contours should be assessed for expansion, erosion, and/or thickening. Bony expansion usually suggests a chronic disease process, while erosion implies a more aggressive, acute pathology. Bony thickening often suggests osteitis resulting from chronic inflammation. Mucosal thickening should be assessed for laterality and extent of sinuses involved. The characteristics of sinus opacification should be noted, as heterogeneity may imply a fungal rhinosinusitis.

TABLE 28.2 COMMON INDICATIONS FOR SINUS CT

Sinonasal Disease	Indication
Acute Rhinosinusitis	Suspected complication
	Severe illness
	Failure to improve with medical management
	Clinical deterioration on medical management
	Immunocompromised state
Chronic Rhinosinusitis	Failure of medical management
	Preoperative planning
Neoplasm	Defining extent of lesion (staging)
Trauma	Suspected frontal sinus fracture
	Suspected cerebrospinal fluid leak

TABLE 28.3 INFORMATION OBTAINED FROM THE DIFFERENT PLANES OF SINUS CT

Sinus CT Plane	Helpful Information
Coronal	Septal deviation
	OMC
	Uncinate attachment type (A,B,C)
	Middle turbinate variations
	Lamina papyracea anatomy
	Ethmoid anatomy
	Skull base anatomy/lateral lamella length
	Anterior ethmoid artery anatomy
	Sphenoid anatomy/sphenoethmoid cell (Onodi)
	Identify optic nerve and carotid artery dehiscence.
Sagittal	Frontal recess anatomy
	Slope of the skull base
	Sphenoid pneumatization pattern
Axial	Sphenoid anatomy/attachment of superior turbinate

Magnetic Resonance Imaging

The technique of MRI involves the application of a strong magnetic field to soft tissue, which results in atom magnetization. Once magnetized, a series of radiofrequency fields are applied, which induce the nuclei to emit a magnetic field specific to each tissue. The scanner detects these differences and produces an image. There are three common MRI sequences, which provide important information: T1-weighted, T2-weighted, and T1-weighted with contrast. Fat appears bright on T1 images, while water is bright on T2 images. Intravenous gadolinium provides an excellent contrast medium, which can provide information regarding the vascularity of tissue.

The major advantages of MRI include: improved soft tissue definition, differentiate between secretions and soft tissue, lack of radiation exposure, and multiplanar reconstruction. The major disadvantages of MRI include: the lack of bony definition, long acquisition time in a small confinement, higher costs, and contraindication with any metal implant (e.g., pacemaker, cochlear implant). Since cortical bone and air both fail to provide a magnetic signal,

TABLE 28.4 COMPARISON OF COMMON SINONASAL RADIOLOGIC MODALITIES

Radiologic Modality	Advantages	Disadvantages
Plain films	Fast acquisition time	Poor anatomic detail
	Low cost	Limited clinical value
CT	Excellent bony detail	Radiation exposure
	Multiplanar reconstruction	Limited soft tissue differentiation
	Surgical planning	
	Fast acquisition time	
MRI	Detailed soft tissue definition	Poor bony definition
	Differentiate secretions from soft tissue	Long acquisition times in confined space
	Lack of radiation exposure	Expensive
	Multiplanar reconstruction	Contraindicated with certain metal implants

MRI cannot differentiate between these two entities. The bony contours of the sinuses and the associated intricate bony lamellae are poorly represented.

Traditionally, MRI was thought to be overly sensitive when evaluating chronic rhinosinusitis (CRS); however, a recent study by Lin et al. (10) demonstrated that MRI and CT Lund-Mackay scores correlated very well ($r = 0.837$, $p < 0.001$). Although MRI may be comparable to CT CRS staging, the lack of bony definition makes surgical planning difficult, and thus precludes its routine use in CRS imaging. The most common indications for MRI include evaluation of: (a) sinonasal mass/neoplasm and (b) suspected intracranial complication of acute rhinosinusitis.

MRI is a useful adjunct during the evaluation of select sinonasal pathologies and is rarely indicated in isolation without obtaining a CT scan. The exquisite soft tissue imaging of MRI combined with the detailed bony anatomy of CT make these two radiographic modalities the ideal options in sinonasal pathology evaluation (Table 28.4).

LABORATORY INVESTIGATIONS

Although most patients with sinonasal pathology do not require routine lab testing, there are certain clinical scenarios whereby the information obtained from lab results can be imperative to the diagnosis and subsequent treatment success. A common scenario where lab testing is indicated is during the evaluation of a young patient with sinus disease and any patient with refractory CRS. Lab testing can identify an underlying congenital abnormality, such as cystic fibrosis (CF) or primary immunodeficiency, or acquired illnesses such as atypical infections and systemic inflammatory diseases.

Cystic Fibrosis Testing

The diagnostic criteria for CF requires the presence of clinical symptoms consistent with CF in at least one organ system, and objective evidence of cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction on any of the following three tests: (a) elevated sweat chloride greater than 60 mmol/L (on two occasions), (b) presence of two disease-causing CFTR mutations on DNA testing, or (c) abnormal nasal potential difference (NPD).

The sweat chloride test remains the primary test used for laboratory confirmation of CF. Sweating is induced by a technique called pilocarpine iontophoresis. It involves placing a pilocarpine-soaked gauze on the skin and applying a gentle electrical current. The current draws pilocarpine into the skin and induces sweat gland secretion. The sweat is then collected and the chloride concentration is quantified (11). For infants older than 6 months, children, and adults, there are three groups of results: (a) Normal (CF very unlikely): ≤39 mmol/L, (b) Intermediate (Possible CF): 40 to 59 mmol/L, and (c) Abnormal (diagnosis of CF): ≥60 mmol/L. The accuracy of sweat chloride testing is operator-dependent and should be performed at experienced labs (12). Patients with an intermediate sweat chloride result should receive DNA analysis, using the multimutation method, to identify a CFTR gene mutation. Approximately 20% of patients with an intermediate sweat test will have an identifiable CFTR mutation on DNA analysis (13). If two CFTR mutations are not identified, then the sweat chloride test should be repeated. A false positive sweat test can occur in any of the following: (a) lab error, (b) malnutrition, (c) dehydration, (d) adrenal insufficiency, (e) hypothyroidism, (f) hypoparathyroidism, (g) mucopolysaccharidosis, and (h) nephrogenic diabetes insipidus. The two most common causes of a false negative sweat test are: (a) lab error and (b) skin edema.

Multimutation genetic testing involves screening at least 23 CF-causing CFTR mutations (14). This panel identifies approximately 90% of CF causing mutations. Molecular analysis should be ordered in cases with an intermediate sweat chloride test. An expanded CFTR mutation panel, deletion evaluation, and/or direct gene sequencing is available for cases when a genetic screen failed to identify

two CF-causing mutations and a repeat sweat test was intermediate (40 to 59 mmol/L).

The NPD measures CFTR function within the nasal respiratory epithelium. The technique involves the following three measurements of the potential difference across the nasal epithelium: (a) basal state, (b) after nasal perfusion with amiloride (blocks sodium transport—the major component of the NPD), and (c) after nasal perfusion with a chloride-free solution containing isoproterenol (a camp agonist—stimulates CFTR chloride transport). Patients with CF will demonstrate a high basal state potential difference, a large decline with amiloride, and minimal response to isoproterenol. Although not widely available, measuring the NPD is useful in cases where the sweat test and genetic analysis results are inconclusive but atypical CF is suspected due to clinical presentation in one or more organs.

Other rare tests for CF include pancreatic function analysis, such a 72-hour stool collection for fecal fat analysis. Pulmonary function tests and bronchoalveolar lavages can be helpful to define the extent of pulmonary disease.

Primary Immunodeficiency Testing

Immunologic testing can evaluate both the cellular and humoral immune systems. Immune dysfunction is common in patients with refractory CRS (15), therefore, knowledge of the available immune testing options is important.

Humoral immunity testing involves both quantifying immunoglobulin (Ig) levels and assessing for a functional immunoglobulin deficiency. Measurements of serum IgG, IgA, and IgM along with IgG subclasses are helpful to quantify a humoral deficiency. The significance of an IgG subclass deficiency remains controversial, while current recommendations state that it is not significant unless it is associated with an impaired specific antibody response. A functional immunoglobulin deficiency is evaluated by assessing the antibody response following administration of an unconjugated polysaccharide vaccine, such as pneumovax. For adults, a functional immunoglobulin deficiency is diagnosed if there was a lower than fourfold increase in antibody titers to 70% of the serotypes tested (16).

Cellular immunity is mediated by T cells and deficiencies with this system often result in severe infections. The complete blood count (CBC) is useful to identify a lymphopenia and other hematologic defects. Flow cytometry uses cell surface markers to evaluate lymphocyte subpopulations and provide subset quantitative information. The cutaneous delayed-type hypersensitivity test is an *in vivo* test measuring the recall response to an intradermal injection of an antigen, which the patient has previously been exposed.

Infectious Testing

Most cases of sinonasal infections can be diagnosed with a thorough history, physical exam, and rigid sinonasal endoscopic exam. However, resistant organisms or atypical infections must be considered in patients with persistent symptoms despite adequate antimicrobial therapy.

Sinus culture and sensitivities can be obtained by a variety of methods, including endoscopic middle meatal swabs, endoscopic suction sinus aspiration, or sinus puncture. Historically, the sinus puncture (either through the canine fossa or inferior antral window) was considered the gold standard sinus culture method; however, it has fallen out of favor due to the morbidity associated with significant patient discomfort. Recent evidence supports that endoscopic middle meatal swab is an accurate and less morbid culture method, with an 82% correlation rate to sinus puncture (17). Additionally, endoscopic sinus suction aspiration has an 88.5% correlation rate to sinus puncture (18). The endoscopic-directed culture methods are tolerated well by patients and can be obtained in the clinic.

When an atypical infection is suspected, tissue should be sent for fungal and mycobacterial culture and staining. The most common fungal stains available include: Gomori Methenamine Silver (GMS), Periodic acid-Schiff (PAS), Potassium Hydroxide (KOH), and Chitin-specific stain. Mycobacterial species can be identified by nucleic acid hybridization probes, polymerase chain reaction (PCR) analysis, or Ziehl-Neelsen staining. The Ziehl-Neelsen technique involves an initial stain with carbolfuchsin (red) and then rinsed with an acid (hydrochloric or sulfuric) and counterstained with methylene blue. Mycobacterial species will retain their red staining, and are thus called acid-fast bacilli.

Systemic Inflammatory Disease Testing

Evaluation of an underlying systemic inflammatory disease must be considered in patients with refractory CRS. Although most patients will already have a diagnosis of a systemic inflammatory disease, some cases may have isolated nasal cavity involvement and prompt a new diagnosis. Common diseases include Wegener granulomatosis, Sarcoidosis, Churg-Strauss, Sjogren syndrome, and Systemic Lupus Erythematosus.

General inflammatory markers include erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP). Nonspecific autoantibody tests include antinuclear antibodies (ANA) and rheumatoid factor (RF). The antineutrophil cytoplasmic antibody (ANCA) is usually an IgG immunoglobulin against two neutrophil cytoplasmic antigens called proteinase-3 (PR-3) and myeloperoxidase (MPO).

Wegener granulomatosis is most commonly anti-PR-3 ANCA positive, while Churg-Strauss is usually anti-MPO ANCA positive. However, 20% of patients with Wegener granulomatosis may demonstrate anti-MPO ANCA. Additionally, negative ANCA results may occur in 52% of limited Wegener cases and in 10% of cases with multisystem involvement.

If sarcoidosis is considered, a serum angiotensin-converting enzyme (ACE) is elevated in 60% of patients and serum calcium levels commonly demonstrate hypercalcemia. If Sjogren syndrome is suspected, then serum

TABLE 28.5 SUMMARY OF COMMON SINONASAL LABORATORY TESTS

Sinonasal Disease	Lab Tests
CF	Sweat chloride test
	DNA testing
	NPD
Primary immunodeficiency	*Humoral*
	Serum immunoglobulin levels (IgA, IgG, IgM)
	IgG subclasses
	Antibody response
	Cellular
	CBC
	T-cell Flow cytometry
	Cutaneous delayed hypersensitivity
Bacterial infection	Middle meatal swab
	Endoscopic suction aspiration
	Sinus puncture
Atypical infection	Fungal stains—GMS, PAS, KOH, chitin-specific
	Mycobacterial—Ziehl-Neelsen stain
	Syphilis testing
Systemic inflammatory	ESR, CRP
	ANA
	RF
	ANCA (anti-PR3 and anti-MPO)
	ACE
	SS-Ro, SS-La

SSA-Ro and SSB-La antibody levels can provide helpful diagnostic information. SSA-Ro is positive in 75% of patients with primary Sjogren syndrome (SS) and 15% of patients with secondary SS. SSB-La is positive in 40% to 50% of patients with primary SS and 15% of patients with secondary SS. See Table 28.5 for a summary of common sinonasal lab testing options.

ALLERGY TESTING

Evaluating for the presence of allergy is an important step in the management of sinonasal disease. Allergy can be tested with either *in vivo* or *in vitro* methods. The term "sensitization" refers to a demonstrable IgE reaction to an allergen, whereas the term "allergy" refers to the presence of corresponding symptoms upon allergen exposure. Therefore, it is important to interpret sensitization in the context of the patient's clinical history, since a positive skin test in an asymptomatic patient is clinically irrelevant. Failure to recognize allergy as a contributory factor in sinonasal disease can result in misdiagnosis and treatment failure.

In vivo Allergy Testing

In vivo skin testing is the preferred method of allergy testing because it is fast, less expensive, and more sensitive than *in vitro* testing. A focused skin testing protocol may be employed if there is a single strong offending allergen in the history, such as a penicillin allergy. However, most cases require a broad skin testing protocol, since patients often describe seasonal or perennial allergy symptoms without a single offending allergen. In this scenario, an appropriate geographical panel of indoor and outdoor allergens would be evaluated for sensitization.

TABLE 28.6 INDICATIONS AND CONTRAINDICATIONS FOR *IN VIVO* (SKIN) ALLERGY TESTING

Indications	Allergic rhinitis
	Refractory chronic rhinosinusitis
	Allergic asthma
	Conjunctivitis
	Food allergies
	Some medication allergies (Penicillin)
	Venom allergies (Wasps, bees, yellow jackets, fire ants, and other)
	Latex allergies
Contraindications	High risk for anaphylaxis
	Recent anaphylactic reaction (within last month)
	On medications that interfere with the treatment of anaphylaxis
	Skin disease

There are several indications for *in vivo* skin testing (Table 28.6). The most common sinonasal indications include: (a) suspected allergic rhinitis and (b) refractory CRS. The four primary contraindications to skin testing include patients with any of the following: (a) high risk for an anaphylactic reaction to testing, (b) recent anaphylactic reaction (within the last month), (c) taking medications that interfere with the treatment of anaphylaxis, and (d) skin diseases. High-risk patients are considered those with poorly controlled asthma, clinical history of severe reactions to minimal allergen exposure, and significant cardiovascular disease. Recent anaphylaxis, within the last month, can render the skin unresponsive to allergen exposure, and therefore, a false negative skin test result can occur if tested too early. Medications such as beta-2-antagonists and ACE antagonists can impair the treatment of an anaphylactic reaction and should be avoided if skin testing is performed. Although skin testing is considered safe, systemic reactions occur in 33 patients per 100,000 (19). Therefore, all testing centers should have emergency anaphylactic equipment readily available. Due to a high false-positive test rate, skin conditions such as severe atopic dermatitis, dermographism, and mastocytosis should not receive *in vivo* testing. In cases where there is a contraindication to skin testing, *in vitro* allergy testing should be performed.

A full medication review needs to be performed prior to skin testing, since there are several medications that can affect testing results (Table 28.7). First generation H1-antihistamines should be stopped at least 3 days prior to testing, while second generation H1-antihistamines

TABLE 28.7 FACTORS AFFECTING SKIN TESTING RESULTS

Medications	*Reduced response in the following:*
	H1-receptor antagonists
	H2-receptor antagonists
	Systemic corticosteroids
	Omalizumab (anti-IgE antibody)
	Tricyclic antidepressants
	Tacrolimus
Physiologic	*Reduced response in the following:*
	Age (Infants and Age >50)
	Location (Forearm)

should be stopped 7 days prior to testing. H2-receptor antagonists should be stopped 48 hours prior to skin testing. The following medications have no affect on skin testing: Inhaled or intranasal topical steroids, decongestants, inhaled beta agonists, intranasal cromolyn, and leukotriene receptor antagonists. It is important to consider the age of the patient prior to testing, since infants and adults (older than 50 years of age) have reduced skin-testing responses.

There are two primary methods to *in vivo* testing: (a) skin prick/puncture, and (b) intradermal technique. The skin prick technique is very sensitive but has a poor specificity (e.g., higher rate of false positives). Therefore, a positive test is only considered an allergy if there are clinical symptoms upon exposure to that allergen. The intradermal technique has a higher sensitivity compared to skin prick; however, it carries a much lower specificity. Since the intradermal test is associated with a higher risk for an anaphylactic reaction, it should only be performed with allergens that resulted in a negative skin prick test.

During skin prick testing, both a positive and negative control should be used to evaluate the patient's skin for a normal response. Positive control usually involves a solution of histamine dichloride (10 mg/mL), while the negative control typically uses a saline solution, similar to the allergen extract. Skin prick wheals are measured at 15 to 20 minutes after the prick. A positive skin prick result is defined by one of two options: (a) wheal larger than 3 mm or (b) a wheal equal to or larger than the positive control.

Intradermal skin testing involves injecting 0.02 to 0.05 mL of allergen extract into the dermis, creating a small bleb. Since it is estimated to be 100 to 1,000-fold more sensitive, intradermal testing is only performed using allergens that created a negative response on skin prick testing. Due to a high rate of false positives and systemic reactions, food and latex allergies are not evaluated using the intradermal technique.

In vitro Allergy Testing

In vitro allergy testing involves the measurement of serum IgE, and can either be allergen-specific or total IgE. Although *in vivo* testing is the preferred method for allergy testing, there are several advantages of *in vitro* testing (Table 28.8). First, since it is a blood test, there is no risk of an allergic reaction to the patient. This is ideal for patients with a history of prior anaphylaxis or severe allergic reactions to minimal allergen exposure. Secondly, *in vitro* testing is not affected by current medication usage. Therefore, patients are not required to stop taking antihistamines, antidepressants, or systemic steroids prior to testing. Thirdly, *in vitro* testing is not affected by skin disease, while cutaneous conditions, such as atopic dermatitis or dermographism, often preclude the use of *in vivo* testing. Other advantages include being more convenient (single blood test) and may be more accurate for detecting food allergies.

TABLE 28.8 ADVANTAGES OF *IN VITRO* ALLERGY TESTING

No risk of allergic reaction during testing
Not affected by concurrent medications
Not affected by skin disease
Convenient
Accurate for food allergy testing

There are two primary forms of *in vitro* allergy testing: (a) immunoassays and (b) total IgE levels. Immunoassays identify the presence of "allergen-specific IgE" by evaluating the interaction between antigens and antigen-specific antibodies to provide both qualitative and quantitative information. There are three common types of immunoassays: (a) Enzyme-linked immunosorbent assays (ELISA), (b) Fluorescent enzyme immunoassay (FEIA), and (c) Radioallergosorbent test (RAST). Both the ELISA and FEIA involve anti-IgE antibodies that are coupled with an enzyme, that when mixed with a specific substrate, result in a change in color or give off a fluorescent signal. The RAST involves an antibody coupled to a radioactive tag.

Immunoassay technique involves placing patient serum (which contains several immunoglobulins, including IgE) onto a premade matrix with known antigens. After a period of incubation, excess immunoglobulins are washed off leaving only the antigen–antibody complex on the matrix. This complex is then incubated with anti-IgE antibodies, which are coupled with one of the above indicators (ELISA, FEIA, or RAST). After a substrate is added or radioactive detector is performed, the IgE-antigen complexes can be quantified. Since IgE from the patient's serum bind to the antigen on the matrix in direct proportion to their concentration in serum, a quantitative IgE value is provided. Immunoassay results are usually reported in units of kIU/L or ng/ml. The conversion rate is 1 kIU/L = 2.4 ng of IgE/mL. Results are reported as a grade between I and VI based on arbitrary cut-points (Table 28.9). Although there is limited clinical significance between immunoassay grades, allergen-specific IgE levels of grade III or higher

TABLE 28.9 GRADES OF IgE IMMUNOASSAY RESULTS

Immunoassay Class	IgE Concentration (kIU/L)
0	<0.35
1	0.35–0.7
2	0.7–3.5
3	3.5–17.5
4	17.5–50
5	50–100
6	>100

have a more consistent correlation with the presence of patient symptoms upon exposure to the allergen (20).

Measurement of total serum IgE must not be confused with measurement of allergen-specific IgE, which is performed by immunoassay techniques. Total serum IgE level does not provide information about which allergens the patient is sensitive to. Currently, total serum IgE has limited clinical value since it can be elevated in a number of different diseases such as: asthma, allergic rhinitis, atopic dermatitis, allergic fungal rhinosinusitis (AFRS), parasitic infections, allergic bronchopulmonary aspergillosis, and Wiskott-Aldrich syndrome. Although controversial, current uses of total serum IgE measurement may include differentiating between CRS and AFRS (21) or early prediction of an AFRS exacerbation (22).

It is important to remember that *in vitro* allergy testing must be evaluated in the context of the patient's clinical presentation and history. A negative immunoassay, in the setting of a strong allergy history, does not exclude the possibility of an allergy. If there is no contraindication, an *in vivo* allergy test should be performed in this scenario. Additionally, a high-grade immunoassay or elevated total IgE result in the setting of an asymptomatic patient has minimal clinical relevance.

OLFACTORY TESTING

The primary purpose of olfaction is to provide protection from potentially harmful agents in the environment, such as: spoiled foods, gas leaks, and smoke. Additionally, when olfaction is altered or lost, it significantly lowers the patient's health-related quality of life since the sense of smell provides a pleasurable component to life. An organized approach to olfactory testing is important since there are an estimated 2.7 million adults in the United States with olfactory dysfunction.

The majority of olfactory disorders can be diagnosed with a thorough history, physical exam, and rigid sinonasal endoscopic exam. Although rarely indicated, objective olfactory testing may be indicated to provide objective information pertaining to the degree of dysfunction. Quantitative olfactory testing can be organized into two categories: (a) Psychological, and (b) Electrophysiologic (Table 28.10). Since psychological tests are easier to administer, they are most commonly used in clinical practice. The electrophysiologic tests are primarily used for research purposes and have limited clinical utility. Although not discussed in this section, a CT scan of the sinuses and MRI of the olfactory cleft and brain should be considered during the evaluation of olfactory disorders. Additionally, a mini-mental exam should be considered when a neurodegenerative disease is suspected.

TABLE 28.10 LIST OF OBJECTIVE OLFACTORY TESTS

Quantitative Category	Olfactory Testing
Psychological	SIT
	Butanol Threshold test
	Sniffin' Sticks
Electrophysiologic	OERP
	EOG

Psychological Olfactory Tests

The Smell identification test (SIT) is a commonly used olfaction test that utilizes a scratch-and-sniff format. It has excellent test-retest reliability and has been validated in several different populations and disease states. It is composed of 40 odors with a selection of four corresponding answer options per odor (Fig. 28.3). Patients take the exam alone and are instructed to guess at the answer even if they cannot smell the odor. Anosmic patients should receive a score of approximately 10/40 since random answer selection should result in a score of 25%. Malingering patients will intentionally pick the wrong answer and often result in a score less than 10/40. The final scores are then compared to normal age-matched norms and the results are analyzed.

The butanol threshold test involves the identification of a solution containing butyl alcohol. The patient sniffs two bottles, one contains water and the other contains a specific concentration of butanol, with each nostril tested separately. After every incorrect identification response, the concentration of butanol is increased by a factor of 3 until one of the following is occurs: (a) the patient is able to correctly identify the butanol bottle five responses in a row or (b) until the concentration of butanol reaches 4%. The concentration threshold is then compared to age-matched norms and the results are analyzed.

Sniffin sticks testing use a series of reusable n-butanol pens, which contain different concentrations of odor. The test contains three parts and should be performed in the following order: (a) threshold test for butanol, (b) discrimination of odors, and (c) identification of odors. The



Figure 28.3 Smell identification test (Sensonics Quick-SIT, www.sensonics.com).

patient is blind folded and the odorant pens are presented 2 cm from an isolated nostril. For threshold testing, the pens are labeled from 1 (highest concentration) to 16 (lowest concentration) and the examiner begins by presenting pen 16 and continues to increase the concentration until the patient correctly identifies the butanol pen at least twice. During discrimination testing, patients are presented with a triplet of pens, with one of the three pens containing a unique odorant. The patient is asked to identify the unique odorant pen. Identification testing is similar to the SIT, whereby an odorant pen is provided and the patient is asked to provide the correct odor from a list of four responses.

Electrophysiologic Olfactory Tests

Olfactory-event related potentials (OERP) utilize the use of an electroencephalogram and electrooculogram and measure the responses after the delivery an odorant stimuli. Odors typically involve both a pure trigeminal stimulant as a control (i.e., carbon dioxide) and a pure olfactory stimulant (i.e., butanol or hydrogen sulfide). N1 is the first negative peak measured and P2 is the second positive trough. The peak amplitudes and latency between N1 and P2 are recorded and compared to age-appropriate norms. Although not clearly defined, olfactory dysfunction typically results in reduced wave amplitudes and prolonged latencies (23).

The electro-olfactogram (EOG) measures the electrical potentials of the olfactory epithelium in response to an odorant stimulus. Using endoscopic visualization, an electrode is placed onto the olfactory epithelium and a reference electrode is placed on the nasal dorsum. Due to difficulties in electrode placement and patient discomfort, combined with minimal human research, EOG has limited clinical utility and remains primarily a research tool (24).

NASAL AIRWAY PATENCY EVALUATION

Nasal obstruction is a commonly presenting sinonasal complaint and contributes to a reduced quality of life. Two objective tests, which have attempted to quantify nasal patency, include: (a) Acoustic rhinometry and (b) Rhinomanometry. The challenge remains that nasal obstruction is a subjective symptom, which is poorly correlated with objective nasal patency testing modalities. Despite limited clinical utility, acoustic rhinometry and rhinomanometry continue to be investigated and may play a role in certain clinical scenarios.

Acoustic Rhinometry

Acoustic rhinometry uses reflected sounds waves to measure the cross-sectional area (CSA) of the nasal cavity. A nosepiece containing a sound generator ("click") and microphone is placed within the nostril, ensuring it does not distort the nasal alae. A sound wave is generated that travels through the nasal cavity and becomes reflected at regions of anatomic narrowing. The reflected acoustic waves are recorded and the CSA is calculated. Two separate recordings are performed, before and after nasal decongestant, to determine the mucosal and structural components of the CSA. An acoustic rhinometry graph will have the distance (cm) on the x-axis and the CSA (cm^2) on the y-axis. According to a consensus report on acoustic rhinometry, the three minimal CSAs include: (a) CSA1: nasal valve area, (b) CSA2: anterior head of the inferior turbinate and/or middle turbinate, and (c) CSA3: mid-posterior aspect of the middle turbinate (25).

TABLE 28.11 THREE METHODS OF RHINOMANOMETRY TRANSNASAL PRESSURE MEASUREMENTS

Transnasal Pressure Measurement Method	Description
Anterior	Pressure detector is placed into the opening of a single nostril
Posterior	Pressure detector is placed within the oral cavity or oropharynx
Postnasal	Pressure detector is passed through one nostril into the nasopharynx

Dual-mode acoustic rhinometry is a variation of the standard technique whereby the nasal valve CSA is measured during apnea and during inspiration. The primary application of dual-mode acoustic rhinometry is during the diagnosis of nasal valve collapse. A normal patient should have an Inspiratory: Apnea CSA ratio equal to 1; while patients with nasal valve collapse have ratios less than 1 due to inspiration-related narrowing.

Rhinomanometry

Rhinomanometry simultaneously measures transnasal pressure (Pa) and airflow (cm^3/s), which is used to calculate the nasal resistance ($Pa/cm^3/s$). Rhinomanometry data is commonly presented using a pressure-flow curve with the change of transnasal pressure (ΔP) on the x-axis and airflow (V) on the y-axis. There are both passive and active methods of rhinomanometry. During the passive method, the patient holds their breath while air is pumped into the nasal cavity at a fixed rate. The active method involves the patient using his/her own nasal respiration as the source of airflow. The active method for rhinomanometry is the most commonly used technique since it is easier to perform and provides a variable pressure-flow curve rather than a fixed-flow curve.

Airflow is measured using a facemask while simultaneous transnasal pressure can be measured using one of three different methods: (a) Anterior, (b) Posterior, or (c) Postnasal (Table 28.11). Due to technical ease and improved patient comfort, anterior rhinomanometry is the most commonly used method of transnasal pressure measurement. The primary disadvantage of anterior rhinomanometry is that it cannot directly measure total airway values, since one side of the nose is plugged. Therefore, left and right values must be combined to calculate total nasal airway values.

CILIARY TESTING

Mucociliary clearance is an essential function for the development of healthy upper and lower airways. Normal human cilia have a basal cilia beat frequency of 9 to 15 Hz, which results in a normal mucus velocity between 3 and 25 mm/min. Although a full review of cilia structure is beyond the scope of this section, the essential components include nine microtubule doublets arranged in an outer circle around two central single microtubules (9 + 2 arrangement). Using adenosine triphosphate as an energy source, motility is accomplished by stimulation of the dyein arms, attached to the doublet microtubules.

Primary ciliary dyskinesia (PCD) is a rare hereditary disease, typically autosomal recessive, which results in abnormal mucociliary clearance. It commonly presents with neonatal respiratory distress, recurrent childhood pulmonary infections, chronic otitis media, and CRS. PCD in the presence of situs inversus, bronchiectasis, and CRS, is called Kartagener disease. Although most cases of PCD are identified in childhood, milder phenotypes may present in adulthood with male infertility and CRS. Testing for PCD often begins with screening tests (saccharin test or nasal nitric oxide [nNO] levels) followed by more definitive tests such as analysis for ciliary motility, structure, and genetic sequencing. The following section will discuss common methods for PCD evaluation.

Saccharin Test

The saccharin test is the traditional screening modality for PCD. It measures mucociliary clearance by placing a saccharin microtablet onto the anterior head of the inferior turbinate and quantifying the time it takes for the patient to taste the sugar. Although there are no standardized normal values for saccharin test results, values shorter than 20 minutes are considered in the normal range. The challenge remains that the saccharin test is unreliable in children (26), and therefore it is not commonly used during the diagnosis of PCD.

Nasal Nitric Oxide

nNO measurement has become the preferred screening modality for PCD. The technique involves placing a nasal catheter through a foam sleeve, which is used to seal the nostril from the atmosphere and measure the concentration of nitric oxide. During nNO measurements, the patient performs maneuvers designed to close the soft palate, which minimizes the contamination of nasal gases by pulmonary gases. Due to technical considerations surrounding the palate closure maneuvers, the youngest age for nNO measurements is 5 years old.

Several studies have demonstrated that patients with PCD will have low levels of nNO (27,28). False-positive low nNO can occur with CF, panbronchiolitis, and nasal polyposis. Therefore, screening results with a low nNO level, require other confirmatory tests, such as ciliary ultrastructure analysis or genetic analysis, before a definitive diagnosis of PCD can be made.

Ciliary Ultrastructure Analysis

Ciliary ultrastructure analysis, using transmission electron microscopy, remains an integral diagnostic modality during the evaluation of PCD. Fresh ciliated mucosal biopsies are performed and placed in glutaraldehyde. The preferred mucosal biopsy technique is a brushing from the bronchi and pharynx; however, other options include endoscopic bronchial tissue biopsy or inferior turbinate biopsy. Although several ciliary structural defects have been described, most common abnormalities include: (a) absence or shortening of dyein arms, (b) absence of radial spokes, and (c) loss of the central pair of microtubules with transposition of a peripheral doublet into the center (29).

Ciliary Motility Analysis

Ciliary motility analysis is a technically challenging diagnostic modality whereby fresh respiratory mucosal biopsies are placed in isotonic saline and rapidly transferred to a lab for high-speed video microscopy. Cilia are then evaluated for the following beat characteristics: (a) coordination, (b) frequency, and (c) pattern. The introduction of digital high-speed video microscopy has significantly improved the diagnostic utility of cilia motility analysis, as certain beat patterns have been correlated with specific ultrastructural defects. For example: (a) immotile or flickering cilia correlate with outer dyein arm defects, (b) low-amplitude stiff beats correlates with either an isolated inner dyein arm defects or radial spoke defect, and (c) a whip-like beat correlates with central microtubule defects, such as a peripheral doublet transposition (30).

Genetic Analysis

Genetic analysis for PCD can be challenging due to genetic heterogeneity and the extensive size of PCD-causing genes. The two most common genes mutated in PCD include DNAI1 (outer dyein arm intermediate chain) and DNAH5 (outer dyein arm heavy chain), both of which have been implicated in 30% to 38% of PCD patients (31). The other four genes with mutations implicated in ciliary dysfunction include: DNAI2, DNAH11, TXNDC3, and KTU. The KTU gene produces a cytoplasmic protein that is required for dyein arm assembly (32).

IN-OFFICE IMAGING

Over the last decade, point of care rhinologic imaging has been made possible with the development and refinement of in-office CT. Although the exact role of this imaging modality has not yet been defined, it is becoming a common diagnostic option and deserves discussion. There are four in-office CT scanners available on the market: (a) Xoran MiniCAT (Fig. 28.4), (b) Neurologica OTOscan, (c) J. Morita 3D Accuitomo 170, and (d) 3M/Imtec Iluma. These new in-office devices provide similar high-resolution CT image detail compared to traditional sinus CT scans



Figure 28.4 In-office CT scanner (Xoran Minicat, www.xorantech.com).

TABLE 28.12 RADIOLOGIC RADIATION EXPOSURE COMPARISONS (34)

CT Studies	Radiation Dose (mSv)
In-office Sinus CT	0.2
Abdomen and Pelvis CT	15
Chest CT (low dose)	1.5
Conventional Sinus CT	0.96
Mammogram	0.40
Chest x-ray PA and Lateral	0.10
Dental intraoral x-ray	0.005

and can be utilized in most image-guidance machines during ESS. Although some scanners can provide ultra high resolution 0.09 mm slice thicknesses, the most common clinically utilized thicknesses range between 0.625 and 1 mm. Acquisition time is usually less than 60 seconds for 600 frames.

The two primary advantages of in-office imaging is optimizing patient convenience and reducing patient radiation exposure. Eliminating both the need for a radiology appointment and the need for a second otolaryngology clinic visit to review the CT and plan management may optimize patient convenience. Patients with CRS often require multiple sinus CT scans throughout their life; therefore, minimizing radiation exposure is important. Compared to traditional sinus CT scans, in-office CT studies have been demonstrated to provide a lower radiation dose (Table 28.12). Another potential advantage would be to correlate current patient symptoms with immediate CT images; however, a recent article by Ryan et al. (33) demonstrated that symptoms correlated poorly with immediate in-office imaging, while endoscopy correlated well with CT images. This supports the literature whereby symptoms correlate poorly with CT stage and minimizes the importance of immediate sinus CT acquisition.

Despite several advantages for in-office CT scanning, there are several disadvantages that must be considered (Table 28.13). Although the radiation dose is low for the patient, the radiation exposure for in-office staff must be considered. Proper space and radiation protection must be implemented to ensure long-term safety for daily office personnel. Another important issue that must be addressed is overutilization and patient self-referral. Since in-office CT scanners are expensive, there is a danger that CT studies may be performed to help curtail some of the costs rather than for clinically indicated reasons. This is a controversial topic but must be considered during in-office imaging. Another concern is determining which medical specialty should interpret the in-office sinus CT scan. While most otolaryngologists are proficient in the interpretation of a sinus CT study, they may not be competent to identify nonrhinologic pathology. This raises the debate whether or not a radiologist needs to evaluate the in-office CT scan to protect against the medicolegal ramifications of missing nonrhinologic diseases, which may occur by an otolaryngologist interpretation.

In-office CT scanners have several advantages, which include improving patient convenience and reducing patient radiation exposure. However, there remain several areas of controversy, which must be elucidated before this novel technology can become widely implemented.

TABLE 28.13 CONSIDERATIONS OF IN-OFFICE CT

Advantages	Disadvantages
Improved patient convenience	Risk of radiation exposure to office staff
Immediate image viewing	Physician cost
Image-guidance capability	Risk of needless imaging
Reduced patient radiation exposure	Lack of optional IV contrast
	Liability for missed nonsinus pathology

HIGHLIGHTS

- Following the history and physical exam, a thorough rigid sinonasal endoscopy is an important first investigation during the evaluation of sinonasal pathology.
- Sinus CT imaging is considered the gold standard radiologic investigation for sinonasal inflammatory disease.
- MRI imaging is a useful adjunct during evaluation of a suspected sinonasal neoplasm or complication of acute rhinosinusitis.
- During cases of medically refractory chronic rhinosinusitis, consider obtaining tests to evaluate for a possible underlying allergy, systemic inflammatory disease, atypical infection, or congenital disease.
- Although there are several options for olfaction and nasal patency testing, they play a limited role in clinical practice, and remain primarily research tools.
- In-office CT imaging is an exciting new investigative tool; however, further research is required to define its exact role in sinonasal evaluation.

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29 Allergic Rhinitis

James T. O'Neil *James W. Mims*

Allergic rhinitis, the second leading cause of chronic disease in the United States, affects up to 60 million Americans, approximately one person in every four households. Of those affected, more than half have experienced symptoms for longer than 10 years (1). Allergic rhinitis has a substantial effect on patient's quality of life, sleep, school performance, and productivity. Physicians should also be aware of the association of allergic rhinitis with other conditions such as asthma. Asthma is both underdiagnosed and suboptimally controlled in the United States (2). This chapter focuses on the epidemiology, diagnosis, and treatment of allergic rhinitis.

DEFINITION AND GENETICS

Allergic rhinitis is clinically defined in the 2008 Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines as "a symptomatic disorder of the nose induced after allergen exposure by an IgE-mediated inflammation" (3). Normally, harmless particles elicit an unnecessary immune response in patients with allergies. It is the inflammation that causes their symptoms. When harmless nonself substances cause inflammation, they are called hypersensitivity reactions. Atopy is the genetic predisposition to develop allergic hypersensitivity reactions. Examples of allergic disease are allergic rhinitis, allergic asthma, atopic dermatitis, and food allergies. One atopic condition tends to put individuals at risk for others.

Atopic conditions occur more frequently in children when parents are atopic, but do not follow simple Mendelian patterns of inheritance. The genetics of allergic rhinitis is complex and not well understood. Initial speculation was that the genetics of allergy was based in alterations of the inflammatory process. Single-nucleotide polymorphisms (SNPs) of inflammatory mediator genes were targeted. Some allergic individuals were found to have more SNPs in genes coding for allergic inflammation including interleukins IL-4, IL-13, and T-cell receptors than nonallergic controls (4). Many SNPs of inflammatory mediators have been found to be weakly associated with allergic patients, but these findings have been hard to reproduce (4). Broader studies such as the Genome Wide Association studies have identified gene candidates that were not directly linked to the allergic inflammatory cascade (5). It is likely that a combination of factors of innate immunity and variable changes in the regulation of inflammation may both contribute toward allergic hypersensitivity.

Allergic rhinitis is genetically a heterogeneous disease. As such, the predisposition for allergic rhinitis is influenced by multiple, perhaps hundreds, of genetic variables. An example of a gene affecting innate immunity influencing allergic disease can be seen in atopic dermatitis. A defect in the protein filaggrin has been identified in about one-third of those with atopic dermatitis (6). Filaggrin is a protein that helps connect or seal the outer layer of keratinocytes, and it is speculated that the genetic "loss of function" makes the skin barrier more porous. A filaggrin barrier defect may augment any genetic tendency toward promoting inflammation through increased allergen exposure through the more porous keratinocyte connections.

BASIC IMMUNOLOGY OF ALLERGY

IgE-mediated hypersensitivity (Gel and Coombs Type 1) defines allergic disease. An allergen is recognized by an antigen-presenting cell (APC) then processed and presented to a T-helper cell lymphocyte. Specific human leukocyte antigen receptors on the APC and a specific T-cell receptor are both necessary for this communication to take place. TH2 cells, a specific type of T-helper cell, are predisposed toward promoting allergic inflammation (7). TH2 cells present the allergen (or allergic epitope) to a B lymphocyte, which must also have a B-cell receptor for

that specific allergen. All of these specific receptors must be present to form an allergic response. IL-4 and other "allergic" cytokines can induce the B cell to change into an IgE-producing plasma cell. IgE can then travel via the circulatory system and bind to IgE receptors on basophils and mast cells throughout the body.

Reexposure to the specific allergen can cause an IgE-mediated degranulation of basophils and mast cells. This releases inflammatory mediators such as histamine. Histamine binds to histamine receptors on endothelial cells and vascular smooth muscle causing vasodilation and increased permeability (8). Patients then experience rhinorrhea, sneezing, and nasal congestion. Other proinflammatory mediators are released including IL-5, which recruit eosinophils and leukotrienes that promote "late phase" inflammation. The promotion of more inflammation is balanced by factors that down-regulate inflammation such as IL-10 and regulatory T cells (9).

EPIDEMIOLOGY

Allergic rhinitis is a common condition throughout the world, as well as in the United States. The prevalence of the disease is rising in developed countries (10). The widespread prevalence of allergic rhinitis places a significant burden on our health care system. There is evidence of an "allergic march" in which infant atopy leads to later problems with allergies. Also, the controversial "hygiene hypothesis" may explain the increase of allergies.

The prevalence of allergic rhinitis is difficult to precisely estimate for several reasons, including regional differences and how allergic rhinitis is diagnosed. Allergic rhinitis is frequently quoted to affect between 10% and 30% of adults, and up to 40% of children (11). In some countries, over 50% of adolescents report symptoms of rhinitis (1). However, larger epidemiologic studies suggest a lower prevalence. In the United States, the 2009 National Health Interview Survey conducted by the Centers for Disease Control reported that 17.7 million adults or 7.8% of those surveyed had been diagnosed with "hay fever" in the last 12 months (12). Over 7 million children were reported to have "hay fever" and 8.2 million (11%) were reported to have "respiratory allergy" in the last 12 months (13). There is often a difference in reported rates by questionnaire and by actual allergy testing. For example, in Sweden, by questionnaire alone 14.2% were allergic when compared to 9.1% who were positive by questionnaire and skin test (3).

The direct cost of allergic rhinitis includes physician charges and medications used to treat rhinitis, both prescription and over-the-counter. In 2011, Meltzer estimated the direct medical cost of allergic rhinitis at $3.4 billion in the United States (14). A 2002 study estimated direct and indirect costs related to rhinitis in the United States to be $11.58 billion (15). These costs, especially indirect costs, are hard to calculate. But given the prevalence of the disease, allergic rhinitis presents a significant burden in terms of cost.

The "atopic march" refers to the observation that young children with atopic dermatitis and food allergies are at risk of developing asthma and allergic rhinitis in later years (16). Identifying children at risk for allergic rhinitis and asthma can provide an opportunity for early detection and intervention. However, allergic rhinitis and asthma also commonly occur in individuals with no history of early childhood atopy.

The "hygiene hypothesis" is a controversial theory that may explain the increasing prevalence of allergic disease. It is postulated that exposure to infections early in life decreases the chance of atopy later in life. Different studies provide conflicting evidence to this theory (17,18). Evidence supporting the "hygiene hypothesis" includes decreased atopy associated with helminth eradication programs (19), measles vaccinations (20), day care attendance in the first 6 months of life (21), living on a farm during early life (22), and having multiple siblings (23). The controversy arises as published exceptions to the hygiene hypothesis are plentiful, including no observed change in atopic disease after an effective decrease in parasitic disease in Ecuador (24) or the increase in atopy observed after *Streptococcus pneumonia* vaccination in South Africa (25). One explanation for the hygiene hypothesis is that early infections shift the bias of T cells from allergic inflammation (TH2) at birth to a nonallergic bias (TH1) (18). If the TH2 (proallergic) bias persists, individuals are more likely to develop allergic hypersensitivity to otherwise harmless exposures.

DIAGNOSIS

History

Taking a thorough history is critical in the diagnosis of allergic rhinitis. The primary symptoms of allergic rhinitis are rhinorrhea, sneezing, and nasal obstruction (3). Determining if the symptoms are due to allergic rhinitis versus nonallergic rhinitis (discussed in detail in another chapter) can be challenging. In general, anterior rhinorrhea may be a more specific sign of allergic rhinitis than of postnasal drip, which is seen more commonly in rhinosinusitis (26).

The time and location that symptoms occur provide clues to differentiating allergic versus nonallergic rhinitis. Symptoms seen during certain seasons of the year can point the diagnosis toward pollen or mold allergy. Pollens tend to have seasonal peaks as discussed below. Patients sometimes observe that certain locations exacerbate their allergic symptoms, which may lead the physician to consider pet or mold pollen if the development of symptoms occurred after the patient moved to a certain geographic location. Most patients with allergies are polysensitized, which complicates pairing their history with pattern of exposure (3). Nonetheless, a history of allergic symptoms is necessary to diagnose allergic rhinitis as testing and physical findings independent of history are nonspecific. Table 29.1 summarizes reasonable topics to explore in taking an allergic history.

TABLE 29.1 TOPICS TO INVESTIGATE WHEN TAKING AN ALLERGIC HISTORY

- Nasal sneezing, itching, congestion, rhinorrhea
- Eye itching, watering, redness, swelling
- Wheezing, urticaria, eczema, ear pressure, cough
- Onset and duration of symptoms
- Episodic vs. perennial symptoms
- Changes in living conditions
- Length of time living in local area
- Symptom changes with travel or vacations
- Symptom changes with seasons
- Animal exposure at home, work, or school
- Medications tried to alleviate symptoms
- Childhood food allergy, asthma, atopic dermatitis
- Family members with allergy

TABLE 29.2 ARIA CLASSIFICATION OF ALLERGIC RHINITIS (3)

Intermittent	Symptoms are present <4 days a week or <4 consecutive weeks
Persistent	Symptoms are present >4 days per week and/or more than 4 consecutive weeks
Mild	None of the "Moderate/Severe" criteria present
Moderate/Severe	One or more of the following are present: Sleep disturbance Impairment of daily activities, leisure, and/or sport Impairment of school or work Troublesome symptoms

It is also important to be knowledgeable of the pollens common to the local geographic region and their seasonal variation. In the southern United States, pollination of trees occurs in the spring months, with peak levels occurring in March. In northern regions, the month of May tends to have the highest levels of tree pollen. Grass pollens are most often encountered in the summer months. Weed pollen levels are primarily high in the fall. Pollens are uncommon after the first frost. Fungal allergens may have seasonal peaks, but are much less predictable than other seasonal allergens (27).

Classically, allergic rhinitis has been divided as seasonal allergic rhinitis or perennial allergic rhinitis (PAR). However, recent ARIA guidelines recommend intermittent (IAR) and persistent (PAR) as there are too many exceptions to the seasonal model. For example, allergens such as molds and dust mites do not consistently fall into seasonal timeframes, but may cause symptoms intermittently (3). Persistent allergic rhinitis is defined by symptoms present for more than four consecutive days per week or for more than four consecutive weeks (28). Intermittent is defined as any timeframe less than persistent. Symptoms tend to be slightly different with the two groups, with intermittent rhinitis having more sneezing, itching, and rhinorrhea, while persistent patients complain more of nasal obstruction.

Rhinitis can be further classified by severity (Table 29.2) (3). Moderate to severe disease is associated with sleep disturbance, impairment of daily activities, or interference with work or school.

When the diagnosis of rhinitis is being considered, asking about asthma symptoms is also appropriate. Studies have shown that up to 80% of asthmatics have rhinitis, and that 10% to 40% of rhinitis patients have asthma (3). Food allergies and eczema in childhood can also point toward atopy. Family history is useful but far from exact. Allergic rhinitis does not follow Mendelian inheritance. A large study in Sweden showed that parental history of allergy had an odds ratio of 1.3 in predicting positive skin prick test in their children (10).

Physical Findings

Many organ systems can be associated with allergic rhinitis, so a thorough physical examination should be part of the allergic rhinitis workup. The examiner should carefully look for any signs of accompanying otitis, eustachian tube dysfunction, acute or chronic rhinitis, sinusitis, allergic conjunctivitis, and asthma. It is important to note that the asymptomatic patient might have minimal or no findings even with a history suggestive of allergic rhinitis.

In children, findings of dental malocclusion, a high-arched palate, and upper lip elevation may suggest long-standing disease (29). Children also wrinkle their face and frequently wipe their nose during acute attacks. This can cause a supranasal tip crease to develop from frequently lifting the nasal tip (30).

Anterior rhinoscopy is useful, but findings are often not specific for allergic rhinitis alone. Mucus tends to be more abundant in allergic rhinitis, and strands can often be seen between the septum and turbinates. Turbinates are often enlarged (Fig. 29.1), and the mucosa can be described as "pale" or "boggy." Polyps are also a sign of chronic nasal inflammation. Interestingly, they are not seen more frequently in allergic patients (31).

Eye findings include swelling of the lower eyelids due to venous congestion, thickening of the scleral surface, prominent conjunctival vessels, and increased mucous secretions (30). Increased vascularity of the lower eyelids can give the classic "allergic shiners," making the patient look bruised or tired.

Oral pharyngeal findings may include postnasal drip, which tends to drain on the sides. Erythema and edema of the posterior pharyngeal wall may also be observed. Cobblestoning of the posterior pharynx may also be seen.

Auscultation of the chest for wheezing is an important part of the exam due to the high concurrence of allergic rhinitis and asthma. Laryngeal edema and thick stranding mucus have also been observed in the allergic patient (32).

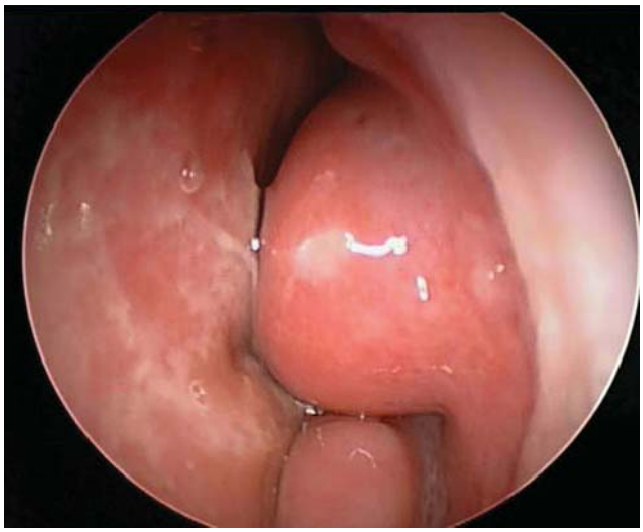


Figure 29.1 Left inferior turbinate hypertrophy. This turbinate was seen in a child with allergic rhinitis. While often seen in patients with allergies, turbinate hypertrophy is not specific for allergic rhinitis.

Testing

Allergy testing is covered in detail in another chapter. Allergy testing is not diagnostic alone, and the patient's history contains the most essential information for diagnosis. However, identification of hypersensitivity to specific allergens can be clinically useful in the management of the allergic patient. Testing is divided into three main categories.

Challenge testing exposes a patient to an allergen, and the subject reports their reaction. Placing allergen directly in the nose of the patient and placing a patient in a room with a circulating airborne allergen have both been used for allergic rhinitis challenges. The subjective nature of the tests along with difficulty in standardization has made it less than ideal for diagnosing allergic rhinitis (33). It is also difficult to test multiple allergens because of the time required between challenges.

Skin testing involves placing an allergen into a patient's skin. This can be accomplished via skin prick or intradermal injection. A wheal and flare are seen if an allergic reaction takes place and this response is compared to positive and negative controls. Physicians should be prepared for the small, but real risk that skin testing can evoke an anaphylactic reaction (34).

Serum-specific IgE levels can also be used to assess the allergic patient. Specific IgE tests assess the presence of IgE that binds to a specific allergen such as cat dander or ragweed. There are several differences between skin testing and specific IgE testing. Specific IgE testing requires only a single venipuncture and does cause local or systemic allergic reactions. Positive skin tests can be suppressed by medication, most commonly antihistamines, while specific IgE testing is unaffected. Skin testing is subject to technique and subjective interpretation, while specific IgE testing is subject to laboratory error. There continues to be some debate about whether allergy skin testing or specific IgE testing is "best," but both are widely accepted in the diagnosis of inhalant allergens (35).

Allergy testing is a valuable tool when combined with a thoughtful history and physical examination. The benefits of allergy testing include its usefulness in differentiating between allergic and nonallergic rhinitis and identifying which exposures may cause symptoms. Allergy testing is required when considering allergen-specific immunotherapy.

TREATMENT

Treatment of allergic rhinitis is traditionally divided into three categories: environmental control, pharmacotherapy, and immunotherapy all have a role. As otolaryngologists are surgeons, a fourth category of surgical interventions is also discussed.

Environmental Control

A logical approach to treat allergic rhinitis is to avoid allergen exposures. However, controlled studies looking at environmental modification for treatment of allergic rhinitis have shown inconsistent results. Varying degrees of environmental control have been attempted. Removing a patient completely from the environment that contains a known allergen has shown success. One study demonstrated improvement of allergic asthma symptoms when students were enrolled in a school located at a high altitude where dust mites could not survive (36). Many studies have evaluated whether measured allergen is decreased in an environment after a control measure is instituted. High-efficiency particulate air (HEPA) filtration (37), low humidity (38), hard surface flooring (removing carpets), hot water laundry (39), barrier protection on pillows and mattresses (40), and acaricides (41) have all been shown to be effective for decreasing allergen levels. These decreased levels do not consistently correlate with decreased symptoms. Studies have not been able to consistently demonstrate control of allergic rhinitis with single environmental control techniques. When multiple environmental control techniques are combined, studies have demonstrated moderate success (37). Avoidance of some allergens is more practical than others. Exposure to outdoor allergens may be decreased by showering and changing clothes after being outside, vacationing during a pollen season to a pollen-free area, sunglasses, or wearing a respiratory mask during activities that cannot be avoided such as mowing the grass. Indoor allergen symptoms may be reduced by combining interventions (42). For dust mite allergy, mattress covers, bedroom HEPA filters, frequent washing of linens, dehumidifiers, and removing carpet may reduce symptoms in a combined approach. Dust mite and cat allergen have

been consistently found in dust sampled from school and work environments (43), making avoidance more difficult. It takes months for the cat allergen levels to decrease after removing a cat from the home; however, some have advocated a pet-free bedroom albeit mixed evidence of efficacy (44). Removing allergenic pets that do not roam freely throughout homes, such as guinea pigs, seems to be effective in the author's experience.

Pharmacotherapy

Pharmacologic therapy is the mainstay treatment for the majority of allergic rhinitis patients. Billions of dollars are spent every year in the treatment of allergies.

Antihistamines have long been a mainstay in the treatment of allergic rhinitis. First-generation antihistamines such as diphenhydramine, clemastine, and chlorpheniramine are generally effective against sneezing, rhinorrhea, nasal itching, and eye symptoms, but are generally less effective on nasal congestion (45). First-generation antihistamines possess significant anticholinergic effects. While the anticholinergic action may help dry secretions, the sedation has been shown to impair school (46), driving (47), and cognitive performance (48). Second-generation antihistamines include cetirizine, levocetirizine, fexofenadine, loratadine, and desloratadine. Oral antihistamines have a quick onset, treat eye and nasal symptoms, and can be administered either daily or as needed. Given their poor efficacy in relieving nasal congestion, they are often combined with decongestants. They cause significantly less or no sedation and have little anticholinergic effect (45).

Intranasal antihistamines include azelastine and olopatadine. Benefits of intranasal antihistamines include a fast onset of action (49), some benefit in allergic and nonallergic rhinitis (50), and some improvement in nasal congestion (51). Intranasal antihistamines work better for allergic nasal symptoms than an oral antihistamine and there is not much benefit in nasal symptoms when oral and topical nasal antihistamines are combined (52). However, when intranasal antihistamines and intranasal corticosteroids are combined, there is an additive effect (53).

Intranasal corticosteroids (INCS) are the single most effective class of medications in the treatment of allergic rhinitis (54). There seems to be little difference in the clinical response between the available intranasal steroids in the United States (55). While nasal steroids can be beneficial when used intermittently (56), the maximal effect is usually seen in 7 to 10 days (57). When used at the recommended dose, INCS have shown to be relatively safe in both children (58) and adults. Studies with intranasal fluticasone propionate, mometasone furoate, and budesonide have indicated no effect on growth in children at recommended doses compared with placebo (58–60). One study indicated growth suppression when beclomethasone dipropionate was given for a year (60). Long-term studies of the effect of INCS on growth have not been published, so caution in children is warranted. Other complications reported with nasal steroids include epistaxis and nasal irritation, which may be exacerbated by the patient tilting the bottle toward their nasal septum during application. Nasal septal perforation is a rare complication. Systemic steroid effects are seen infrequently with INCS, but can occur.

Systemic steroids are effective at decreasing the inflammation from allergic rhinitis, but few studies have addressed their optimal role or dose. However, systemic steroids carry a significant complication profile. Other medications should be tried before using systemic steroids. For severe intermittent allergic rhinitis that is otherwise not well controlled, a short course of systemic steroids may be reasonable.

Leukotriene modifiers are effective for allergic rhinitis and control symptoms comparable to antihistamines (61). They have also been shown to have an added effect when combined with antihistamines similar to INCS (62). Monteleukast is currently the only leukotriene modifier in the United States that is FDA approved for the treatment of allergic rhinitis. There have been reported concerns with behavioral changes, depression, and suicidality with leukotriene modifiers (63). Leukotriene modifiers can be a good choice for patients who suffer from allergic rhinitis and asthma (64).

Cromolyn sodium is a mast cell stabilizer, decreasing the ability for mast cells to release proinflammatory mediators, including histamine. Cromolyn requires frequent dosing and has low efficacy. Ideally, cromolyn is optimally used just before allergen exposure for maximum effect. However, cromolyn has been shown to have an excellent safety profile (3).

Decongestants are most effective with nasal congestion. As such, they work well when combined with oral antihistamines. Side effects include hypertension and sleep disturbance. Decongestants seem to be best fit as an "as needed" medication for those patients with intermittent allergic rhinitis (3).

Selecting and combining allergy medication is based on frequency of use, needed onset of action, and which symptoms are targeted. Table 29.3 lists the relative benefits of the different classes of allergy medication.

Surgery

Inferior turbinate hypertrophy appears to be at least partially responsible for nasal congestion seen with allergic rhinitis. A recent study showed radiofrequency ablation of the inferior turbinate provided decreased nasal resistance and improved congestion when compared to intranasal mometasone spray (INCS) (65). A follow-up study showed that these results provide quality of life benefit at 5 years after turbinate reduction (66). Others have shown that allergic rhinitis patients refractory to medical therapy had improved symptoms at 1 year after radiofrequency turbinate reduction (67). This data underscores turbinate reduction playing a role in the treatment of allergic rhinitis in selected patients.

Other anatomic abnormalities can complicate allergic rhinitis. Surgically addressing nasal valve collapse, septal

TABLE 29.3 PHARMACOLOGIC OPTIONS FOR RHINITIS: EFFECTS ON SYMPTOMS

Medication	Strengths	Weaknesses
Oral antihistamines	Fast onset Sneezing, itching, rhinorrhea Ocular symptoms Safe	Nasal congestion Sedation with 1st Generation
Nasal antihistamines	Fast Onset Sneezing, itching, rhinorrhea Helps some with congestion Useful in Nonallergic rhinitis Safe	Taste Some sedation
Intranasal corticosteroids	Very effective for allergic rhinitis Nasal congestion, Sneezing, itching, rhinorrhea Useful in sinusitis	Nasal irritation Epistaxis Rare systemic steroid effects Slower onset
Leukotriene modifiers	Treats allergic rhinitis and asthma Lesser rhinitis efficacy	Behavioral changes Some require monitoring liver enzymes
Oral decongestants	Fast onset Nasal congestion, rhinorrhea	Sleep disturbance Hypertension
Mast cell stabilizers	Safety Few side effects	Frequent dosing Lesser efficacy
Topical anticholinergics	Watery rhinorrhea Helps with nonallergic rhinitis Helps in viral rhinitis	Nasal congestion Sneezing, itching

deviation, septal spurs, adenoid hypertrophy, nasal polyps, and chronic sinusitis may benefit the symptoms experienced by an allergic rhinitis patient. As surgical procedures are not thought to decrease allergic inflammation, it is appropriate to consider these procedures as adjuncts to other allergic therapy.

Immunotherapy

Immunotherapy, also known as allergy desensitization, promotes tolerance by regularly exposing a sensitized patient to the allergen(s) to which they are sensitized (68). Immunotherapy holds the most promise for patients to permanently decrease or eliminate their symptoms to an allergen. Immunotherapy can be given subcutaneously (shots), sublingually, intralymphatically (69), orally, or nasally. The two most common methods are subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), both of which are discussed in more detail below. Changes in T-helper cells and T-regulator cells that down-regulate inflammatory mediators is one proposed theory of how immunotherapy works, but a precise mechanism is not known.

Subcutaneous Immunotherapy

SCIT involves injecting allergens to which the patient is sensitized into the subcutaneous tissue. SCIT has been shown to be effective for allergic rhinitis in a Cochrane meta-analysis of placebo control single allergen trials (70). SCIT also decreases the development of new inhalant allergen sensitivities (71) and may decrease the incidence of developing allergic asthma in patients with allergic rhinitis (72). There are two phases of SCIT: escalation and maintenance. Escalation involves starting with a very dilute dose for safety, then gradually increasing the concentration of the allergen with each shot delivered once or twice weekly in most schedules. The concentration is escalated to an effective dose range. Maintenance therapy involves giving the same effective dose at regular intervals usually weekly to monthly. These intervals between shots are spaced out over time. The average patient continues the maintenance schedule for 3 to 5 years. Most patients can continue to see decreased allergic response even after stopping the scheduled shots. Occasionally, patients need to return to SCIT when allergic symptoms return (73).

Patients undergoing SCIT receive high levels of allergen. This poses the risk of anaphylaxis each time a shot is administered. Risk factors for either developing anaphylaxis or difficulty in managing anaphylaxis during allergen immunotherapy include poorly controlled asthma, escalation of the immunotherapy dose, prior episodes of anaphylaxis, and beta-blocker therapy (74,75). Offices giving SCIT must be prepared to handle anaphylaxis if allergy shots are administered. The time, expense, and anaphylactic risk indicate that immunotherapy should be reserved for patients with moderate to severe disease that is not well controlled with other measures (68).

Sublingual Immunotherapy

SLIT is performed by placing drops of allergen extract under the tongue. It is postulated that this method allows the allergen to be absorbed by the lymphatics draining the floor of mouth. Multiple studies using different techniques (spit or swallow), durations, frequencies, and doses have been published and meta-analysis has suggested effectiveness (76,77). Demonstrating efficacy in children has been inconsistent (78). Most studies have shown SLIT to be safe (77). However, some reports of systemic reactions have been presented, especially after the first dose (79). The combination of safety, efficacy, and convenience make SLIT a compelling option in the properly selected patient.

CONCLUSION

Allergic rhinitis is a common disease affecting patients who seek care from otolaryngologists and places a substantial burden on both quality of life and productivity. Otolaryngologists should develop an understanding of the diagnosis and treatment of allergic rhinitis. Although genetics plays a role in the disease, a simple Mendelian mode of inheritance is not seen. Allergic rhinitis is primarily a clinical diagnosis and allergy testing is complementary. Most individuals with allergic rhinitis are managed using a combination of environmental control, pharmacotherapy, and allergen immunotherapy. There may be a role for turbinate reduction in selected patients with allergic rhinitis refractory to other means of disease control.

HIGHLIGHTS

- Allergic rhinitis is a common disorder. Common symptoms include rhinorrhea, sneezing, and nasal congestion.
- The symptoms of allergic rhinitis impact quality of life, sleep, productivity, and school performance substantially.
- History of atopic dermatitis and food allergy in infancy and early childhood is a risk factor for allergic rhinitis and asthma later in life.
- Family history of allergy can help distinguish allergic rhinitis from other causes of nasal inflammation.
- The history of the patient's symptoms remains the primary tool for diagnosing allergic rhinitis.
- Allergic rhinitis and asthma are frequently concurrent. A patient with one should be considered for the other.
- Management options for allergic rhinitis include environmental control, pharmacotherapy, and immunotherapy.
- Turbinate reduction may be useful in selected patients with allergic rhinitis.

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Nonallergic Rhinitis

30

Teresa V. Chan

Nonallergic rhinitis is a consortium of loosely related syndromes and diseases associated with symptoms of nasal inflammation in the absence of identifiable allergic triggers. Patients may present with varying degrees of nasal congestion, anterior or posterior rhinorrhea, sinus pressure, hyposmia, cognitive impairment, sleep disturbance, and fatigue. Sneezing and pruritus of the eyes, nose, or palate may also accompany these symptoms but less commonly than is seen with allergic rhinitis (1). Environmental irritants, medication side effects, autonomic dysfunction, autoimmune diseases, and hormonal influence are all potential etiologies.

Rhinitis is often divided into three main categories: allergic, nonallergic, and infectious. Nonallergic rhinitis can be further subdivided into idiopathic rhinitis (IR), nonallergic rhinitis with eosinophilia syndrome (NARES), autonomic rhinitis, work-related rhinitis, drug-induced rhinitis, hormonal rhinitis, atrophic rhinitis (AR), and systemic causes of rhinitis. This is largely a symptom-driven categorization as the underlying pathophysiology is multifaceted and incompletely understood.

Though it comprises a heterogeneous group, a few generalizations can be made about nonallergic rhinitis. It is more prevalent after age 20 (2,3). Overall, there is a slight female predominance (1,2). Patients tend to have a heightened sensitivity to irritants (2). Symptoms are typically perennial rather than seasonal, and nasal eosinophilia is present in 33% of patients (2).

EPIDEMIOLOGY AND SOCIAL IMPACT

Chronic rhinitis is one of the most common complaints in medical offices worldwide. While it is safe to say that everyone at some point in their lives has experienced symptoms of rhinitis, the true prevalence of chronic nonallergic rhinitis is not known and is difficult to study. The current classification system is in evolution. In its current state, it is imprecise and restricts a patient's disease process to a single designation. Mixed rhinitis (combined allergic and nonallergic rhinitis) is under recognized. It is more common than either pure allergic rhinitis or nonallergic rhinitis and occurs in approximately 44% to 87% of patients with allergic rhinitis (4,5).

There are also multiple biases in reporting. Firstly, patients with positive allergy testing results are assumed to have only allergic rhinitis, but as mentioned above, rhinitis in an individual patient may have multiple contributing factors. Secondly, patients who present with rhinitis symptoms and respond to a trial of empiric pharmacologic therapy are often presumptively given the default diagnosis of "allergic rhinitis" by their primary care providers without confirmatory testing. This empiric trial of pharmacotherapy is more cost-effective and efficient than allergy testing every patient with rhinitis symptoms but leads to problems when trying to quantify the prevalence of disease. Finally, most prevalence data are collected from physician reporting and retrospective data from the clinical offices of allergists and otorhinolaryngologists where specialty referral patterns may not represent the true prevalence of the general population.

According to extrapolation from population studies, the estimate for patients suffering from either pure nonallergic rhinitis or mixed rhinitis is 45 million persons in the United States (2,4). Twenty-five to thirty-three percent of patients presenting with rhinitis have nonallergic rhinitis (4,5).

The human cost of rhinitis is assessed in terms of symptoms, medication needs, interference with sleep, interference with activities of daily living, work impairment, absences from work and school, impaired learning efficiency, and interference with social activities. Comorbid conditions such as asthma, sleep apnea, sinusitis, and

otitis media contribute to the individual and societal burden of both nonallergic and allergic rhinitis. A recent study by Meltzer et al. compared sleep, productivity, and quality of life in subjects with allergic rhinitis, nonallergic rhinitis, and controls. Self-reported scores on all of these parameters indicate that allergic rhinitis and nonallergic patients perceive their symptoms to adversely impact sleep, quality of daily living, and productivity. Self-reported scores were significantly worse in allergic rhinitis patients (6).

PHYSIOLOGY

A brief review of relevant nasal physiology is discussed here. This is discussed in more detail in other chapters.

The functions of the nose and paranasal sinuses include filtration, conditioning, and humidification of inspired air; regulation of nasal airway resistance; and sensation of the environment through olfaction and general sensory nerves. A mucosa rich in blood vessels and secretory glands allows the relatively large surface area of the nose to adjust quickly to moment-to-moment changes in the environment. This rapid response can be easily appreciated when the paradoxical nasal vasculature expands with exposure to cold air and quickly produces nasal congestion and rhinorrhea in an attempt to warm and humidify the incoming air. Optimal nasal function depends on a working mucosa and a delicate balance between adrenergic, cholinergic, and sensory inputs. There is a marked α-adrenergic predominance in nasal blood vessels, so vasoconstriction generally prevails.

Norepinephrine and neuropeptide Y are the neurotransmitters responsible for regulation of sympathetic tone, which produces a vasoconstricted decongested state. The sympathetic nervous system has less control over the production of mucus than the parasympathetic system. The parasympathetic autonomic nervous system is largely responsible for rhinorrhea and congestion. Acetylcholine, vasoactive intestinal peptide, neuropeptide Y, nitric oxide, enkephalin, and somatostatin are the primary parasympathetic neurotransmitters. Sensory nerves from trigeminal nerve branches V_1 and V_2 can also regulate blood vessels in response to chemical and mechanical injury. Mucosal injury, inhalation of irritants, mast cell degranulation, substance P, and neurokinin A all cause nasal secretion and dilation of blood vessels. Nociceptive input also initiates systemic reflexes, such as the sneeze, and other autonomic reflexes.

The nose also performs the work of a sentry. It samples and traps particles entering the nares using the vibrissae and mucus. Cilia beat these trapped foreign particles at a rate of 3 to 35 mm/min to the natural sinus ostia and the pharynx. The nasal mucosal lining contains secretory IgA, proteins, and enzymes that help protect from infections. Disruption of any of these processes threatens to alter this delicate nasal homeostasis.

CLASSIFICATION

The term "nonallergic rhinitis" suffers from being too inclusive. For example, rhinitis of pregnancy and rhinitis symptoms related to Wegener granulomatosis both fall under the umbrella of nonallergic rhinitis but are clearly different disease processes. Only recently have we begun a concerted effort toward better classification and separation of these diseases through consensus definitions, deeper understanding of the pathophysiology of these diseases, and subcategorization by both pathophysiology and phenotype.

Classification of an individual patient's disease process is further complicated by the fact that many patients likely suffer from multiple underlying causes of rhinitis simultaneously. The prevalence of mixed rhinitis is likely underappreciated (2). Furthermore, there are, as of yet, no reliable biomarkers of disease or confirmatory tests like skin prick testing for allergic rhinitis. Differentiating between subcategories of nonallergic rhinitis, after allergic causes have been ruled out, relies largely on good history taking and exclusion of other potential diagnoses.

This chapter reviews the major subcategories of nonallergic rhinitis according to contemporary classification schemes and terminology.

IDIOPATHIC RHINITIS

IR is a diagnosis of exclusion but comprises roughly 60% of nonallergic rhinitis. Over the years, IR has been known by several terms, including noninfectious nonallergic rhinitis, nonallergic noninfective perennial rhinitis, perennial nonallergic rhinitis, intrinsic rhinitis, and vasomotor rhinitis. When allergy, mechanical obstruction, and infections have been excluded as the cause of rhinitis, a patient is given a diagnosis of nonallergic rhinitis. When occupational hazards, environmental irritations, hormonal contributions, nasal eosinophilia, medication effect, age-related changes, and autonomic disturbances have been ruled out, the remaining nonallergic diagnosis is IR. The fact that IR accounts for more than half of the constituency of nonallergic rhinitis reflects our incomplete understanding of the pathophysiology of rhinitis.

By definition, IR does not have a singular demonstrable etiology. Many theories continue to be investigated including: a chronic inflammatory state, an imbalance between sympathetic and parasympathetic input to the nasal mucosa, a nonadrenergic noncholinergic mechanism of stimulating nasal mucosa via peptides such as substance P and vasoactive intestinal peptide acting on sensory fibers, central nervous system sensory dysregulation, and nitric oxide synthase induction in vascular smooth muscle cells causing vasodilation (7). These are worth mentioning as currently outstanding theories. Likely it will be revealed that IR makes up a collection of heterogeneous diseases with equally heterogeneous pathophysiologies.

Patients presenting with IR will complain of refractory nasal congestion and rhinorrhea predominantly. Sneezing and pruritus are less common. Quantifying patient symptoms and impact of disease allow the physician to translate this constellation of symptoms into a treatable disease process. The workup reviewed here for IR applies to all of the following subcategories of nonallergic rhinitis.

The patient presenting with rhinitis symptoms should be asked not only how long the symptoms have been present but more specifically, "For how many hours per day are you affected by these symptoms." This will help to differentiate what is problematic disease from what may be a normal physiologic nasal reaction. A standardized daily record chart of symptom duration and intensity can be helpful for quantifying disease burden and is often discrepant from the verbal report at the first visit (7) (see Table 30.1). Impact of the symptoms on the individual and his/her daily activity is a crucial piece of information and can be ascertained with the simple question, "Which symptom is most bothersome to you?" Without this information, it is sometimes difficult to focus the treatment plan and measure improvement.

A thorough history should help the physician to rule out other causes of nonallergic rhinitis. Exacerbating and alleviating factors and where these factors occur (e.g., in the workplace) should be ascertained. It is important to clarify the patient's current and previous nasal regimens including what medications were/are being used, the frequency of use (i.e., compliance), what worked, and the reasons for cessation of the medication. Saline and over-the-counter medications are pertinent. Review of the patient's entire list of medications is also necessary to look for possible drug-induced rhinitis. Smoking history and other potential irritant exposures in the past 6 months should be sought. If the patient is a woman, recent and current pregnancy status should be asked.

TABLE 30.1 EXAMPLE OF A DAILY RECORD CHART FOR DEFINING NASAL SYMPTOMS IN IR PATIENTS

Daily Record Chart of Nasal Symptoms

Nasal blockage (not being able to breathe freely through the nose)	0—absent 1—between 0 and 1 h per half day 2—between 1 and 2 h per half day 3—more than 2 h per half day
Clear nasal discharge	0—absent 1—between 0 and 1 h per half day 2—between 1 and 2 h per half day 3—more than 2 h per half day
Sneezing	0—absent 1—<5 periods per half day 2—between 5–10 periods per half day 3—more than 10 periods per half day
Coughing	0—absent 1—<5 periods per half day 2—between 5–10 periods per half day 3 —more than 10 periods per half day
Green/Yellow mucus production	0—absent 1—present

From van Rijswijk JB, Blom HM, Fokkens WJ. Idiopathic rhinitis, the ongoing quest. *Allergy* 2005;60(12):1471–1481, modified and printed with permission.

Anterior rhinoscopy and nasal endoscopy should be performed to rule out structural contributions to the patient's complaints. A computerized tomography (CT) scan of the sinuses can be helpful to evaluate for evidence of chronic sinusitis or nasal masses not seen on exam; however, clinical suspicion should guide the pursuit of imaging studies. A CT scan is not required for the diagnosis of IR. Allergy testing either by skin prick or allergen-specific serum testing is important to rule in or out possible allergic rhinitis. In practice, however, an empiric trial of saline irrigations with either a topical antihistamine or topical steroid nasal spray is typically first initiated for 6 to 8 weeks. If symptoms persist, allergy testing should be pursued.

The cold dry air (CDA) provocation test may provide an additional objective test to differentiate between patients with IR and controls but is currently a research tool not yet in clinical use. Pulmonary CDA provocation of patients with asthma results in bronchial obstruction, and it has been found to be a suitable method for assessing bronchial hyperreactivity (8,9). Histamine and methacholine have been used to test nasal reactivity in allergic rhinitis patients. However, histamine could not differentiate controls and IR patients (10). Methacholine similarly could not differentiate IR patients with congestion as their primary complaint from control subjects (11). Braat et al. (12) demonstrated that IR patients had increased mucus production and nasal blockage in a dose-dependent manner to a standardized CDA challenge. CDA in their study proved less sensitive than histamine but more specific.

A wide variety of both pharmacologic and surgical therapies exist for symptom-directed treatment of IR. Azelastine is FDA approved for the treatment of nonallergic rhinitis. A recent randomized double-blind parallel-group multicenter trial showed efficacy of both available topical antihistamines (e.g., azelastine and olopatadine) for relief of nasal congestion, rhinorrhea, postnasal drip, and sneezing associated with IR (13). Two older placebo-controlled studies lend additional support to the use of intranasal antihistamines as first-line therapy for IR (14,15). Azelastine has been shown to have both antihistamine and anti-inflammatory effects *in vitro* and *in vivo* (16), which may explain its effectiveness in the treatment of both seasonal allergic rhinitis and nonallergic rhinitis (17). The most commonly reported side effect is taste disturbance.

Beclomethasone aqueous and fluticasone aqueous are FDA approved for the treatment of nonallergic rhinitis. It is reasonable to trial a topical nasal steroid alone or in conjunction with an intranasal antihistamine for treatment of IR. The combination of a nasal steroid with a topical antihistamine has not yet been shown to have added benefit

in IR though the combination has been shown to be beneficial in the treatment of patients with seasonal allergic rhinitis (18).

Ipratropium bromide aqueous is most effective for the rhinorrhea associated with nonallergic rhinitis and is a good pharmacologic option if this is the patient's primary complaint. It has also been shown to be effective at improving mood and quality of life scores in nonallergic rhinitis patients but was no better than placebo at relieving congestion, sneezing, or postnasal drip (19). The recommended starting dose is two sprays three to four times daily but once a therapeutic effect has been achieved, this can often be decreased to once or twice daily dosing.

Nasal saline spray or irrigation is often thought as an "active placebo" in clinical trials due to its reported effectiveness for nonallergic rhinitis patients. Saline irrigations have been shown in multiple studies and in a systematic Cochrane review to be well tolerated and beneficial in a majority of patients with rhinosinusitis (20). Daily isotonic nasal irrigations should be a component of the daily nasal regimen for any patient with IR.

Systemic antihistamines are a consideration if sneezing or pruritus is a major symptom, however, this is not as common with IR. Oral decongestants may be an adjunct for decongestion of a severely congested nose when starting topical therapies or for temporary symptom relief of episodic exacerbation of symptoms. Oral decongestant use should be limited in those with a history of hypertension or cardiac disease due to the potential to exacerbate these conditions. Topical decongestants play a very limited role in treatment of IR and patients should always be counseled to avoid these medications for any longer than 3 days at a time.

Capsaicin is a substance found in hot peppers that induces rhinorrhea and congestion when ingesting spicy foods. Nasal capsaicin provocation results in rhinorrhea, nasal blockage, and sneezing via stimulation of the unmyelinated sensory C fibers or pain receptors. Repeated intranasal applications of capsaicin in some individuals, however, lead to desensitization by prolonged stimulation of an ion channel receptor which is sensitive to physical and chemical nociceptive stimuli. This ion channel receptor, called Transient Receptor Potential Vanilloid type 1 or TRPV1, is found on epithelial cells, vascular endothelial cells, submucosal glands, and nerves in human nasal mucosa and is capable of regulating nasal secretion and congestion (21).

One recent randomized double-blind placebo-controlled trial demonstrates that capsaicin is effective for relief of symptoms in patients with IR without significant side effects or rebound (22). This supports the findings of several previous randomized trials (23,24). The onset of the relief occurred within 60 seconds and was present for at least 9 months without change in cellular mediators or neural tissue density (22,24). Capsaicin has not reliably shown this same benefit in allergic rhinitis patients (25,26).

Capsaicin spray is currently available under the brand name *Sinus Buster* in the United States. There is no current consensus regarding the dose and frequency of administration but all recent studies have demonstrated that less than 2 weeks of treatment is adequate for relief and can be repeated when symptoms recur (22–24). In one study, one spray given every 2 to 3 days over 2 weeks was found to be as efficacious as a single day treatment during which one spray was given each hour for 5 hours (24). From its initial studies, capsaicin seems to be an appealing potential option for treatment of IR. It has a quick onset of action, a short course of treatment, and aside from a slight burning sensation upon administration, has minimal reported side effects. However, larger clinical trials are needed before formal recommendations can be made regarding its safety and use intranasally. Caution should be used in patients with concomitant lung disease. Inhaled capsaicin is a well-documented stimulator of the cough reflex and severe, fatal asthma attacks have been reported with inhalation of capsaicin when used as an incapacitating agent (i.e., pepper spray) in asthmatics (27).

Surgical options for refractory symptoms of rhinitis include various methods of inferior turbinate reduction and vidian neurectomy. A myriad of approaches to turbinate reduction have been described including steroid injection, electrocautery, cryotherapy, coblation, laser reduction, microdebrider-assisted partial turbinectomy, complete inferior turbinectomy, and simple out-fracture (28). In general methods that are destructive or disruptive to mucociliary function such as complete turbinectomy and electrocautery should be avoided. Submucosal methods prevail over extramucosal approaches (29). Steroid injection into the turbinate can be temporarily effective but topical decongestion for 5 minutes prior to a slow steady injection is paramount as there are remote case reports of blindness after steroid injection. From a recent review of techniques, microdebrider-assisted partial turbinoplasty and holmium-YAG laser turbinate reduction demonstrated the most durable improvement in nasal patency lasting for at least 3 years (28,30–32).

Vidian neurectomy was introduced in the 1960s as a means of reducing severe rhinorrhea related to "vasomotor (autonomic) rhinitis" from presumed overstimulation of the parasympathetic system. This was initially described through a transantral approach to the pterygoid canal. Initial reports demonstrated lasting efficacy (33) but subsequent studies showed recurrence of symptoms in 71% of patients at 1 year postprocedure (34). Over the years, the original transantral approach to vidian neurectomy has evolved into an endoscopic approach that carries less surgical morbidity. A recent study showed long-term effectiveness of endoscopic vidian neurectomy at controlling rhinorrhea and nasal congestion up to 7 years (35).

The aim of the vidian neurectomy is to cut the efferent pathway of the parasympathetic reflex, which causes rhinorrhea from irritation of the nasal mucosa. Dry eye is a

common side effect of the procedure as there are preganglionic parasympathetic fibers from the greater superficial petrosal nerve which pass through the pterygoid canal as part of the vidian nerve to supply to lacrimal gland. However, in a recent study of the endoscopic approach most patients eventually recovered from xerophthalmia within months (35). This may be due to the fact the nerve was addressed with bipolar cautery or laser without removal of a segment of nerve as originally described.

Studies from Japan report a modification of vidian neurectomy that affords the same relief of rhinitis symptoms as vidian neurectomy with theoretically less risk of xerophthalmia (36–38). In the posterior nasal neurectomy technique, sensory and autonomic branches are ligated distal to the pterygoid canal just after exiting the sphenopalatine foramen as they travel alongside the sphenopalatine artery. Endoscopic vidian neurectomy and posterior nasal neurectomy are ultimate surgical options for patients with intractable rhinitis refractory to other management strategies.

NONALLERGIC RHINITIS WITH EOSINOPHILIA SYNDROME

NARES is a clinical syndrome in which symptoms such as sneezing, pruritus, and profuse watery rhinorrhea seem decidedly allergic, however, there is (a) an absence of demonstrable systemic atopy and (b) marked eosinophilia on nasal smear. Nasal smear must show greater than 20% eosinophils to be diagnostic. Nasal symptoms in patients with NARES are often more severe than in their allergic rhinitis counterparts (39) and anosmia is present more frequently (2).

NARES represents roughly 15% to 33% of adults with nonallergic rhinitis (39,40). There is an association of NARES with aspirin-exacerbated respiratory disease (AERD) and a number of these patients go on to experience aspirin sensitivity and polyposis in the future. Some reports have suggested that NARES is an early manifestation of AERD and the presence of eosinophilia should be interpreted as a marker for future aspirin intolerance and polyps (39).

The pathophysiology of NARES is not yet understood. Eosinophils and activated mast cells seem to play an important role. Eosinophils have been shown to release toxic substances such as major basic protein and eosinophilic cationic protein into the nasal mucosa (41). Physiologic studies on patients with nonallergic rhinitis have shown a correlation between eosinophilia and prolonged mucociliary clearance on saccharin clearance tests (42). Stasis from prolonged mucociliary clearance may set up a predilection for infection and further exacerbate the cycle of inflammation. Mast cells and chronic histamine release also appear to be relevant to this disease process though their roles have not been fully elucidated (41).

The symptoms of allergic rhinitis and NARES are quite similar yet these conditions are categorized separately solely based on results of systemic allergy testing. Interestingly, though nonallergic rhinitis patients test negative on systemic tests for allergy, nasal provocation challenge studies have been positive in 10% to 65% of nonallergic rhinitis patients (43–46). The concept of a localized allergic reaction in the nasal mucosa or "entopy" (as opposed to "atopy") was formally introduced by Powe et al. in 2003 and remains an area of debate and continued study (47,48).

Powe et al. proposed that on a cellular level the inflammatory reaction that occurs in the nasal mucosa in nonallergic rhinitis patients is akin to the systemic allergic reaction in atopic patients (47). This theory is further supported by the following:

1. Antigen-specific IgE antibodies are detectable in the nasal mucosa of some nonallergic rhinitis patients as well as allergic rhinitis patients but not normal controls (45,47).
2. A similar pattern of localized Th2-driven, IgE-mediated cellular infiltrate is seen in the nasal mucosa and secretions from allergic rhinitis and nonallergic rhinitis patients (49,50). Specifically mast cells, eosinophils, IgE-positive cells, and similar T-cell subpopulations are present in both subgroups (50). Released mediators from these cells such as eosinophilic basic protein and tryptase have been found in all studied forms of chronic nasal inflammation including allergic rhinitis, nonallergic rhinitis, and nasal polyposis (though in notably varying degrees) (41).
3. Nasal provocation studies are positive in the absence of systemic atopy as previously mentioned above (43–46).

Despite our reliance on skin and serum testing for detection of atopy, the association between systemic atopy and localized nasal symptoms is not well understood. In patients with a history suggestive of allergy with negative tests for systemic allergy, nasal smear and nasal provocation challenge testing should be performed to look for evidence of local nasal reactivity.

Intranasal corticosteroids are the mainstay of treatment for NARES and the presence of significant eosinophilia on nasal smear signals a favorable response to these medications (51). Oral steroids are more effective than topical steroids in alleviating the symptom of anosmia in NARES patients (52). Antihistamines in one study provided added benefit in conjunction with topical steroids (53). Presumably leukotriene antagonists would be effective given the association of NARES with AERD and polyposis; however, no randomized controlled studies to date have corroborated this (54). Immunotherapy similarly may be an effective choice for patients who test positive on nasal provocation challenges though this remains to be studied (54). In patients who test positive on nasal provocation, it is reasonable to counsel avoidance of provocative substances. More directed therapies will likely emerge as the pathophysiology of NARES is better understood. Anti-IgE and a monoclonal antibody to IL-5 are two areas of potential research in pharmacologic solutions (54).

WORK-RELATED RHINITIS (OCCUPATIONAL RHINITIS)

Work-related rhinitis or occupational rhinitis (OR) is nasal irritation and inflammation due to workplace exposures. In addition to primary nasal symptoms, ocular irritation, ocular pruritus, and cough are common symptoms of OR. Over the past 10 to 15 years, renewed research in this area has revealed that classification and confirmation of this diagnosis is more complex than previously appreciated and there is currently no accepted consensus definition of OR. The 2008 position paper from the European Academy of Allergy and Clinical Immunology (EAACI) Task Force on OR proposes this definition: "OR is an inflammatory disease of the nose, which is characterized by intermittent or persistent symptoms (i.e., nasal congestion, sneezing, rhinorrhea, itching), and/or variable nasal airflow limitation and/or hypersecretion due to causes and conditions attributable to a particular work environment and not to stimuli encountered outside the workplace" (55).

The prevalence of work-related rhinitis has not been well established as this number is largely dependent on the criteria used to define the disease. OR is not an uncommon disease and likely occurs more frequently than is currently appreciated. OR is a part of a continuum of airway disease brought on in the workplace and is known to be two to four times more common than occupational asthma (56–58). Development of occupation rhinitis may be a herald sign of development of lower airway symptoms in 2 to 5 years (56–58).

Causes of rhinitis in the workplace can be either allergic, irritative, or a combination of both. Agents that cause OR are divided into high molecular weight compounds (HMWCs) and low molecular weight compounds (LMWCs). HMWCs can be thought of as plant- or animal-derived proteins. For almost all of these HMWCs an IgE-mediated mechanism has been proven causative of OR (58). Examples of HMWCs include animal dander, latex, grain dust, flour, dust mites, and biologic enzymes (see Table 30.2 for a listing of HMWC and LMWC). LMWCs are typically too small to be immunogenic on their own. They must be coupled with a protein as a hapten–protein complex in order to elicit an IgE-mediated hypersensitivity response. For this reason it is often difficult to isolate LMWC for skin and serum IgE-mediated allergy testing. The few LMWCs that have demonstrated IgE-mediated OR include platinum salts, acid anhydrides, and reactive dyes. Aerosolized agents such as tobacco smoke, perfumes, air fresheners, and solvents are examples of irritative causes of OR.

According to data from the Finnish Register of Occupational Diseases from 1986 to 1991, patients in the following fields have a higher risk for developing OR: fur

TABLE 30.2 PREVALENCE AND ETIOLOGIC AGENTS IN OR

Agents	Occupation	Prevalence (%)
High molecular weight agents		
Laboratory animals	Laboratory workers	6–33
Other animal-derived allergens	Swine confinement workers	8–23
Insects and mites	Laboratory workers, farm workers	2–60
Grain dust	Grain elevators	28–64
Flour	Bakers	18–29
Latex	Hospital workers, textile factory workers	9–20
Other plant allergens	Tobacco, carpet, hot pepper, tea, coffee, cocoa, dried fruit, and saffron workers	5–36
Biologic enzymes	Pharmaceutical and detergent industries workers	3–87
Fish and seafood proteins	Trout, prawn, shrimp, crab and clam workers, aquarists and fish-food factory workers	5–24
Low molecular weight agents		
Diisocyanates	Painters, urethane mould workers	36–42
Anhydrides	Epoxy resin production, chemical workers, electrical condensers workers	10–48
Wood dust	Carpentry and furniture making workers	16–36
Metals (platinum)	Platinum refinery workers	43
Drugs (psyllium, spiramycin, piperacillin)	Health care and pharmaceutical workers	9–41
Chemicals	Reactive dye, synthetic fiber, cotton, persulfate, hairdressing, pulp and papers, shoe manufacturing workers	3–30

From EAACI Task Force on Occupational Rhinitis; Moscato G, Vandenplas O, Gerth Van Wijk R, et al. Occupational rhinitis. *Allergy* 2008;63: 969–980, printed with permission.

industry workers; bakers; livestock breeders; food-processing workers; veterinarians; farmers; assemblers of electrical, electronic, and telecommunication products; and boat builders (57). A separate population-based study in Sweden found that workers whose employment involved exposure to wood dust, textile dust, fire fumes, quick-drying glues, paint hardeners, or paper dust were at increased risk for developing rhinitis (59).

Patients with OR often have a coexisting history of atopy which predisposes them to additional nasal mucosal inflammation from agents encountered in the workplace. This phenomenon was illustrated by Shusterman et al. (60) in a study which challenged allergic rhinitis patients and nonallergic patients with inhaled intranasal chlorine. He found that patients with preexisting allergic rhinitis were more prone to non-mast-cell-mediated nasal inflammation measured by acoustic rhinometry. In a related positive control study, rye-grass provocation caused the seasonal allergic rhinitis patients to develop both objective nasal inflammation and mast cell degranulation. The relationship of cigarette smoking and risk for developing OR, interestingly, is still unclear; results from various studies have been contradictory.

The diagnosis of OR requires both (a) documentation of rhinitis and (b) causation by a workplace exposure. Documentation of rhinitis is accomplished by a careful medical history, occupational history, and exam. Medical history should include preexisting nasal symptoms, onset of symptoms, exacerbation and relief of symptoms in and out of the workplace, severity of symptoms, and impact of symptoms on work productivity, and the individual's well-being. Pertinent occupational history includes: duration of employment (latency) prior to onset of symptoms, length and frequency of exposure to potential rhinitis triggers or other irritant exposures. The nasal exam can be accomplished with anterior rhinoscopy and nasal endoscopy but findings are typically consistent with nonspecific mucosal irritation or inflammation. The nasal exam can be helpful in ruling out additional causes of the patient's nasal symptoms such as deviated nasal septum or nasal polyposis.

There are two main options for establishing causation by a workplace exposure. The first is immunologic testing either by skin-prick testing or by serum allergen-specific IgE antibodies. Immunologic testing is widely available and likely adequate for confirmation of suspected allergic reactions due to HMWCs. However, immunologic testing has limitations in evaluation of OR caused by LMWCs. Commercially available, standardized extracts of these LMWCs are not readily available. LMWCs are also prone to a high false-positive rate in skin testing due to nonspecific interactions with histamine (61).

Nasal provocation challenge remains the standard of care for establishing a diagnosis of OR. This can be conducted in the office or in the natural setting of the workplace. It can be used to confirm both IgE-mediated and non-IgE–mediated OR. Reproduction of nasal symptoms has been used as acceptable proof for diagnosis of OR but increasingly physiologic measurements like rhinomanometry, acoustic rhinometry, and peak nasal inspiratory flow are being utilized for objective documentation of nasal patency before and after provocation (62,63). These physiologic measurements do not have interindividual consistency and data obtained from these measurements cannot be compared between individuals or to standardized norms. Nasal lavage and volume of mucus production have been used in some studies as measures of inflammation but similarly there are no standardized norms for comparison (64,65).

There are three primary tenets to treatment of the individual with OR (a) limit the impact of disease on the individual's well-being, (b) limit untoward effects on work productivity, and (c) prevent additional adverse health sequelae (e.g., occupational asthma) from continued occupational exposure. Avoidance of causative exposures is the first line of defense in OR. When complete avoidance of one's workplace or specific work-related tasks is not possible, limited exposure with medications for symptom control is acceptable. Treatment with saline irrigations, steroid nasal sprays, decongestants, and antihistamines is guided by similar principles as in allergic rhinitis. Immunotherapy has a role if specific allergic triggers have been identified and avoidance and pharmacotherapy are not sufficient.

Though OR shares many similarities with other causes of rhinitis, one major difference is the ability to effect change on a system-wide scale. Whereas all other forms of rhinitis focus on the individual, OR provides the opportunity to identify a potential organizational problem and effect change for the entire system. Diagnosis of the affected patient can be likened to a sentinel event. This initial diagnosis should ideally prompt internal analysis and system-wide action to limit future workplace morbidity.

DRUG-INDUCED RHINITIS

Drug-induced rhinitis is divided into three categories (a) neurogenic, (b) inflammatory, and (c) idiopathic. There are a number of medications that list rhinitis in their side-effect profiles. The most widely used and notable of these are antihypertensive medications, erectile dysfunction medications, and some psychiatric medications. Topical decongestants, when overused, notoriously lead to rhinitis medicamentosa by a different mechanism. (A list of common rhinitis-inducing medications and their mechanisms of action can be found on Table 30.3. A list of common topical agents, which can cause rhinitis medicamentosa is found in Table 30.4.)

Systemic anti-hypertensive medications are examples of drugs that cause rhinitis through neurogenic mechanisms. They tip the balance between sympathetic and parasympathetic regulation of the nasal mucosa toward parasympathetic dominance through direct or indirect inhibition of

TABLE 30.3 SYSTEMIC MEDICATIONS ASSOCIATED WITH RHINITIS

Drug or Drug Class	Examples	Mechanism of Action
Neurogenic		
Beta-blockers (antihypertensive)	Atenolol Propanolol Pindolol Carvedilol	Blocks EPI and NE-mediated stimulation of the sympathetic nervous system
Alpha-adrenergic antagonists (antihypertensive, BPH)	Phenoxybenzamine Phentolamine Prazosin Doxazosin Tamsulosin Yohimbine	Blocks EPI and NE-mediated stimulation of the sympathetic nervous system
Hydralazine (antihypertensive)	Apresoline (brand name)	Increases GMP levels, decreasing the action of the IP_3, limiting calcium release in the smooth muscle resulting in vessel relaxation. Dilates arterioles more than that of veins
Guanethidine (antihypertensive)	Ismelin (brand name)	Inhibits NE release from sympathetic nerve ending; gradually depletes NE stores in the nerve ending
Reserpine (antipsychotic/ antihypertensive)	Serpasil (brand name)	Blocks the vesicular monoamine transporter which normally transports free NE, 5-HT, and DA from the cytoplasm of the presynaptic nerve terminal into storage vesicles for subsequent release at synaptic cleft
Methyldopa (Alpha-adrenergic agonist antihypertensive)	Aldomet	Two mechanisms: (a) Competitively inhibits the enzyme DOPA decarboxylase, which converts L-DOPA into DA. DA is a precursor for NE and subsequently EPI (b) Its metabolite, α-methylnorepinephrine, is stored in neurosecretory vesicles in place of NE and is a potent $\alpha 2$ agonist causing negative feedback on NE release
Tricyclic antidepressants	Amitriptyline	Binds NE reuptake receptors on the presynaptic side to keep NE circulating, but also depletes NE stores over time
Some antipsychotics (typical and atypical)	Thioridazine Chlorpromazine Perphenazine Risperidone	Blocks central adrenergic receptors, blocks DA-blocking, and has minor anticholinergic activity. DA is the precursor for NE. Rhinitis listed as a minor side effect, possibly worse with newer antipsychotics
Clonidine (antihypertensive/pain control/antistimulant)	Catapres	Alpha 2 agonist, inhibits NE release, functions primarily in the CNS but has peripheral effects
Phosphodiesterase type-5 inhibitors (erectile dysfunction)	Sildenafil Vardenafil Tadalafil	Inhibits enzyme PDE5 which breaks down of cGMP in smooth muscle cells. Increased cGMP causes relaxation of smooth muscle and vasodilation
Inflammatory		
Aspirin and COX-1 inhibiting nonsteroidal anti-inflammatory (anti-inflammatory)	Aspirin Ibuprofen	Exacerbates excessive production of leukotrienes and prostaglandins due to anomaly in the arachidonic acid cascade
Angiotensin-converting enzyme inhibitors (antihypertensive)	Enalapril Lisinopril	(Proposed) Decreases angiotensin II, increases bradykinin resulting in reduced vasoconstriction and increased vasodilation
Idiopathic		
Hypnotic + Benzodiazepine	Chlordiazepoxide	Unknown
Nonbenzodiazepine, nonbarbiturate hypnosedative	Zolpidem tartrate, zaleplon	Not well understood but reported. Acts on central GABA receptors
Amiloride(potassium sparing diuretic)	Midamor (Brand name)	Partial effect of drug is inhibition of cGMP-gated ion channels
Apomorphine	Apokyn (Brand name) (Injectable dopamine)	Nonselective DA agonist used in the treatment of Parkinson disease and erectile dysfunction

Key: NE, norepinephrine; EPI, epinephrine; 5-HT, serotonin; DA, dopamine; IP_3, inositol triphosphate; cGMP, cyclic guanosine monophosphate; GABA, Gamma-Aminobutyric acid.

TABLE 30.4 TOPICAL MEDICATIONS THAT CAN CAUSE RHINITIS MEDICAMENTOSA

Topical Agent	Alias
Imidazolines	
Oxymetazoline	Afrin
Xylometazoline	Otrivin
Naphazoline	Clear eyes
	Naphcon eye drops
Sympathomimetics	
Ephedrine	Ma-Huang
Levomethamphetamine	Vicks Vapor Inhaler
Phenylephrine	Neosynephrine
Tramazoline	(Not available in US)
Amphetamine	Benzedrine
Cocaine	Coke[a]

[a]An exhaustive list of aliases for cocaine is beyond the scope of this table.

norepinephrine. Many antipsychotics and antidepressants similarly alter the availability of norepinephrine by their interference with norepinephrine and dopamine reuptake pathways at the synaptic cleft. Treatment in the case of neurogenic rhinitis consists of identification of the offending medication and substitution with alternatives if possible.

Some of the rhinologic effects of psychiatric medications such as hypnosedatives (e.g., zolpidem) are less well understood. These act centrally on gamma-aminobutyric acid (GABA) receptors yet have effects in the peripheral nasal mucosa. These are examples of idiopathic drug-induced rhinitis.

Aspirin Exacerbated Respiratory Disease

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) can exacerbate an inflammatory rhinitis in a susceptible subset of the population with altered arachidonic acid metabolism. This rhinitis is a part of a larger constellation of symptoms collectively recognized as AERD. Though AERD is colloquially referred to as *Samter's triad*, it is in fact a tetrad consisting of (a) sensitivity to aspirin and other cyclooxygenase isoenzyme 1 (COX-1) inhibiting nonsteroidal anti-inflammatory medications, (b) asthma, (c) nasal polyposis, and (d) chronic eosinophilic rhinosinusitis. The underlying medication sensitivity is sometimes referred to as an "aspirin allergy"; however, this is incorrect as no IgE-mediated allergic mechanism is responsible. The most accurate description of AERD is a *nonallergic hypersensitivity reaction* (66).

AERD occurs most commonly in early adulthood between 20 and 40 years old with a 3:2 female to male predilection (67). It affects roughly 1% of the general population (68), but the prevalence rises to 21% in asthmatics (69). In asthmatics with nasal polyposis, up to 30% to 40% are affected (70).

Symptoms of rhinitis often precede the onset of asthma (71). Some patients will present with a self-recognized history of aspirin or NSAID-induced asthma attack or worsening of rhinitis symptoms after using these medications. Onset of upper or lower airway symptoms typically occurs within 90 minutes of ingestion of the COX-1 inhibiting medication. It is important to note that ingestion of aspirin or NSAIDs does not initiate the disease, but can exacerbate symptoms once the disease process is underway (72).

Diffuse nasal polyps filling the nasal cavity and quick recurrence of polyps after surgical resection are hallmarks of AERD. A CT scan of the sinuses often shows pansinusitis with near-total opacification of the sinuses. There may be lateral bowing of the lateral walls of the nasal cavity or bony thinning of the intersinus septa from the mass-effect of polyps on the confined space of the nasal cavity. Polyps contribute to the severe nasal congestion, anosmia, and sleep disturbance often seen in these patients (73).

The pathophysiology of this disease is well studied but only partially understood. An underlying anomaly in arachidonic acid metabolism leads to overproduction of eicosanoids, namely leukotrienes and prostaglandins (74–76). Eicosanoids are lipid-based local signaling molecules that function much as neurotransmitters do to activate membrane-bound G-proteins and induce signal transduction and cellular responses. However, because they are lipid-based they cannot be stored in vesicles like neurotransmitters and are instead produced on demand.

Both leukotrienes and prostaglandins are proinflammatory. They work via receptors on target cells to contract bronchial and vascular smooth muscle; increase permeability of blood vessels; enhance secretion of mucus in the airway and gut; and recruit leukocytes such as mast cells, eosinophils, and neutrophils to sites of inflammation. Leukotrienes LTC4, LTD4, and LTE4 make up the slow-reacting substance of anaphylaxis. Compared to histamine, this mixture of leukotrienes is more potent and has a slower onset but longer duration of action.

In addition to increased production of leukotrienes, upregulation of leukotriene receptors have been demonstrated in the respiratory mucosa of AERD patients (77). Proinflammatory cytokines IL-2, IL-3, IL-4, IL-5, IL-13, GM-CSF, and eotaxin are also present and facilitate the production, recruitment, and longevity of eosinophils and mast cells (78–81). Biopsy of the upper and lower respiratory mucosa of AERD patients demonstrates this abundance of eosinophils and activated mast cells (82,83).

The eosinophils release toxic substances such as eosinophilic cationic protein, major basic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase furthering the cycle of tissue damage and inflammation (72). Mast cells release preformed mediators such as histamine and tryptase; synthesize prostaglandins and leukotrienes; and participate in bronchoconstriction, vasodilation, and ongoing chemotaxis of eosinophils (72). What is not known is what triggers this cascade of inflammation and how to specifically

interpret this data in patients with AERD given the fact that some aspirin-tolerant patients with polyps or asthma have shown activation of the exact same proinflammatory leukocytes and mediators, albeit to a lesser degree.

This underlying overproduction of leukotrienes and prostaglandins is exacerbated by the ingestion of COX-1 inhibiting medications. Inhibition of COX-1 shifts arachidonic acid metabolism toward leukotriene production. Specifically diminished COX-1 leads to decreased production of prostaglandin E2 (PGE2), an anti-inflammatory mediator and inhibitor of leukotriene production. Less PGE2 also translates into decreased mast cell stability and release of histamine and tryptase. This manifests clinically as varying degrees of rhinitis, conjunctivitis, laryngospasm, and bronchospasm.

Not all cyclooxygenase inhibiting medications exacerbate respiratory disease by this mechanism. Multiple separate studies have shown that selective COX-2 inhibiting medications (e.g., celecoxib/Celebrex) do not worsen airway symptoms in AERD patients (84–86). Separate studies also demonstrated that AERD patients can tolerate partial COX-2 inhibitors (e.g., meloxicam/Mobic), which have some COX-1 activity at high doses and the poor COX-1 inhibitors such as acetaminophen in low doses (87–92) (see Table 30.5). However, caution is still advised when prescribing *any* COX-2 inhibiting medications to a patient with confirmed AERD. Rare case reports of severe adverse reactions with selective COX-2 and partial COX-2 inhibitor medications do exist and continue to arise (93). The first reaction is typically the most severe and if a COX-2 inhibiting medication is medically necessary for an individual patient, it would be prudent to trial this first in the office under medical observation.

The prevalence of AERD is both overestimated and underestimated by self-reported patient history alone (94). Currently there is no reliable *in vitro* test for aspirin/NSAID hypersensitivity and aspirin challenge remains the gold standard for diagnosing AERD. There are four routes available for provocation challenges: oral, bronchial inhalation, nasal inhalation, and intravenous. In the United States, oral aspirin challenges are performed. According to one study, 45 or 60 mg of aspirin was the typical provoking dose for naso-ocular and bronchial reactions in patients undergoing oral aspirin challenge (95).

Treatment for AERD falls into two categories—emergency management of acute exacerbations and long-term control. Acute respiratory reactions caused by accidental aspirin or NSAID ingestion are treated with inhaled β-agonists, systemic antihistamines, and systemic corticosteroids. Management follows the principles and protocols for acute airway management, which can be found in other chapters. If hypotension, urticaria, or other signs of systemic

TABLE 30.5 NSAID MEDICATIONS, THEIR PREFERENTIAL CYCLOOXYGENASE INHIBITION AND REACTIONS ELICITED IN AERD PATIENTS

Preferential COX-1 Inhibitors	Poor COX-1 Inhibitors	Selective COX-2 Inhibitors
Piroxicam (Feldene)	Acetaminophen (Tylenol)	
Indomethacin (Indocin)	Salsalate (Disalcid)	Celecoxib (Celebrex)
Sulindac (Clinoril)		Rofecoxib (Vioxx)
Tolmetin (Tolectin)		Valdecoxib (Bextra)
Ibuprofen (Motrin, Advil)		Etoricoxib (Arcoxia)
Naproxen (Naprosyn)		Parecoxib (Dynastat)
Naproxen sodium (Aleve)		Lumiracoxib (Prexige)
Fenoprofen (Nalfon)	**Preferential COX-2 Inhibitors**	
Meclofenamate (Meclomen)		
Mefenamic acid (Ponstel)	Nimesulide (Aulin, Nimesil)	
Flurbiprofen (Ansaid)	Meloxicam (Mobic)	
Diflunisal (Dolbid)		
Ketoprofen (Orudis, Oruval)		
Diclofenac (Voltaren, Cataflam)		
Ketorolac (Toradol)		
Etodolac (Lodine)		
Nabumetone (Relafen)		
Oxaprozin (Daypro)		
⇓	⇓	⇓
Universally elicit reactions in AERD patients	Reactions occur with higher doses of these NSAIDs	No reactions occur in multiple controlled studies; however, case reports of severe reactions still exist

histamine release are present, intramuscular epinephrine should be given. For ocular or nasal reactions only, oral antihistamines may be sufficient. The patient should be observed for several hours as aspirin-induced reactions can last for several hours.

Multimodality therapy is required for the long-term management of AERD. Daily leukotriene inhibitors, intranasal steroids, and saline along with avoidance of aspirin and other NSAIDs are the foundations of medical treatment. Patients with simultaneous allergic rhinitis should be identified and treated accordingly. Treatment of lower airway disease should be managed in conjunction with a pulmonologist. Endoscopic sinus surgery is a necessary adjunct and follows principles of sinus surgery found in other dedicated chapters. Patients should be counseled regarding the recurrent and recalcitrant nature of their disease and forewarned of the potential need for multiple sinus surgeries.

Aspirin desensitization can be considered in anyone with respiratory symptoms of confirmed AERD. Those who would benefit most include (a) patients with refractory airway symptoms despite daily compliance with intranasal steroids and leukotriene inhibitors, (b) those who require aspirin or other NSAIDs for antiplatelet activity long-term (e.g., cardiac stent patients), (c) those whose polyposis is so severe as to require frequent sinus surgeries, or (d) those who require unacceptably high doses of systemic steroids to control symptoms. Aspirin desensitization is very effective for airway symptoms associated with AERD but not as reliable for cutaneous manifestations of aspirin sensitivity.

The most commonly used aspirin desensitization protocol was devised by physicians at Scripps Clinic and Research Institute. This consists of an oral ingestion of aspirin starting in the early morning at 30 mg and proceeding at 3-hour intervals through 45, 60, 100, 150, and 325 mg up to a final dose of 650 mg over a 2- or 3-day period. Doses are repeated if a naso-ocular or bronchial reaction occurs (95,96). Pulmonary function and symptoms are followed with each dose escalation. After desensitization, patients are maintained on 325 to 650 mg twice daily indefinitely. Multiple permutations on this protocol exist regarding dosage and timing of escalation (97). Data suggests that this is a safe protocol when performed in an experienced clinic with long-term improvement in symptoms and reduction of medication use over 5 years (98).

Rhinitis Medicamentosa

Rhinitis medicamentosa is a special category of drug-induced rhinitis that occurs by a different mechanism than the drug-induced rhinitis described above. Overuse of topical nasal vasoconstrictors induces a rapid tolerance, or tachyphylaxis, with a severe rebound rhinitis. These rebound symptoms encourage an on-going dependence on the offending agent. Topical nasal decongestants containing oxymetazoline hydrochloride and phenylephrine hydrochloride are by far the most popular culprits. Similar rebound rhinitis can also be caused by use of cocaine topically in the nose.

The primary complaint is of severe nasal congestion. There is usually a paucity of actual rhinorrhea though there is the sensation of rhinorrhea and chronic sniffling. Pruritus and sneezing are notably absent. On exam, the nasal mucosa is typically described as edematous, "beefy red," and dry. These findings are by no means pathognomonic or specific for rhinitis medicamentosa but are noted in contrast to the bland, nonspecific exam findings seen in other cases of drug-induced rhinitis. There is a poor response to application of topical decongestants in the office.

Oxymetazoline and phenylephrine are categorized as imidazole derivatives and sympathomimetic amines, respectively. Their mechanism of action is α- and β-adrenergic stimulation of the sympathetic nervous system. In the nasal mucosa, the predominant adrenergic receptor is the α_1 receptor. This is located on the smooth muscle and stimulation causes release of norepinephrine and vasoconstriction. The α_2 receptor is located on the presynaptic neuron and induces negative feedback on the release of norepinephrine (see Fig. 30.1). There is also a less pronounced but possibly longer lasting β-adrenergic effect of the sympathomimetic amines, which leads to smooth muscle relaxation in the airway mucosa.

Tachyphylaxis has been proposed to occur by many mechanisms including (99):

1. Exhaustion of the presynaptic supplies of norepinephrine from continued stimulation.
2. Decease in sensitivity and number of the α_1 receptors on the postsynaptic side due to the inhibitory effects of α_2 receptor on the presynaptic neuron.
3. Prolonged β-adrenergic vasodilation outlasting the α-adrenergic effects.

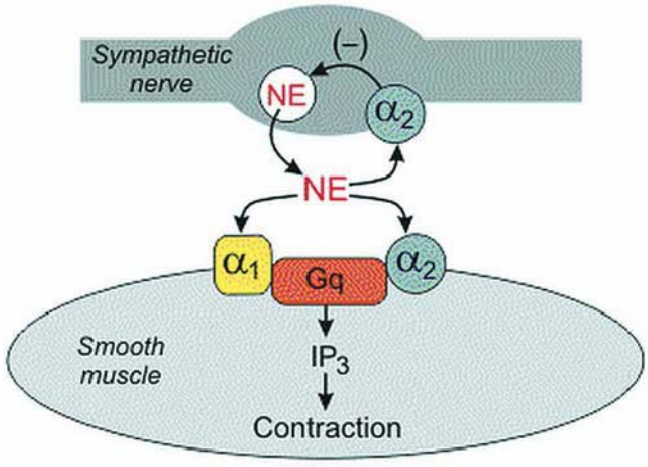


Figure 30.1 Mechanism and feedback of α-adrenergic receptors.

4. Tissue hypoxia from prolonged vasoconstriction leading to eventual rebound vasodilation either from vascular fatigue or need to resupply nutrients to these hypoxic tissues.
5. Increased parasympathetic tone leading to vascular permeability and increased edema.

None of these theories has been proven definitively. Histologically, the changes seen in rhinitis medicamentosa include nasociliary loss, squamous cell metaplasia, epithelial cell denudation, increased intercellular widening, increased vascularity, fibrosis, edema of the epithelial cell layer, goblet cell hyperplasia, increased expression of the epidermal growth factor receptor, and inflammatory cell infiltration (100).

Topical nasal decongestants can be found under common trade names such as Afrin, Neosynephrine, and Sinex but there are a myriad of other brand names on pharmacy shelves. The best way to elicit a salient history is to ask directly, "What over-counter nasal sprays are you using and how often?" At times, patients will not list these nonprescribed medications and will not offer up this portion of the history unless specifically asked. Patients who have been using these medications chronically often develop a psychological as well as physiologic dependence on these medications and need first to be educated about the hazards of prolonged topical decongestant use.

Treatment of rhinitis medicamentosa is directed at cessation of the offending agent, replacement with more therapeutic pharmacologic options, and identifying possible underlying causes of rhinitis. Patients should be weaned quickly off these medications within a matter of days and may be helped by replacement with nasal saline sprays and topical nasal steroids. Consideration must be given to the fact that a disease process often underlies the initiation and chronic use of these medications. It is important to investigate other medical causes of rhinitis such as allergic rhinitis, nasal polyposis, or deviated nasal septum and treat these accordingly. Patients should be counseled to be off topical decongestants for at least 1 to 2 months prior to any endonasal surgery.

There are instances when the short-term use of topical decongestants is warranted. For instance, if a patient's turbinate congestion is so severe as to preclude application of other topical therapies, a short course of topical decongestants serves as a necessary adjunct. Patients who are advised to use these medications acutely must always be counseled against prolonged use longer than 3 days at a time. Patients with poorly controlled hypertension or a cardiac history should be given topical and oral decongestants cautiously due to potential to exacerbate these conditions.

HORMONE-INDUCED RHINITIS

Nasal congestion is thought to occur secondary to elevated estrogen and progesterone levels. This is a well-recognized phenomenon in pregnancy; however, it is less clear whether this occurs in other states of endogenous or exogenous hormone excess. There is some evidence to suggest increased nasal congestion occurs during the preovulatory peak of estrogen during menses (101–104). However, studies have failed to show a consistent correlation between sources of exogenous female hormones (e.g., modern lower-dose oral contraceptives, hormone replacement therapy, or fertility treatment) and rhinitis (105–107). This may be because current doses of estrogen in oral contraceptives and hormone replacement therapy are quite low (50 to 300 units pmol/L) compared to pregnancy (70 to 150,000 units pmol/L).

About one-third of pregnant women have symptomatic nasal congestion during pregnancy defined by Ellegård and Karlsson as "a nasal congestion present in the last 6 or more weeks of pregnancy without other signs of respiratory tract infection and with no known allergic cause, disappearing completely within 2 weeks after delivery" (108,109). Up to 65% of women self-report nasal congestion at some time during their pregnancy (110). This typically becomes more pronounced in the second trimester of pregnancy and abates soon after delivery. It is more common in multiparous women compared to nulliparous women and is not influenced by age, smoking habits, or body mass index (110).

Though an association between pregnancy and rhinitis seems to exist, the mechanism of hormone-influenced rhinitis is still under debate. Clearly hormone-induced rhinitis is not just a dose–response phenomenon. It appears that either a cyclical pattern of hormone delivery or slowly increasing plasma levels is required to elicit a nasal mucosal effect (111). The decrease in estrogen and progesterone after delivery is known to correlate well with the rapid resolution of rhinitis symptoms after delivery. However, studies to date have failed to show consistent difference in levels of estrogen and progesterone between symptomatic pregnant women and asymptomatic pregnant women or even nonpregnant women (111). Similarly equivocal results have come out of histologic and physiologic studies comparing these groups of women.

Treatment is focused on a balance between symptom relief for the mother and consideration for the developing fetus. Medications are safety rated for use in pregnancy based on animal and human studies. Only Category D and Category X are based on existing human studies that have demonstrated harm to the fetus. Categories B and C are based on extrapolation from animal reproduction studies only without clear evidence from human studies. The FDA requires a relatively large amount of high-quality data on a pharmaceutical for it to be defined as Pregnancy Category A.

Saline irrigations are very effective for rhinitis of pregnancy and should be the first-line agent before trying pharmaceuticals. Nasal cromolyn sodium is a Category B medication, which is effective for symptoms of

rhinorrhea, sneezing, and itching. The first- and second-generation oral antihistamines are listed as Category B except for fenofexadine and desloratadine, which are designated as Category C. Ipratropium bromide is Category B but it is typically more effective for rhinorrhea and less so for the primary complaint of congestion. Nasal steroids are all Category C except budesonide aqua, which was recently upgraded to Category B. Intranasal antihistamines, oral decongestants, and intranasal decongestants are all considered Category C and should be used sparingly as second-line therapies if symptoms are severe and unresponsive to other agents. Leukotriene inhibitors are Category B and have been proven to be well-tolerated in pregnancy without major malformations to the developing fetus (112). However, the effectiveness of leukotriene inhibitors in the rhinitis of pregnancy has not been specifically studied and would largely depend on the underlying pathophysiology of rhinitis of pregnancy (see Table 30.6 for a listing of pregnancy safety classification of common medications used in the treatment of rhinitis). In pregnant patients for whom a component of allergic rhinitis contributes to their symptoms during pregnancy, maintenance subcutaneous immunotherapy may continue if it is providing benefit without causing systemic reactions but injections should not be started or escalated (113).

Hypothyroidism is an infrequent cause of rhinitis symptoms. If not previously diagnosed, a thorough review of systems should elicit positive responses such as fatigue, cold intolerance, nonvolitional weight gain, brittle hair, and skin changes, which would prompt initial laboratory testing with TSH and T4 levels. Replacement with exogenous thyroid hormone relieves symptoms of rhinitis caused by hypothyroidism (114).

TABLE 30.6 SAFETY IN PREGNANCY OF MEDICATIONS COMMONLY USED TO TREAT RHINITIS

Medication Class	Pregnancy Class B	Pregnancy Class C
Systemic antihistamines, first generation	Chlorpheniramine (Chlortrimeton) Clemastine (Tavist) Dimenhydrinate[a] (Dramamine) Diphenhydramine (Benadryl) Hydroxyzine (Vistaril)	Pheniramine (Avil) Promethazine [a](Phenergan)
Systemic antihistamines, second generation	Cetirizine (Zyrtec) Levocetirizine (Xyzal) Loratadine (Claritin)	Desloratidine (Clarinex) Fenofexidine (Allegra)
Systemic decongestants		Phenylephrine Pseudoephedrine
Leukotriene inhibitors	Montelekast (Singulair) Zafirlukast (Accolate)	
Nasal anticholinergics	Ipratropium bromide (Atrovent)	
Nasal antihistamines		Azelastine (Astelin, Astepro) Olopatadine (Pataday)
Nasal decongestants		Oxymetazoline (Afrin) Phenylephrine (Neosyneprhine) Xylometazoline (Otrivin)
Nasal Mast Cell Stabilizers	Cromolyn Sodium (Nasylcrom)	
Nasal Steroids	Budesonide Aqua (Rhinocort Aqua)	Beclomethasone (Beconase, Vancenase) Ciclesonide (Omnaris) Fluticasone furoate (Veramyst) Fluticasone propionate (Flonase) Mometasone furoate (Nasonex) Triamcinolone acetonide (Nasacort)
Pregnancy Category B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR. Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester	
Pregnancy Category C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks	

[a]Primarily used as antiemetic.

AUTONOMIC RHINITIS (VASOMOTOR RHINITIS)*

Autonomic nervous system dysfunction has long been thought to play a role in chronic nasal inflammation and rhinitis. This was first demonstrated quantitatively by abnormal tilt table testing in patients with autonomic rhinitis (115). More recently, studies have shown that it is likely a hypoactive sympathetic nervous system rather than a hyperactive parasympathetic system that drives symptoms of autonomic rhinitis (116,117).

The symptoms of autonomic rhinitis may occur in response to physical, emotional, or gustatory stimuli. Some common provocative stimuli include cold air, changes in humidity, exercise, sexual arousal, alcohol, emotional stress, spicy foods, and direct manipulation of the nasal mucosa. The patient typically complains of profuse watery rhinorrhea elicited by one of these factors. Nasal congestion may also be present but often to a lesser degree. Pruritus is rare but the sneeze reflex is an autonomic host defense mechanism and may be present.

Autonomic rhinitis is unique among other causes of rhinitis in the fact that it responds particularly well to ipratropium bromide nasal sprays two to four times daily (117). Intranasal topical corticosteroids and intranasal antihistamines have also been found to be effective agents for autonomic rhinitis (118,119).

ATROPHIC RHINITIS

AR is a disease of paradoxical nasal congestion and mucociliary stasis. Patients present with the primary symptom of chronic severe nasal obstruction and on exam the nasal cavities are often remarkably patent or even widened. There are primary and secondary forms of AR that differ in their epidemiology and etiology. Characteristic findings in both forms include nasal crusting, enlarged nasal cavities, mucosal atrophy, and paradoxical nasal congestion. It may be that primary and secondary AR are similar clinical manifestations of disparate inciting factors.

Some terms that have been used interchangeably with AR include *rhinitis sicca*, *empty nose syndrome*, and *ozena*. These may be diseases along a spectrum or different diseases altogether (120,121). The loose use of nomenclature has contributed to confusion in categorization and study of this disease.

The primary form of AR is seen most often in underdeveloped countries. Children and young adults seem predominantly affected though some studies have shown an average age of 50 in their study populations (121). There is a slight female predilection. These patients often present with chronic nasal obstruction accompanied by significant nasal crusting and cacosmia consistent with the triad originally described by Fraenkel of fetor, crusting, and atrophy of the nasal structures. The patients themselves may complain of anosmia but the fetor is often so severe that it is perceived by others. Clinical depression is not uncommon in these patients due to the social stigma of a chronically odiferous nose (121). Prior to the onset of symptoms, a significant history of sinonasal disease is absent in the primary form.

The secondary form of AR presents similarly with paradoxical chronic nasal obstruction; however, the presence of a fetid odor is less common or less pungent. Nasal crusting also tends to be more limited than in the primary form and resorption of turbinates and bone is seen less frequently (121,122). Secondary AR occurs more often in later adulthood and is the predominant form seen in the United States and developed countries. Aggressive sinus surgery with overzealous resection of the turbinates accounts for the great majority of cases of secondary AR. Other causes include: chronic granulomatous diseases such as Wegener granulomatosis, severe nasal trauma, history of radiation to the head and infections such as leprosy, tuberculosis, syphilis, or rhinoscleroma.

The sense of paradoxical nasal obstruction in both primary and secondary AR is not completely understood. Several theories exist (122–124):

1. The turbinates normally direct and eddy inspired air. Atrophy of these areas leads to disruption of normal airflow, which is perceived as obstruction.
2. Some degree of resistance is likely an important factor in the sense of a satisfying breath. The nose contributes 50% of the airway resistance and this is lost with a widely patent nose.
3. Though the nasal cavity is abnormally patent, an atrophic nose has less mucosa surface area for hydration and conditioning of inspired air.
4. There is a general loss of sensory and olfactory input including the perception of inspired air.

The unremitting dry nasal airflow leads to chronic changes to the respiratory epithelium. Histologically, this is reflected in the transformation of the nasal mucosa from normally stratified squamous respiratory epithelium to keratinizing squamous epithelium. There is loss of cilia, goblet cells, serous and mucous glands, and a diffuse endarteritis obliterans (121).

Many possible cofactors have been proposed for the underlying pathophysiology of AR including infection, nutritional deficiency, hormonal imbalance, poor hygiene, vasculitis, autoimmune processes, and hereditary factors. The most often reported of these possible factors is *Klebsiella ozaenae* infection.

*The term vasomotor rhinitis has often been used to describe rhinitis secondary to presumed autonomic dysfunction. It has also been used synonymously with what is now more appropriately called idiopathic rhinitis. Because it has been so ubiquitously applied to multiple categories of nonallergic rhinitis, continued use of the term here adds confusion to the discussion. In this chapter, as in the 2008 ARIA consensus statement, the term vasomotor rhinitis will not be used primarily.

K. ozaenae is the most frequent organism cultured from the crusts of patients with AR (121,125). This occurs more often in primary AR than secondary. In the largest case series to date, out of 242 patients with AR, 45 out of 45 patients with primary AR were culture-positive for *K. ozaenae* whereas only 1.5% of secondary AR patients were positive (121). Whether the presence of *K. ozaenae* is the inciting event in AR or simply an opportunistic superinfection is uncertain, but this organism likely contributes in some part to the ongoing disease process in primary AR. Ciliary beat studies have shown that *K. ozaenae* has ciliostatic properties, which may help in the establishment of chronic colonization and infection (126).

Further implications for an infectious etiology in primary AR comes from a natural correlate which exists in swine called progressive AR. In swine the bacteria *Pasteurella multocida*, alone or in combination with *Bordetella bronchiseptica*, has been established as the causative organism of progressive AR. Vaccines against *P. multocida* are protective against symptoms and signs of progressive AR in swine (127).

AR is a clinical diagnosis. On exam, the nasal mucosa is pale, shiny, and dry. It may appear thinned or cobblestoned. Once the extensive yellow-green crusts are removed, there is a widely patent nasal cavity with loss of normal intranasal landmarks.

Distinguishing between primary and secondary forms in the studies to date has been based on consensus. Patients with *de novo* sinonasal symptoms in the absence of history of nasal trauma, sinonasal surgery, granulomatous disease, or radiation are designated primary AR whereas all others are deemed secondary. The country of origin and recent immigration status of a patient, severity of cacosmia, and radiographic presence of turbinate regression may also be distinguishing characteristics between primary and secondary forms though this has yet to be studied in a case-controlled fashion. In a study by Ly and deShazo, the diagnosis of secondary AR was made with a specificity 0.95 and a specificity of 0.77 if two or more of the following clinical findings were present: epistaxis, anosmia, nasal purulence, nasal crusting, chronic inflammatory disease of the upper airway for 6 months, or two or more sinus surgeries (128).

The extent of bony destruction is often best appreciated on CT scan, which demonstrates a cavernous nasal cavity with loss of normal nasal structures (Fig. 30.2). Pace-Balzan et al. and Moore separately noted the following findings to be consistent with AR: (a) mucosal thickening of the paranasal sinuses, (b) loss of definition of the ostiomeatal complex secondary to destruction of the ethmoid bulla and uncinate process, (c) hypoplasia of the maxillary sinus, (d) enlargement of the nasal cavities with destruction of the lateral nasal wall, and (e) bony destruction of the inferior and middle turbinates (121,129).

Laboratory studies including a complete blood count, basic metabolic profile, rapid plasma reagin, HIV, angiotensin converting enzyme level, calcium level, antineutrophil cytoplasmic antibodies (c-ANCA, p-ANCA, myeloperoxidase, and proteinase 3) are recommended as part of the initial evaluation of a patient with suspected secondary AR. A chest x-ray is an effective and low-cost method to evaluate for coexisting pulmonary disease.



Figure 30.2 Coronal CT scan at the level of the right anterior ethmoid artery shows abnormally patent sinuses with resection of major endonasal structures including bilateral inferior and middle turbinates, bilateral uncinates, bilateral total ethmoids.

Positive nasal cultures can help support the diagnosis and direct antibiotic therapies but are not required for the diagnosis. Nasal biopsy should be performed whenever granulomatous causes of secondary AR are under question. If there is associated weight loss, chronic dyspnea, or other symptoms of coexisting pulmonary disease, a nasal biopsy is warranted. Similarly, if a septal perforation is present without history of iatrogenic intervention or intranasal drug abuse, clinical suspicion should be raised for an underlying vasculitis and a biopsy should be taken. A primary etiology for AR should always be sought first and treated accordingly.

The mainstay of treatment for AR is moisture and debridement. Debridement should initially occur in the office at 4- to 6-week intervals followed by isotonic nasal saline irrigations of at least 200 mL 2 to 4 times a day. A non–petroleum-based salve should be used twice daily in between irrigations to improve nasal moisture. Once the patient is improved from the standpoint of excessive crusts and foul smelling rhinorrhea, nasal surveillance and debridement in the office can be performed less frequently but the patient must be counseled regarding the persistence of this disease and the importance of daily compliant therapy. Occasionally topical antibiotic solutions in addition to saline for 2 to 4 weeks are helpful in eradicating the chronic infection and foul-smelling crusts. Some commonly used topical antibiotic preparations include 200 mL of gentamycin (80 to 160 mg/1,000 mL) twice daily or mupirocin (22 mg of 2% in 1,000 mL) twice daily. A systemic quinolone or tetracycline can be considered if patients remain refractory despite daily compliant therapy.

Decongestants and antihistamines should be avoided as these will exacerbate the dried mucosa.

Surgical options are aimed at improving nasal humidity and/or nasal resistance. A modified Young's procedure develops anterior mucosal flaps to close off one naris at a time and allows for rehumidification of the nasal mucosa. Periodic nasal endoscopy is facilitated by leaving a small 3 mm orifice. A subsequent recanalization procedure is required. Limited studies have shown a decrease in nasal crusting at 6 months and increase in length but not number of cilia (130).

There are a number of different removable nasal stents that are available for narrowing the diameter of the nares to increase nasal resistance. There are a variety of methods for surgical vestibuloplasty in the literature. These involve the development of mucosal flaps or injection of various autografts or allograft implants at the internal nasal valve. Results of all surgical options have been varied at best and should be pursued with caution after exhausting all conservative options over a prolonged period of time.

SYSTEMIC CAUSES OF NONALLERGIC RHINITIS

Systemic diseases may present with clinical symptoms of chronic rhinitis and must be considered in the differential of refractory chronic nonallergic rhinitis. Autoimmune and granulomatous diseases such as Wegener granulomatosis and sarcoidosis are the most common considerations. Exam findings may be nonspecific but a review of systems may reveal positive constitutional, pulmonary symptoms, or musculoskeletal symptoms which should raise one's clinical suspicion for an underlying systemic process. Infectious agents such as tuberculosis, rhinoscleroma, and chronic fungal infections may also incite granulomatous reactions in the nose and chronic rhinitis. "Snuffles" is a term used to describe the persistent and at times blood-tinged rhinorrhea that is a manifestation of congenital syphilis. Directed serum studies and intranasal biopsy are indicated to rule out infectious and autoimmune causes of refractory rhinitis. A chest x-ray is an efficient, low-cost modality that should also be employed when investigating the potential of coexisting pulmonary disease.

Extraesophageal reflux (EER) is recognized as a common cause of refractory rhinitis in children (131) and is increasingly recognized as a contributor to chronic rhinosinusitis in adults (132). EER has also been associated with autonomic rhinitis in adults and may be a manifestation of generalized autonomic dysfunction (116). Chronic phlegm, excessive throat clearing, globus, cough, and throat irritation are symptoms that could be equally attributable to refluxed stomach contents from below or inflammatory mediators in nasal discharge from above. A history of heartburn, regurgitation, sour brash, or dyspepsia is important to seek from patients with chronic rhinitis symptoms; however, the absence of these symptoms does not exclude the diagnosis of EER. Koufman (133) demonstrated that even trace amounts of reflux, three times a week, are enough to cause mucosa trauma to the larynx. A specialized dual pH probe with separate esophageal and nasopharyngeal arms can detect events of acid reflux into the nasopharynx but there is currently no standardized data to delineate what is normal or what is significant. An empiric trial of antireflux medication may be warranted for patients with refractory rhinitis symptoms.

Both hematogenous and solid organ malignancies may mimic nonallergic rhinitis symptoms. Nasal neoplasms should always be investigated with nasal endoscopy and CT scan of the sinuses. NK/T-cell lymphoma, formerly called lethal midline granuloma, can cause an aggressive erosion of intranasal structures consistent with AR. Chronic lymphocytic leukemia has also been reported to masquerade as chronic rhinitis (134).

Patients with Parkinson Disease demonstrate a fivefold increased incidence of rhinorrhea against age-matched controls in self-reported studies (135). This appears predominantly autonomic in description and responds to ipratropium bromide. This may be due to the sympathetic dysregulation seen in Parkinson Disease. (See Table 30.7 for a listing of potential systemic and structural causes of chronic rhinitis.) These disease processes are discussed in more detail in separate chapters.

TABLE 30.7 SYSTEMIC AND STRUCTURAL CAUSES OF RHINITIS

Inflammatory or immunologic conditions
- Wegener Granulomatosis
- Sarcoidosis
- Systemic lupus erythematous
- Churg–Strauss
- Relapsing polychondritis
- Amyloidosis
- Immunodeficiency (e.g., Selective IgA deficiency)
- NK/T-cell lymphoma
- Chronic lymphocytic leukemia

Structural or mechanical conditions
- Choanal atresia
- Deviated septum
- Enlarged adenoids
- Foreign bodies
- Nasal polyps
- Nasal tumors
- Ciliary dyskinesia (e.g., Primary ciliary dyskinesia, CF, Kartagener syndrome)
- CSF leak

Other
- EER
- Parkinson disease

AGING AND RHINITIS

Rhinitis in children is predominantly infectious and allergic. After age 20, nonallergic rhinitis is more common. After the sixth and seventh decades of life, changes in the nasal mucosa, weakening of the cartilaginous nasal structure, and polypharmacy predispose older adults to a condition, which some have dubbed "geriatric rhinitis" or "senile rhinitis" (136).

With aging, the nasal mucosa becomes more atrophic with a loss of submucous serous glands and goblet cells and a decrease in microvascular flow. Laxity in the cartilaginous support of the nose with age-related loss in collagen may also accentuate symptoms of nasal airflow obstruction. The aged population is also likely to be on chronic medications such as diuretics, beta-blockers, anxiolytics, and antivertigo drugs with known side effects of nasal dryness and congestion.

Patients may present with complaints of thickened nasal secretions and crusting, excessive postnasal drip and phlegm, excessive throat clearing, nasal congestion, and occasionally decreased sense of smell and taste. Alternatively elderly patients may report watery rhinorrhea and exacerbation with meals, temperature changes, or exercise that is more consistent with autonomic rhinitis. The differential for new-onset geriatric rhinitis includes allergic rhinitis, vasomotor rhinitis, atrophic rhinitis, chronic sinusitis, EER disease, benign and malignant nasal masses, and CSF leak. It is paramount to investigate and eliminate more morbid conditions prior to commencing presumptive therapy.

The goals in the treatment of geriatric rhinitis focus on increasing nasal moisture and mucociliary clearance. To this end, saline nasal sprays and irrigations are the mainstay of treatment. Addition of a mucolytic such as guaifenesin can also help to thin nasal secretions. There is some debate about the role of topical nasal steroids in geriatric rhinitis. Some have cautioned to use these sparingly as they may exacerbate nasal dryness but in many patients the combination of saline and a topical nasal steroid is effective. A trial of nasal steroids is reasonable with close monitoring for local side effects. Nasal steroids should be used with caution in patients with narrow angle glaucoma as steroids can raise intraocular pressures. If treatment with steroids is necessary in a patient with a history of narrow-angle glaucoma, the patient should have frequent intraocular pressure checks by their ophthalmologist. Ipratropium nasal sprays are very effective for autonomic rhinitis but compliance may be limited due to the frequency required.

Medications to be avoided in this population include antihistamines and decongestants. Antihistamines, particularly first-generation antihistamines, can exacerbate mucosal dryness and compound sedation from other medications. Antihistamines should be limited to second-generation antihistamines when indicated. Topical and systemic nasal decongestants do not provide long-term solutions for geriatric rhinitis, may exacerbate nasal dryness and irritation, and may also worsen underlying comorbid conditions such as hypertension and cardiac disease.

HIGHLIGHTS

- Nonallergic rhinitis is a common problem, which is likely underrecognized.
- There are no definitive tests for confirmation of nonallergic rhinitis (or its subcategories). Diagnosis is arrived upon with a thorough history, temporal associations to the patient's symptoms, and exclusion of other potential diagnoses.
- Though the terminology may be murky and categorization may be challenging, in the practical management of patients with chronic nonallergic rhinitis the approach to treatment is similar.
- Chronic rhinitis may be alleviated by many nonpharmacologic, nonsurgical therapies including patient education, environmental control, and nasal saline irrigation.
- Topical antihistamines demonstrate both antihistaminic and anti-inflammatory properties and are effective, first-line therapies for patients with idiopathic rhinitis.
- Topical nasal corticosteroids are particularly effective in nonallergic rhinitis patients with significant nasal eosinophilia.

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Systemic Diseases that Affect the Nose and Sinuses

31

David A. Zopf *Mark A. Zacharek*

The role of the otolaryngologist in the diagnosis and treatment of the following systemic diseases discussed in this chapter is multifaceted. Certain disorders may manifest their initial presentation in the nasal/paranasal sinuses. In this instance, an opportunity is presented for an initial workup and diagnosis while obtaining appropriate consultation of additional medical specialists when necessary.

Many of the following diseases present a challenge to the head and neck surgeon. They are oftentimes chronic in nature, with suspicion of an underlying, more widespread issue arising after failure of response to several interventions. A thorough history and physical examination, followed by the appropriate laboratory assays, diagnostic imaging, and tissue biopsies are essential to guiding patients to treatment and relief.

Surgical interventions and procedures may be offered for symptomatic relief in certain pathologies, though treatment for systemic disease is more often medical. For example, a septal button may alleviate symptoms in a patient with septal perforation secondary to granulomatosis with polyangiitis (a newer nomenclature for Wegener granulomatosis [WG]), but the otolaryngologist's interventions provided in the clinic or operating room cannot replace steroid immunotherapy.

Furthermore, it is often possible to view several of the discussed systemic diseases as pathology on a continuum rather than distinct afflictions. As such, addressing individual conditions while keeping in mind their general pathophysiologic category will assist in understanding successful treatment and diagnosis.

Systemic diseases affecting the nasal and paranasal sinuses are presented in the following sections by pathophysiologic process: genetic/congenital, granulomatous, autoimmune, and hematologic (Table 31.1). However, these groupings are not mutually exclusive, and disease processes discussed may actually fit in more than one of these categories.

CONGENITAL/GENETIC

Cystic Fibrosis

Cystic fibrosis (CF), the most common autosomal recessive disorder in whites (1 case:2,500 live births) is a systemic disease affecting mucous viscosity secondary to a genetic mutation. Mutation in the CF transmembrane conductance regulator gene of chromosome 7 alters a transmembrane channel protein affecting chloride ion movement. An inflammatory reaction ensues leading to cellular breakdown and an accumulation of intracellular/intranuclear products, such as DNA (1). This affects the viscoelastic properties in the pancreas, reproductive organs, and respiratory tract, including the sinonasal cavities (2). In addition, increased bacterial colonization occurs, particularly with *Pseudomonas aeruginosa* and *Staphylococcus aureus* (3). Sinonasal disease is a proposed contributor of lung disease, a leading cause of death in CF (2).

Dysfunctional mucus clearance may lead to obstruction of the sinus ostia and mucosal edema leading to nasal obstruction, chronic sinusitis, and sinonasal polyposis. Nearly 100% of CF patients exhibit some aspect of sinus disease (4). The most common CT-imaging findings in CF include sinus opacification followed by the presence of pseudomucoceles. In one series of Brazilian patients, these findings were absent in only two of fifty patients. Hypoplasia or agenesis of the frontal sinuses has also been noted (3). Approximately 36% of carriers of recessive CF mutations reported chronic rhinosinusitis symptoms, versus 14% in the general population (5). In another series of homozygous recessive CF, 117/126 patients exhibited rhinosinusitis. Nasal polyps were discovered in 20% of this series (6).

Diagnosis is made with a positive sweat chloride test and/or genetic test with at least one of the following:

TABLE 31.1 SUMMARY OF SYSTEMIC DISEASES AFFECTING THE NOSE AND SINUSES

		Diagnostic	Therapeutic
Congenital/Genetic			
	CF	History, sweat chloride, genetic screen	Selective ESS
	Lymphoma	History, biopsy	XRT; XRT+CRT
Granulomatous			
	Sarcoidosis	History, biopsy, ACE levels	Corticosteroids, nasal irrigation, selective ESS
Autoimmune			
	Granulomatosis with Polyangiitis (Wegeners)	History, c-ANCA, biopsy	Corticosteroids, cyclophosphamide
	Relapsing Polychondritis	History	Corticosteroids, cyclophosphamide
	CSS	History, biopsy, ANCA	Corticosteroids, cyclophosphamide, nasal irrigation
	Sjogren syndrome	History, biopsy, SS-A,B	Corticosteroids, artificial moisture
Hematologic			
	HHT	History	[laser]coagulation, systemic therapies, hormonal therapy, septodermoplasty, Young procedure
	Thrombocytopenia	History, CBC, bleeding/clotting parameters	Transfusion, addressing underlying pathology

(a) typical chronic obstructive pulmonary disease, (b) documented exocrine pancreatic insufficiency, or (c) positive family history.

Treatment should be symptom directed based on severity. Mild symptoms may be managed with nasal irrigations (1). More severe symptoms can be addressed with mucolytics, nasal corticosteroids, and antibiotics (7). Surgical intervention in CF should be utilized with the intent to reduce sinonasal symptoms and improve quality of life, though not with curative expectations. Revision surgery is required in approximately one-third (2) to one-half (8) of CF cases and may be predicted by polyp severity (2). In a randomized double-blind prospective trial, dornase alpha (recombinant human deoxyribonuclease) has been shown to be effective in extending benefits of surgery when used as an adjuvant therapeutic (1).

Lymphoma

Lymphoma may present with nasal involvement that is clinically restricted to the sinonasal airway. The cell lineage of the lymphoma origin is variable. One report investigated the cellular origins of nasal lymphomas in a western patient population and found that 55% of tumors were comprised of natural killer (NK)/T cells, 29% B cells, and 16% T cells. However, these estimates differ in Chinese and Japanese populations where tumors derived from the NK/T-cell lineage are more common (9). An association with Epstein-Barr virus has been proposed for NK/T-cell lymphoma.

Midline destructive lesions have historically been described by several different variations in nomenclature, such as idiopathic midline granuloma, lethal midline granuloma, polymorphic reticulosis, and Stewart syndrome. Improvements in cellular and molecular diagnostics, including immunohistochemistry and flow cytometry, have revealed that many of these lesions are actually WG or lymphomatous (10). Furthermore, extensive investigation into subdivision of classifications of NK/T-cell lymphoma is an active area of current research. Subdivision into upper aerodigestive tract NK/T-cell lymphoma (nasal cavity, nasopharynx, oral cavity, oropharynx, hypopharynx disease) and nonupper aerodigestive tract NK/T-cell lymphoma has been proposed (11).

Clinical presentation of lymphoma involving the sinonasal compartments includes epistaxis, nasal obstruction, nasal swelling, and constitutional or B-type symptoms (malaise, weight loss, fever). More advanced disease may reveal a friable necrotic mass, potentially obstructing the nasal cavity/nasopharynx. Local extension, when present, has been reported to involve the maxillary sinus (42%), ethmoid sinuses (36%), nasopharynx (25%), and rarely skull base or cranial nerves (9).

Diagnosis may be particularly challenging in instances of mild or early stage disease. An initial routine workup with baseline serologic assays and clinical/endoscopic examination are followed by biopsy of suspicious nasal mucosal disease. Sufficient fresh samples should be obtained for immunophenotyping by flow cytometry. Histologic analysis may reveal lymphocytic infiltrates with angiocentric necrosis.

TABLE 31.2 ANN ARBOR CLASSIFICATION FOR LYMPHOMA

Ann Arbor Classification for Lymphoma	
Stage I	Involvement of a single lymph node region or single extralymphatic site
Stage II	Involvement of two or more lymph node regions on the same side of diaphragm, localized contiguous involvement of only one extralymphatic site and lymph node region
Stage III	Lymph node involvement on both sides of the diaphragm
Stage IV	Disseminated involvement of one or more extralymphatic organs with or without lymph node involvement

Table 31.2 details the Ann Arbor Lymphoma staging system. Alternate staging based on various classifications, such as anatomic subsites, or treatment responses have been proposed (11).

Treatment and follow-up should be directed by hematology/oncology specialists. No advantage for the addition of chemotherapy to radiation has been shown in early stage (I/II) NK/T- cell lymphoma (overall 5-year survival (OS) rates of 38%-RT versus 35%-CRT (12); 66%-RT versus 76%-CRT (13); 59.2%-RT versus 52.3%-CRT (14)). Lack of success with chemotherapy alone may be a result of P-glycoprotein expression that confers increased multidrug resistance in CD56+ NK cells (15). Studies of combination therapy reveal sequence impacts outcomes. In chemotherapy followed by 45 Gy of radiation, the complete response (CR) rate was 49.1%, compared to 100% in those who received radiation followed by chemotherapy (16). A review by Kohrt and Advani cite several studies lending support for combined chemoradiation in high-risk or advanced-stage disease (stage III/IV), where 5 year OS drops to 20%. Several aspects of the therapeutic strategy in nasal NK/T-cell lymphoma are topics of current investigations.

GRANULOMATOUS

Sarcoidosis

Sarcoidosis is a noncaseating granulomatous disease, oftentimes involving multiple systems (Fig. 31.1). A demographic predisposition for African American and Scandinavian individuals of age range in the twenties and thirties has been demonstrated (17).

Development is likely multifactorial, leading to an abnormal immune response, of which T cells and their proinflammatory cascades are thought to be at the center. Mycobacterial tuberculosis catalase-peroxidase protein was reported to be present in approximately 50% of sarcoidosis tissue samples (18). Activated tissue macrophages are the primary source for angiotensin-converting enzyme elevations (19). Genetics appear to contribute to predisposition of development of sarcoidosis. In one study involving 210 pairs of monozygotic and dizygotic twins and at least one proband, concordance rates of sarcoidosis were found to be significantly higher in monozygotic than in dizygotic twins. Compared with the general population, there was an 80-fold increased risk of developing sarcoidosis in cotwins of effected monozygotic brothers or sisters (20). Responsible genes, such as butyrophilin-like 2 gene, have been proposed (19). It is hypothesized that an environmental factor prompts an aberrant immunologic response, though no strong associations in the literature have led to a specific environmental offender.

The wide range of symptomatology makes recognition of sarcoidosis a challenge. Incidental discovery on chest x-ray (CXR) in asymptomatic patients accounts for a large proportion of presentations. In the symptomatic patient, one or more of the following systems may be involved: respiratory (cough, dyspnea, chest pain), integumentary (lupus pernio, erythema nodosum, papules, nodules, plaques), ocular (orbital pain, uveitis, visual changes), rheumatologic (arthralgia, myalgia), and constitutional (fevers, night sweats, fatigue) (21). Lupus pernio, the most characteristic skin lesion for sarcoidosis, occurs at a higher preponderance in sarcoidosis with sinonasal features (Fig. 31.2).

As pulmonary findings are a hallmark of sarcoidosis, a close collaboration with a pulmonologist is recommended. Chest radiographic findings are classified as follows: stage 0, normal CXR; stage 1, isolated intrathoracic adenopathy; stage 2, intrathoracic adenopathy and parenchymal disease; stage 3, parenchymal disease; and stage 4, pulmonary fibrosis (22).

Sinonasal manifestations occur in approximately 1% to 5% of cases, of which only 10% are present in absence of pulmonary disease (23–25), and include nasal congestion, nasal obstruction, rhinorrhea, nasal crusting, epistaxis, nasal mass, facial/nasal pain, and anosmia (23,26). On physical examination, purplish, friable nasal mucosa, mucosal

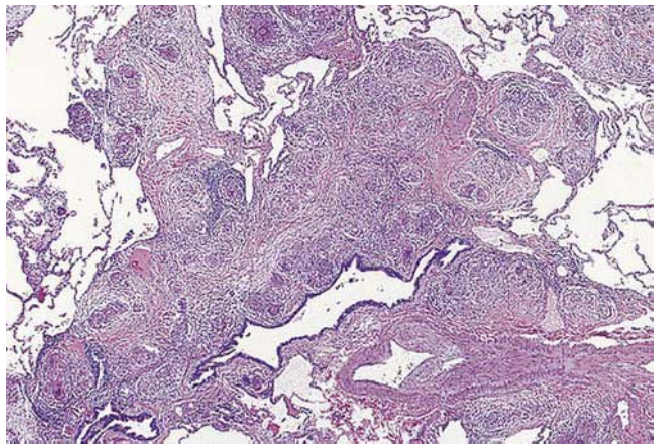


Figure 31.1 Sarcoidosis. Multiple noncaseating granulomas are present along the bronchovascular interstitium. Image from Rubin E, Farber JL. *Pathology*, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 1999.



Figure 31.2 Raised lesions of lupus pernio. (From Crapo JD, Glassroth J, Karlinsky JB, et al. *Baum's textbook of pulmonary diseases*, 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2004.)

hypertrophy, nasal polyps, and yellow submucosal nodules may be observed, most commonly involving the septum and inferior turbinates (Fig. 31.3). Thickening of sinus mucoperiosteum and radiologic paranasal opacification mark sinus involvement (24,27). Of 15 patients undergoing CT with sarcoidosis and sinus symptoms, the maxillary (14), ethmoid (9), frontal (6), and sphenoid (3) sinuses demonstrated complete or partial opacification (23).

When presented with sinonasal findings in suspected sarcoidosis, histological biopsy revealing noncaseating granulomas is the definitive mode of diagnosis. With the differential diagnosis including fungal and mycobacterial infections, the respective histopathology and tissue cultures are required to rule these out. However, patients who present with Lofgren syndrome (erythema nodosum, hilar adenopathy, and polyarthralgias) can be clinically diagnosed without the necessity of biopsy (19). ACE levels and serum calcium levels may be elevated. Though nonspecific, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels are often elevated. Equally important are ruling out other potential disease processes and assessing the extent of pathology, for example, antineutrophil cytoplasm antibodies (ANCA) should be measured to rule out WG.

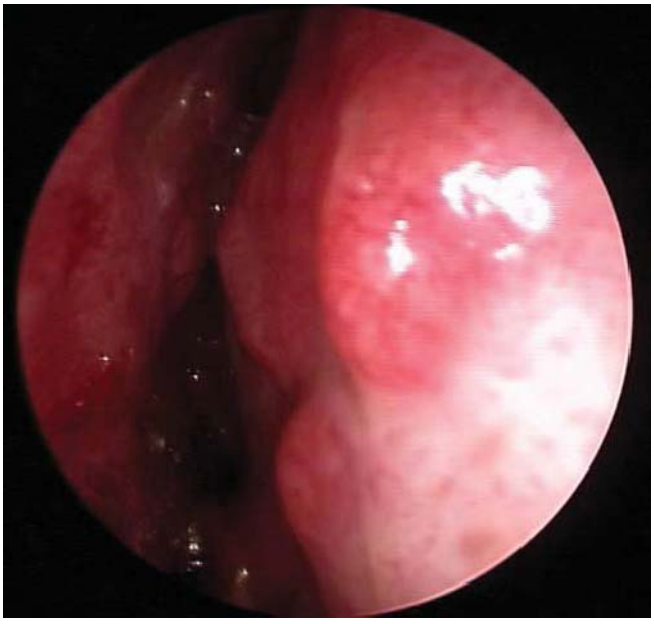


Figure 31.3 Endoscopic view of nasal sarcoidosis. The septal mucosa, as well as the lateral nasal wall reveals nodular, erythematous swellings.

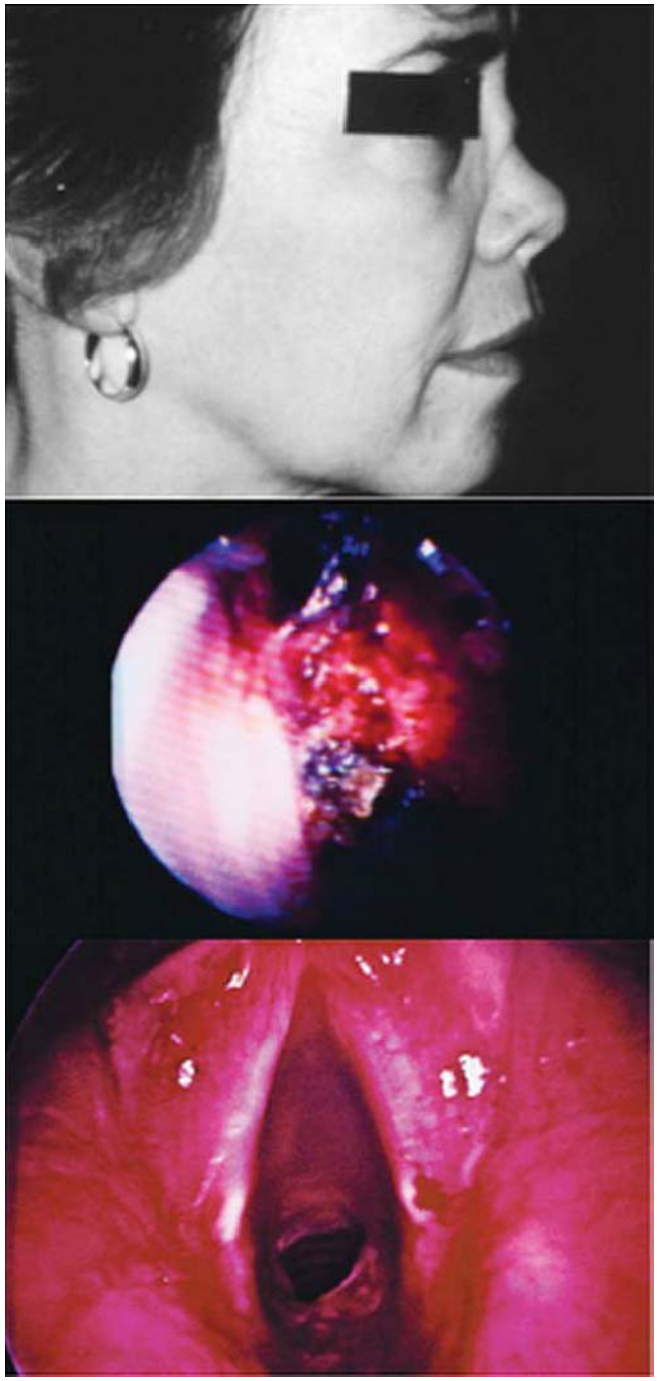


Figure 31.4 Saddle-nose deformity in WG, bloody crusts in WG, subglottic stenosis in WG. (From Koopman WJ, Moreland LW. *Arthritis and allied conditions a textbook of rheumatology*, 15th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005).

Treatment should be tailored to the severity and extent of disease involvement. Many patients diagnosed with sarcoidosis do not require treatment. In symptomatic patients, nasal corticosteroids for skin disease and non-steroidal anti-inflammatory drugs (NSAIDs) may be utilized for mild disease, where higher dose systemic corticosteroids and immunomodulators for more extensive disease may be initiated with close medical follow-up. Six to nine months of prednisone, initiated at a dose of 30 to 40 mg daily followed by a 5 mg/day taper to a 10 to 20 mg/day maintenance dose, is recommended (19). Methotrexate has been shown to be an effective therapeutic and allows for decreased doses of systemic steroid administration in a randomized double-blind trial (28). Additionally, hydroxychloroquine, azathioprine, pentoxifylline, statins, and tumor necrosis factor (TNF-α) TNF-alpha binding proteins/inhibitors, such as infliximab, etanercept, and adalimumab, have been described for the same intent (29). A multicenter randomized, double-blind, placebo controlled trial of infliximab has shown improvements in pulmonary function with pulmonary sarcoidosis, though the remaining biologics mentioned have otherwise not shown dramatic efficacy to date (19). Sinonasal involvement has been shown to be a poor prognostic indicator with a high frequency of recalcitrant disease involving multiple vital organs, thus oftentimes necessitating systemic therapy (23).

The goal for surgical intervention in sarcoidosis is not eradication of disease, but potential quality of life improvement. Kay and Har-El examined the role for endoscopic sinus surgery in sarcoidosis. Six of 86 sarcoidosis patients underwent endoscopic sinus surgery with indications including granulomatous or polypoid lesions causing severe nasal obstruction or blocking the osteomeatal complex leading to symptomatic chronic or acute recurrent sinusitis. CO_2 laser surgery has also been described for treating such granulomas (29). Patients should be informed of the uncertainty of duration and extent of symptom relief, with the risk of worsening sinonasal symptoms. Finally, prompt consultation of additional specialists should be elicited to assist in instances of multiorgan involvement.

AUTOIMMUNE

Granulomatosis with Polyangiitis (Wegener Granulomatosis)

The American College of Rheumatology has proposed a nomenclature free of eponyms, working towards etiology-based terminology (30). The term granulomatosis with polyangiitis, or GPA is now the preferred title for the disease entity WG. In the spirit of collaborative and cooperative efforts, we provide the reader with awareness of this anticipated shift, though we will utilize the previously used eponym for ease and accessibility, as this proposed change will take time and effort to gain widespread awareness.

WG is an idiopathic systemic small-medium vessel vasculitis characterized by necrotizing granulomas. Age of diagnosis is often 20 to 40 years old and there does not appear to be gender preponderance (31).

There is no definitive etiology established, though involvement of circulating ANCA in response to an environmental stimulus, such as an infectious agent or toxin in combination with a genetic predisposition is suspected (31). Genetic predisposition is supported by reports suggesting association with HLA DR4 and DR8. Moreover, there is an increased incidence of autoimmune diseases in first degree relatives of WG patients compared to a control population (32, 34). Serum levels of IgA and IgE are often found to be elevated, further supporting an autoimmune mechanism (32). A direct role of proteinase 3 (PR3) (and myeloperoxidase [MPO]) has been hypothesized through a delay in clearance of inflammation inducing neutrophils (33). *S. aureus* and silica have been implicated as possible etiologic triggers. Support for a role of staphylococcus involvement in pathogenesis include higher incidence of carrier status in WG and the success of antistaphylococcal antibiotics in treatment regimens (32).

WG is known to affect the upper respiratory tract, lungs, and kidneys. Limited forms of the disease are restricted to one or two of these systems. Constitutional symptoms including fever, weight loss, weakness, and arthralgias are common. Involvement of other systems including ophthalmologic, cardiac, and neurologic are also reported.

The nasal cavity/paranasal sinuses are the most frequently affected sites in the head and neck, with between 64% and 80% of patients exhibiting manifestations. Isolated nasal involvement is seen in approximately one-third of cases, with the septum and turbinates being the most commonly involved sites. Mucosal crusting, increased friability, and inflammation can be seen on rhinoscopy/endoscopy. Septal involvement can result in perforation or saddle-nose deformity, the latter of which is seen in 10% to 25% of WG patients (Fig. 31.4, top, middle). Chronic sinusitis occurs in approximately half of cases with nasal/paranasal involvement (32). Symptoms include obstruction, pain, malodorous sensation, rhinorrhea, epistaxis, and epiphora.

Clinical diagnosis of WG is based on the American College of Rheumatology Diagnostic Criteria of WG (Table 31.3). Serologic diagnosis of WG is made by assaying serum c-ANCAs. If assays for c-ANCA are positive, clinical testing for antibodies against PR3 and MPO should be sought since they have increased specificity (36). Additionally, tissue biopsies should be obtained, oftentimes sinonasal, which if positive show characteristic necrotizing granulomas and vasculitic inflammation. Of note, review of diagnostic data have shown c-ANCA to be negative in approximately 30% of biopsy positive WG and additionally false positives have been seen in amebiasis, leprosy, and infectious endocarditis. Important factors in a reliable biopsy include sampling sinonasal disease if present and obtaining a generous sample that includes adjacent healthy appearing mucosa. CT or plain films may demonstrate a multitude of findings from mucosal thickening to bony changes. The most common sinuses involved are the maxillary sinuses (32).

TABLE 31.3 THE AMERICAN COLLEGE OF RHEUMATOLOGY DIAGNOSTIC CRITERIA OF WG (TWO OF FOUR REQUIRED)

The American College of Rheumatology Diagnostic Criteria of WG
Oral ulcers and nasal discharge
Nodules, fixed infiltrate, or cavities on chest film
Nephritis urinary sediment (red cell cast or >5 red blood cells per high power field)
Granulomatous inflammation on biopsy

Respiratory symptoms, such as cough or hemoptysis, should prompt radiologic evaluation. Subglottic stenosis is a common finding and can be diagnosed on endoscopic examination (Fig. 31.4, bottom). Workup may also include urinalysis for monitoring renal involvement for possible progressive renal failure histologically seen with pauci-immune necrotizing crescentic glomerulonephritis (32).

Clinical presentation of WG can be very similar to other systemic diseases such as sarcoidosis and Churg-Strauss. Sarcoidosis generally does not manifest with the ulceration and more destructive lesions seen in WG. Ultimately, serologic and pathologic differences distinguish the two entities. WG is characterized by loose, caseating granulomas whereas sarcoidosis displays tight, noncaseating granulomas (32). Churg-Strauss is distinguished by relatively milder sinonasal findings and the presence of serum eosinophilia and asthma.

Immunosuppressive therapy is the general tenet to mollify symptomology of WG. Glucocorticoids and cyclophosphamide are the mainstays of initial treatment for symptomatic disease. Acute and chronic side effects—hyperglycemia, fluid retention, osteoporosis, infections, and joint and ophthalmologic disease—may prevent prolonged therapy with these agents. Methotrexate for maintenance therapy as well as a variety of newer immunomodulators such as rituximab, infliximab, etanercept, and leflunomide may be utilized (31,35). Trimethoprim-sulfamethoxazole is also employed as a component of a maintenance regimen to prevent remission.

Surgical treatment should be tempered with the risk for scarring and the potential for worsening of symptoms. It should be strongly recommended to only be performed when the systemic disease is in remission. The role of endoscopic surgery should be limited to refractory chronic sinusitis after failed maximal medical therapy. Close postoperative care and continued adjuvant medical management should be practiced to optimize the chances for symptom resolution (32). Septal perforation repair is an area of controversy and should be approached cautiously. Conservative management using a silicone button is one technique to address whistling. Surgery should only be considered in the setting of small perforations with adjacent healthy mucosa (32). Repair of saddle-nose deformity in WG should also be approached with caution and only considered when the patient is in remission (37).

Relapsing Polychondritis

Relapsing polychondritis (RPC) is an autoimmune disease resulting in inflammation of cartilaginous tissues. It is an extremely rare entity and thus epidemiologic data are sparse. The suspected mechanism of pathogenesis involves an autoimmune response to an innate cartilaginous component by either exposure, damage, alteration, or a mechanism of molecular mimicry involving an infectious agent. Approximately 30% of cases have a concurrent vasculitis, autoimmune disease, connective tissue disorder, or malignant disease (38).

Hyaline cartilage is the tissue that is chiefly involved in the pathogenesis of RPC, and clinical presentation is the result of an inflammatory response to these structures. The auricle is the most common site of inflammatory response, with most cases manifesting a lobule-sparing pattern of inflammation (Fig. 31.5). Inflammation in ophthalmic structures ([epi]scleritis, ulcerative keratitis, uveitis), distal airway (stridor, dyspnea, cough), joints (arthralgias), cardiac (aortic/mitral valve disease), and skin (aphthous ulcers, purpura, nodules) are commonly observed (38).

Nasal involvement manifests as crusting, epistaxis, rhinorrhea, chronic sinusitis, and nasal structural abnormalities secondary to nasal chondritis.

Clinical diagnosis is based on the presence of at least three of the McAdam criteria (Table 31.4) with histologic evidence of chondritis at two or more locations (39).

Histologic findings include an infiltration of lymphocytes (CD4 cells predominate over CD8), disrupted cartilage structure with invading granulation tissue, sequestered islands of cartilage, and degeneration of cartilage to cystic material and/or bony calcification (generally in later stages of the disease process) (38).

At the present time, there are no serologic markers that have demonstrated a high specificity for RPC in humans. Nonspecific markers of inflammation, such as ESR and CRP, may be assayed to support a systemic disorder.

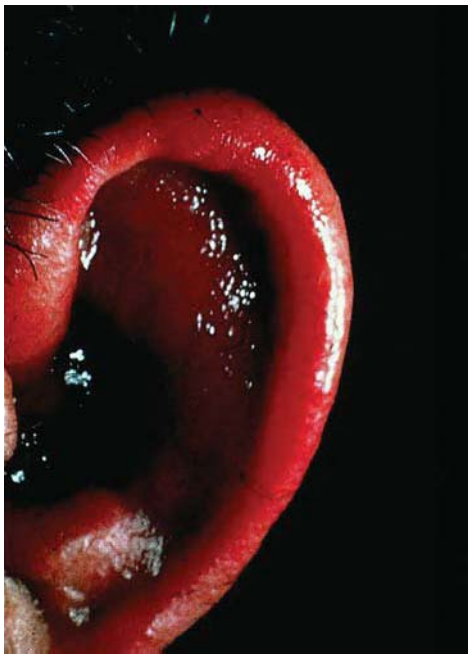


Figure 31.5 Auricular inflammation in relapsing polychondritis. (From Rubin R, Strayer DS. *Rubin's pathology: clinicopathologic foundations of medicine*, 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2008.)

Antinuclear antibodies are positive in 20% to 60% of RPC (38). More specific antibodies to type II, type IX, and type XI collagen as well as matrillin-1, a cartilage matrix protein, have shown potential in animal data, but trials with humans are pending (38).

Systemic treatment depends on severity of clinical symptoms. Mild, local involvement may be managed with NSAIDs. More involved disease warrants systemic corticosteroid therapy. Furthermore, severe cases may call for immunosuppressives such as cyclophosphamide, azathioprine, cyclosporine, methotrexate, adalimumab, infliximab, etanercept, or anakinra. However, data supporting immunosuppressive therapies for RPC are largely based on case reports.

TABLE 31.4 McADAM CRITERIA FOR DIAGNOSIS OF RELAPSING POLYCHONDRITIS

McAdam Criteria for Diagnosis of Relapsing Polychondritis
Bilateral auricular chondritis
Nonerosive, seronegative inflammatory polyarthritis
Nasal chondritis
Ocular inflammation
Respiratory tract chondritis
Cochlear/vestibular dysfunction

Churg-Strauss Syndrome

Churg-Strauss syndrome (CSS) is a rare small to medium vessel necrotizing granulomatous vasculitis associated with bronchial asthma and eosinophilia. It is thought to be Th2-mediated with activation by eosinophils. Several rhinologic symptoms may appear early in the course of the disease, creating an opportunity for the otolaryngologist to make an early diagnosis. In fact, one series revealed approximately one-third of patients' reason for seeking care was worsening nasal symptoms (39). Furthermore, head and neck involvement was seen in approximately 75% of patients who participated in one retrospective case series, with allergic rhinitis (48%) and polyposis (53% to 76%) being the most common presenting symptoms (41,42). It is important for otolaryngologists to be familiar with these symptoms, since some estimates suggest that they diagnose up to 10% of all cases of CSS (40).

Clinical presentation oftentimes starts with a prodromal phase of asthma, allergic rhinitis, sinonasal polyposis, and/or rhinosinusitis. Initial presentation may also include crusting and epistaxis, making distinction from WG difficult. The next phases include eosinophilia and finally systemic vasculitis and its resultant manifestations (Fig. 31.6). Although involvement of many organ systems has been described, the sinonasal, respiratory, and peripheral nervous systems are predominantly affected by CSS (41).

The constellation of nasal polyps, asthma, constitutional symptoms, and additional systemic complaints should prompt evaluation with hematologic (CBC with differential blood count to examine the proportion of eosinophils) and metabolic serologies. It should be noted that eosinophilia may be masked if systemic steroid therapy is being utilized. Elevated ESR and CRP, though nonspecific, will further support a systemic inflammatory process. Immunoglobulin analysis may note

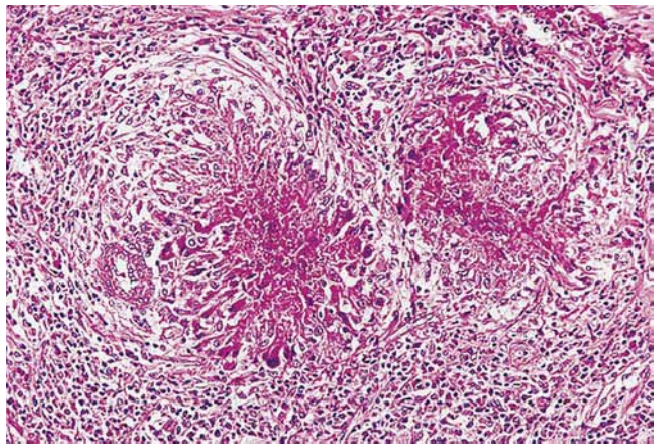


Figure 31.6 Churg-Strauss syndrome. A necrotic ("allergic") granuloma has a central eosinophilic area of necrosis surrounded by palisading macrophages and giant cells. Image from Rubin E, Farber JL. *Pathology*, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 1999.

TABLE 31.5 THE AMERICAN COLLEGE OF RHEUMATOLOGY CRITERIA FOR DIAGNOSIS OF CSS (AT LEAST FOUR REQUIRED FOR DIAGNOSIS)

The American College of Rheumatology Criteria for Diagnosis of CSS
History of asthma
Eosinophilia > 10%
Neuropathy
Nonfixed pulmonary infiltrates
Paranasal sinus abnormalities
Extravascular eosinophils on biopsy

hypergammaglobulinemia and elevation of IgE. Of note, ANCA has not been shown to be a reliable assay for CSS (40). The American College of Rheumatology requires four of six criteria detailed in Table 31.5 for diagnosis of CSS. Further biopsy findings include necrotizing vasculitis and extravascular necrotizing granulomas.

Treatment of CSS generally consists of treatment and subsequent maintenance therapy. Induction therapy involves treatment with oral or intravenous steroids in order to suppress the active disease process. Maintenance therapy follows for approximately 1 year with low-dose oral steroids and cyclophosphamide or methotrexate (41). In a retrospective analysis that utilized a Lund-Mackay grading scale, seventeen out of 29 patients had endoscopic evidence of polyposis with CSS. After initiation of medical treatment in this series, none of these patients required surgical intervention (42). We advise consultation with a rheumatologist for long-term follow-up and multidisciplinary coordination with otolaryngologists, medical pulmonologists, cardiologists, and/or nephrologists.

Sjogren Syndrome

Sjogren syndrome (SS) is a relatively common autoimmune entity marked by progressive inflammation of the salivary and lacrimal glands leading to xerostomia and keratoconjunctivitis sicca. Females are predominantly affected (9:1) and onset is commonly between 30 to 60 years of age. The classification of primary SS is used when exocrine dysfunction occurs in the absence of other autoimmune disorders, whereas secondary SS is seen with an associated autoimmune condition such as rheumatoid arthritis (43). Sicca syndrome describes the combination of xerostomia and keratoconjunctivitis sicca without salivary gland involvement.

Pathogenesis of SS has implicated viral infection and the resultant inflammatory response as an inciting event. Hepatitis C, human immunodeficiency virus, and human T lymphotropic virus type I have been proposed (44). HLA associations have been cited for SSA- and SSB-positive individuals (45). Extraglandular symptoms, similar to other rheumatologic conditions, likely result in a similar mechanism with autoantibodies, immune complexes, and lymphocytic infiltration (46). Several pharmacologic agents have been implicated in sicca syndrome, including antidepressants, anticholinergics, beta-blockers, diuretics, and antihistamines.

Retrospective analysis reveals approximately half of primary SS, secondary SS, and sicca syndrome will present with sinonasal symptoms, though physical exam findings are seen in only 20%. The most common complaints were obstruction and dryness, followed by epistaxis. Crusting, hyposmia, and recurrent sinusitis were rare. The most common physical examination finding was dry mucosa, with septal ulceration and crusting occurring less commonly (47).

Diagnosis is confirmed by parotid or labial mucosa (minor salivary gland) biopsy. At least four salivary gland lobules should be acquired for diagnosis. SSA/anti-Ro and SSB/anti-La autoantibodies are commonly used diagnostic serologies. SSB/anti-La is more specific and less sensitive, whereas SSA/anti-Ro has a higher sensitivity but may be positive in various other autoimmune conditions. Histopathologic findings include glandular lymphocytic infiltration and HLA-DR expression (48). Sialography may be used to exclude salivary duct obstruction or stricture. A multitude of additional serologic assays and diagnostics may be performed suggesting SS or a variant, though their presence or absence is not necessarily confirmatory (49). There are a number of salivary analysis assays currently under investigation, which may hold promise for improving the diagnosis of SS in the future (48) (Figs. 31.7 and 31.8).

Treatment of SS should be symptom targeted. For xerostomia and keratoconjunctivitis sicca, artificial lubricants and moisturizers, as well as pharmacologic and natural secretogogues may be utilized. For sinonasal symptoms, nasal saline sprays/irrigations and increasing environmental humidification are recommended. Immunomodulatory therapy may also hold promise. Rituximab was recently found to show improved salivary flow rate and lacrimal gland function in primary SS (50).

A 40-fold increased incidence of B-cell lymphoma are reported in SS, and as such, clinicians should have heightened surveillance in patients with positive predictive factors of palpable purpura and low serum C4 (51,48).

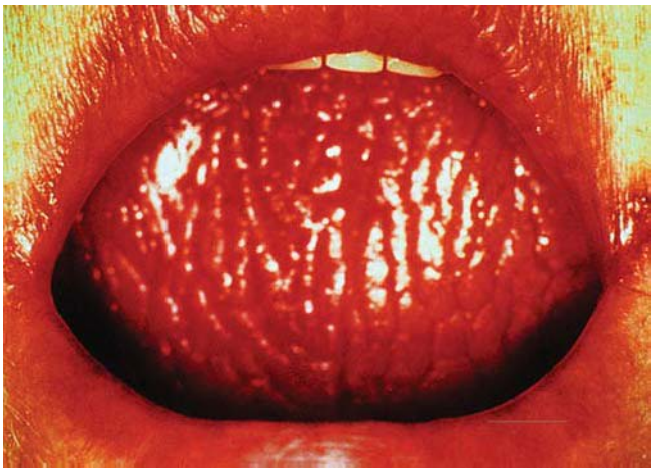


Figure 31.7 Dry fissured tongue in Primary Sjogren syndrome. From Gold DH, Weingeist TA. *Color atlas of the eye in systemic disease.* Baltimore, MD: Lippincott Williams & Wilkins, 2001.

HEMATOLOGIC

Epistaxis in individuals with normal clotting and vascular components can cause alarming amounts of blood loss. When combined with a congenital or acquired bleeding or clotting disorder, this risk is amplified.

Hereditary hemorrhagic telangiectasia (HHT), or Osler-Weber-Rendu disease, is an autosomal dominant disorder affecting approximately 1:10,000 individuals. Characteristic vascular malformations are caused by mutations in the ENG gene and/or activin receptor-like kinase-1, which encode for factors (endoglin) involved in the transforming growth factor-β-vascular endothelial growth factor (VEGF) pathways. Dysregulation of angiogenic signals leads to abnormal endothelial–mural architecture and weakened vessels that are prone to bleeding (52). Presentation is often in middle age, occurring most commonly in the third and fourth decades. Diagnosis of HHT (Curacao criteria, Table 31.6) is based on signs and symptoms of epistaxis, telangiectasias, visceral vascular malformations, and family history (53,55). Telangiectasias are predominantly found in the anterior nasal septal mucosa (54), though also commonly seen in the circumoral/lip regions, helical rim of the ear, soft palate, and nail beds and finger tips (Fig. 31.9).

As the otolaryngologist, the opportunity for initial diagnosis of HHT arises due to the presentation of recurrent epistaxis. An essential component to patients' evaluations is addressing the possibility of multiorgan arteriovenous malformations (AVMs). Thirty percent of HHT patients have pulmonary AVMs, 30% have hepatic involvement, and 10% to 20% have central nervous system involvement. Cerebral AVM hemorrhage rates approximate those of non-HHT AVMs, 1.4% to 2.0% (56). A helical chest CT may be considered in evaluating for a pulmonary AVM. MRI and MR angiography should be considered in evaluating for cerebral lesions. Utilization of these modalities for screening in the nonsymptomatic HHT patient is currently under debate.

TABLE 31.6 CURACAO DIAGNOSTIC CRITERIA FOR HHT

Curacao Diagnostic Criteria for HHT
Epistaxis
Telangiectasias
AVMs of the lungs, liver, or central nervous system
Family history in first degree relatives

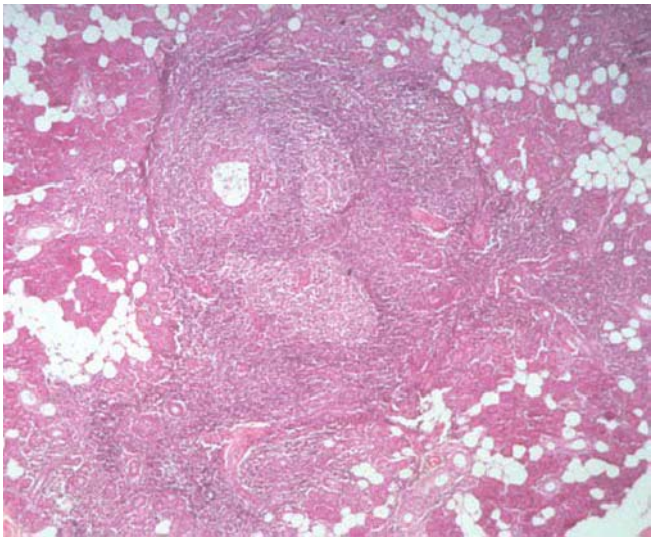


Figure 31.8 Sjogren syndrome involving a major salivary gland. An intense lymphoid infiltrate destroys the gland's acini but spares the ducts. Image from Rubin E, Farber JL. *Pathology*, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 1999.



Figure 31.9 Multiple small red spots on the lips strongly suggest HHT. From Langlais RP, Miller CS. *Color atlas of common oral diseases.* Philadelphia, PA: Lea & Febiger, 1992, with permission.

Conservative treatment begins with nasal ointment, irrigation, and humidification. Episodes of epistaxis can be treated with high-dose antifibrinolytic agents, such as tranexamic acid (57). Recalcitrant epistaxis can be further addressed with Nd:YAG (58), argon, and potassium titanyl phosphate (KTP) laser treatment. CO_2 lasers have also been used, though with less success (59). Attention to preventing injury to large areas of perichondrium, septal cartilage, and abutting nasal cavity mucosal surfaces can limit complications of septal perforation and synechiae. Due to severe potential complications, such as cerebrovascular events, embolization is preserved for severe and unresponsive epistaxis (60). Septodermoplasty involves replacing delicate nasal mucosa with stronger, keratinized split-thickness skin graft. A recent description of this technique in combination with bilateral inferior turbinectomies resulted in cessation or marked reduction of epistaxis in 90% of patients with HHT (61). Young's procedure, involving closure of the nasal vestibule, is mentioned as a last resort. Though likely to resolve epistaxis, side effects are severe and include loss of orthonasal olfactory input and creation of obligate mouth breathing (55). An algorithmic approach has been proposed for treatment of HHT epistaxis and is based on requirements of blood transfusion (59).

Advances in medical therapeutics for HHT show several promising avenues for modern treatment. Recent studies are showing potential for a role of thalidomide, which acts through an antiangiogenic-type mechanism. Enhanced mural wall coverage with endothelial cells was demonstrated in animal and human subjects. In a very small number of patients tested, thalidomide appeared to show promise with decreases in the number of nose bleeds incurred and number of blood transfusions required, and increased hemoglobin concentration, presumably due to decreased epistaxis (52). Bevacizumab, a monoclonal VEGF inhibitor has been shown to significantly improve epistaxis severity (62) when applied topically (intranasal), locally injected, or intravenously administered (55). Complications from bevacizumab injections include septal perforation, though this risk may be avoided if septal cartilage is avoided in injection with concurrent laser vessel coagulation (62). In a double-blind placebo controlled trial that enlisted 21 patients, antiestrogen therapy showed a significant decrease in frequency and severity of epistaxis (63). Whether these agents will have a significant role in the future treatment of HHT, will require additional investigation and remains to be answered.

Another important hematologic entity that may manifest in the sinonasal cavity is thrombocytopenia. Thrombocytopenia may occur secondary to impaired platelet production, excessive platelet destruction, sequestration in hypersplenism, or secondary to dilutional effect, such as in high volume transfusion. Impaired bone marrow production of platelets may occur due to infiltration in neoplastic processes, infection, or from toxic response to pharmacologics. Excessive platelet destruction can occur in aberrant immune responses, such as autoimmune thrombocytopenic purpura. Platelets may also be reduced in consumptive processes such as disseminated intravascular coagulation or thrombotic thrombocytopenic purpura. Regardless of the etiology of thrombocytopenia, the most common presenting symptom is epistaxis (64). Treatment should be aimed at addressing the underlying pathophysiologic issue.

Coagulation disorders may also manifest with severe, recurrent epistaxis. Acquired coagulopathies secondary to disseminated intravascular coagulation, liver disease, and vitamin K deficiency are more common than inherited coagulopathies. von Willebrand disease (vWD) is an autosomal dominant disorder. It is the most common hereditary bleeding disorder, affecting approximately 1% to 2% of the population (65). Epistaxis was the most common symptom and otolaryngologic surgery was found to be the surgical area with the highest proportion of postoperative bleeding in vWD (44%) (66). Preoperative evaluation and screening varies, though a recent cost-effective strategy analysis recommends not performing preoperative screening (67). In fact, the American Society of Pediatric Otolaryngology recommends preoperative coagulation testing only when indicated by history and physical examination. Obtaining a hematology consultation prior to pursuing surgical treatment with vWD is recommended. The medical goal is to correct the coagulation defect—low levels of FVIII coagulant activity and primary hemostasis. The surgical goal should be meticulous, atraumatic dissection minimizing intraoperative bleeding. Desmopressin acetate has been used with effectiveness that varies on the type of vWD mutation. Several protocols have been described. A recent prospective study examines a protocol used in pediatric adenoidectomy on patients with vWD. A preoperative desmopressin challenge (0.3 μg/kg in 50 mL of isotonic saline over 30 minutes) is performed. If activated partial thromboplastin time and factor VIII coagulant improved without evidence of side effects and with a negative history of seizures, desmopressin was used. Alternatively, factor VIII concentrate was used. Desmopressin was administered 1 hour preoperatively, then daily for 1 to 4 days. Tranexamic acid was administered daily at 10 mg/kg until postoperative day 7. In 41 patients with vWD, 5% had immediate postoperative hemorrhage and 0% had delayed hemorrhage (68). A recent cohort study showed treating with desmopressin alone resulted in comparable posttonsillectomy bleeding rates as in non-vWD (69). Aminocaproic acid (Amicar) (70) has been used as an alternative to tranexamic acid and is administered IV or orally at a dose of 50 to 70 mg/kg every 4 to 6 hours. Randomized prospective controls delineating an ideal, cost-effective regimen are needed.

Hemophilia A and B are X-linked factor VIII and IX deficiencies respectively. Presentation may be from intractable epistaxis or from upper airway bleeding. Of paramount importance is ensuring the patient has a protected airway followed by controlling the source of bleeding. Intravenous

concentrates of the deficient factor are used to treat severe bleeding episodes. Similarly to vWD, a hematology consult should be obtained prior to proceeding with surgical intervention.

OTHER

Reactive processes to trauma (such as giant cell reparative granuloma), infectious agents (*Mycobacterium, Actinomyces,* fungi) and foreign bodies (cocaine-induced granuloma) may lead to inflammatory and/or granulomatous lesions. These processes should be considered in the differential of many of the pathologies discussed above, but are out of the scope of this topic as they are reactions to local triggers.

Furthermore, additional systemic diseases manifest in the nasal and paranasal sinuses. In fact, the list can easily be extended well beyond the list of systemic diseases discussed in this chapter. We have attempted to highlight the more common diseases that the otolaryngologist will likely encounter. The ability to direct the diagnosis and care of these patients should equip the surgeon with the ability to improve these patients' lives.

HIGHLIGHTS

- Medical interventions are often the basis for treatment of systemic diseases, though surgical expertise is necessary in particular instances, such as when biopsy or other diagnostic is indicated.
- Early diagnosis and treatment results in improved therapeutic outcomes and prevents disease progression with associated complications.
- Systemic disease processes are often manifested in the sinonasal cavities. The highly vascular mucocutaneous area lends otolaryngologists the opportunity to observe some of the first pathologic changes and provide early diagnosis of these conditions.
- Understanding and addressing the underlying pathophysiology oftentimes allows optimal treatment of systemic conditions. For example, immunomodulation is the cornerstone of addressing autoimmune pathology.
- There is significant overlap in the presentation of many of the systemic diseases. This requires the astute clinician-surgeon to take into account the entirety of the patient's history, directed diagnostic workup, and disease responses when considering evaluation and management.
- The relative rarity of systemic conditions makes formulating strong randomized prospective based evidence a challenge; however, this must remain the goal in an attempt to achieve optimization of patient care.

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Epistaxis

32

Benjamin S. Bleier *Rodney J. Schlosser*

EPIDEMIOLOGY

Incidence

Epistaxis is a common problem ranging from minor traces of blood or clot to isolated massive bleeds that may be life-threatening. Most patients have self-limiting episodes that do not require medical care and thus the true incidence is unknown. In spite of this, there is an estimated global lifetime incidence of 60% (1). From an otolaryngologic standpoint, epistaxis may account for up to 33% of emergency admissions with a median age of 70 years (2). The overall age of onset describes a bimodal distribution with an increased incidence in childhood followed by a peak incidence in the sixth decade. While younger individuals overwhelmingly present with minor bleeding derived from the anterior septum, older patients are far more likely to present with a severe acute bleed. Of note, epistaxis in children under 2 years old is rare and should raise the suspicion of an underlying illness or child abuse (3).

Some studies have also suggested a seasonal variation in the incidence of epistaxis with episodes being more common in the fall and winter. While this may reflect an overall decrease in the ambient humidity during the colder months these findings have not been universally accepted (4).

Etiology

When considering the management and prognosis of patients with epistaxis, it is useful to classify the bleeding site into anterior or posterior. There is no precise anatomic distinction between the two; however, anterior bleeds are more common (5) and tend to originate on the septum while posterior bleeds are generally higher volume and arise laterally from branches of the sphenopalatine artery (SPA). Bleeding may also be classified as primary (or idiopathic), which accounts for the majority of cases, or secondary, which results from known local or systemic factors. Spontaneous mucosal bleeding may occur in all age groups but is particularly problematic in children as this region is subject to mucosal desiccation, irritant exposure, and digital trauma. While the advent of the endoscopic era has greatly improved our ability to identify and manage the specific site of bleeding, many patients presenting to a general emergency department will continue to lack a definitive diagnosis and thereby remain in the idiopathic category.

Secondary epistaxis refers to bleeding resulting from a known cause (Table 32.1). Any disorder that disrupts the mucosal epithelium or impairs clotting and platelet function may result in nosebleeds. Management of secondary epistaxis requires addressing the underlying etiology and thus it is useful to subcategorize it into local or systemic causes.

There are many local causes of epistaxis including sinonasal tumors, granulomatous disease, and septal perforation; however, the majority are iatrogenic or posttraumatic. In adolescent males with unilateral epistaxis and nasal obstruction, the presence of a juvenile nasopharyngeal angiofibroma should be ruled out (6). Postoperative bleeding following endoscopic skull base surgery also deserves special consideration not only because of the potential for exposure of critical neurovascular structures but also for the fact that blind packing may potentiate a neurologic catastrophe. Isolated vascular lesions such as hemangiomas, pyogenic granulomas, and telangiectasias are another local source of epistaxis that can sometimes be difficult to identify but may result in recurrent large volume bleeding (Fig. 32.1).

In patients with epistaxis and multiple cutaneous, lip, oral, and intranasal telangiectasias, the diagnosis of hereditary hemorrhagic telangiectasia (HHT) must be considered (Table 32.2). This entity represents both a diagnostic and

TABLE 32.1 SECONDARY CAUSES OF EPISTAXIS

Local	Systemic
Trauma (blunt, digital, devices)	Drugs (Coumadin, NSAID, aspirin)
Surgery (sinus, endoscopic skull base)	Bleeding diatheses
Anatomic deformities (septal deviation, spurs)	Hematologic malignancy
Sinonasal tumors (benign, vascular, malignant)	Hypertension
Foreign bodies	Hepatobiliary disease
Inflammation, granulomatous disease	Alcoholism
Topical medications	Vascular/connective tissue disorders
Low humidity	Malnutrition

TABLE 32.2 CURAÇAO CRITERIA FOR THE CLINICAL DIAGNOSIS OF HHT

Criteria	Description
Epistaxis	Recurrent
Telangiectasia	Multiple at characteristic sites (lips, oral cavity, fingers, nose)
Visceral lesions	GI telangiectasia; pulmonary, cerebral, hepatic, spinal AVMs
Family history	A first degree relative with HHT according to these criteria
0–1 criteria	Unlikely
2 criteria	Possible or suspected
3 or more criteria	Definite

From Faughnan ME, Palda VA, Garcia-Tsao G, et al. International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. *J Med Genet* 2011;48(2):73–87.

therapeutic challenge as patients may have underlying life-threatening intracranial, gastrointestinal (GI), hepatic, and pulmonary arteriovenous malformations, (AVMs) which must be concomitantly evaluated. A recent international guidelines statement also recommended genetic testing of all patients to allow for identification of family members who have not yet met the diagnostic criteria for HHT (7). Due to the presence of multiple local sources of potential bleeding, HHT patients often require repeated and aggressive epistaxis interventions, which is covered later in the chapter.

Systemic causes of epistaxis typically relate to disorders or medications resulting in impaired clotting or platelet function including renal failure, NSAID, and salicylate use. For example, low-dose aspirin has been shown to increase the risk of epistaxis when compared with placebo (19.1% vs. 16.7% respectively) (8). Warfarin use may also

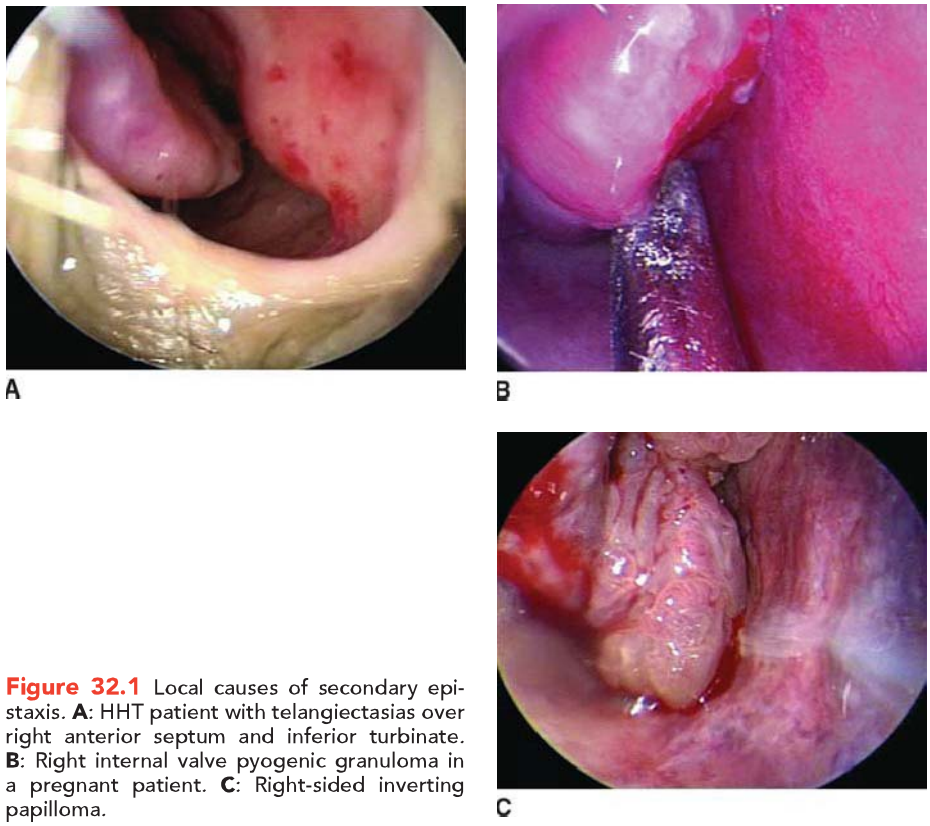


Figure 32.1 Local causes of secondary epistaxis. **A**: HHT patient with telangiectasias over right anterior septum and inferior turbinate. **B**: Right internal valve pyogenic granuloma in a pregnant patient. **C**: Right-sided inverting papilloma.

predispose to epistaxis, particularly when the INR is not tightly controlled. Epistaxis patients should also be questioned regarding the use of over-the-counter supplements including garlic, ginkgo, or ginseng, which can result in a mild systemic coagulopathy (9).

Inherited bleeding diatheses, the most common of which being hemophilia A followed by von Willebrand disease, and hematologic malignancies are less common causes of epistaxis although they should be considered in any broad differential diagnosis. Hepatobiliary disease may also result in coagulopathy related epistaxis secondary to a reduction in the production of vitamin K–dependent factors (prothrombin, factors VII, IX, and X, proteins C and S).

While hypertension exacerbates epistaxis, it has not been shown to be an independent causative factor (10). When hypertension is suspected in the setting of epistaxis, it should be investigated and managed appropriately.

VASCULAR ANATOMY OF THE NOSE

The nasal mucosa is supplied by a robust vascular arcade derived from both the internal and external carotid arterial systems. These arborizations travel within the mucoperiosteal/perichondrial layers except for small branches that traverse bony canals within the inferior and middle turbinates (Fig. 32.2).

The Internal Carotid Arterial System

The internal carotid artery supplies the nose via the ophthalmic artery, which traverses the superior orbital fissure to give off the anterior and posterior ethmoidal arteries. These arteries penetrate the anterior and posterior foramina within frontoethmoid suture line to travel in bony canals within the ethmoid roof finally entering the anterior cranial fossa through the lateral lamella of the cribriform plate. Intracranially, both arteries give rise to terminal branches that supply the anterior fossa dura and superior nasal cavity.

Occasionally, the bone over the paraclival and parasellar carotid may be thin or dehiscent within a well pneumatized sphenoid sinus. This anatomic relationship provides the opportunity for massive epistaxis derived from this segment of the internal carotid artery secondary to trauma or idiopathic aneurysmal/pseudoaneurysmal dilatation.

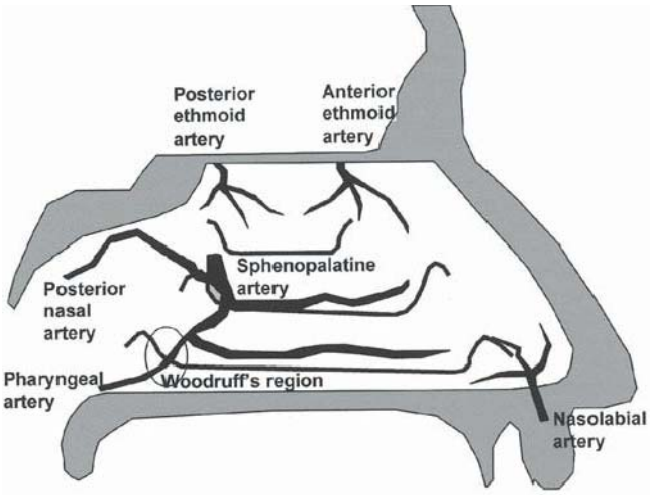


Figure 32.2 Vascular contributions to the nasal mucosa.

The External Carotid Arterial System

The external carotid system provides contributions to the nasal mucosa via the facial artery and internal maxillary artery (IMA). Anteriorly, the facial artery branches give rise to the superior labial artery, which projects a septal branch onto the anterior septum. Posteriorly, the IMA traverses the pterygopalatine fossa where it undergoes a complex series of branching patterns prior to entering into the posterolateral nasal cavity as the SPA via the sphenopalatine foramen. This branch carries the greatest volume of blood to the nose and is the source of most posteriorly based bleeds.

The crista ethmoidalis represents an important landmark for the position of the SPA and is located anteromedial to the sphenopalatine foramen in almost all cases (11). Although the number of SPA branches varies according to the reports, in one study 73 of 75 cadaveric specimens demonstrated 2 or more branches of the SPA medial to the crista ethmoidalis (12). Consequently, when performing an SPA ligation it is essential to explore the lateral wall of the nose, a maneuver that often requires resection of the crista ethmoidalis to enhance exposure. Once the SPA exits the sphenopalatine foramen, its more distal posterolateral contributions may continue to exhibit significant variability. Lee et al. noted that in 38% of cases, some portion of the artery may run anterior to the posterior maxillary wall. Furthermore in 50% of cases, a branch of the inferior turbinate artery extends anterosuperiorly to supply the posterior fontanel (13). These studies suggest that in a significant portion of patients, a large tributary of the SPA may be encountered within the posterior maxillary fontanels.

The posterior nasal branch of the SPA passes over the anterior sphenoid face approximately 1 cm above the choanal arch and travels anteriorly to anastomose in Kiesselbach plexus.

Venous Drainage

Generally speaking, the intranasal veins follow the course of the arteries within the nasal mucosa. However, there are mucosal emissary and pterygoid plexus branches that lead to the cavernous sinus. In 1949, Woodruff described a venous plexus located in the posterior section of the nasal cavity adjacent to the inferior turbinate. This

region comprises large, thin-walled veins enclosed by a thin mucosal layer, which is relatively devoid of other structures (14).

Vascular Anastomoses

The anterior nasal septum represents a highly consistent anastomotic loop (15) supplied by the septal branch of the SPA, the greater palatine artery via the incisive canal, the superior labial artery, and branches from the anterior ethmoidal artery superiorly. Within the literature, this area has been referred to as both Little's area after James Little, an American physician who described four patients with a bleeding ulcer at this site, and Kiesselbach's plexus after Wilhelm Kiesselbach, who subsequently described three patients with bleeding from distended vessels from this site.

CLINICAL MANAGEMENT

Initial Management of Acute Epistaxis

The vast majority of nose bleeds are self-limited with minimal blood loss. However, in rare situations bleeding can be significant and even fatal and thus each patient should be appropriately evaluated. A clear and logical plan of action should therefore be adopted. The American Heart Association Basic Life Support protocol guides prioritization of consideration in the management of emergent situations. As applied to epistaxis, the first consideration is always protection and management of the airway. Once this is deemed secure, attention may then be turned toward controlling the bleeding while simultaneously establishing vascular access for the provision of volume replacement and hemodynamic support.

The patient should be seated with the body tilted forward and mouth open. Assuming a recumbent position should be avoided in order to reduce venous pressures and prevent aspiration. The patient should be advised to compress the upper lateral cartilages for 10 to 15 minutes without releasing in an effort to tamponade the anterior septal vasculature. If available, topical decongestants such as oxymetazoline HCl may also be applied. For epistaxis that persists or is not controlled by this simple measure, direct visualization and more aggressive measures are mandated.

Assessment and treatment should take place in a room with monitoring, suction, adequate lighting, and preferably endoscopic equipment. Universal precautions should be strictly obeyed as the risk of blood exposure is high (16). Blood clot should be evacuated followed by topicalization using a vasoconstrictor and anesthetic agent. The nose may initially be examined with a nasal speculum and headlight. In the case of anterior bleeds, a site may be identified using this method, however the practitioner should not hesitate to proceed to rigid endoscopy for more posteriorly located sources.

Endoscopic-Assisted Nasal Cautery

After attaining adequate topicalization the nasal cavities can be carefully examined with the aid of a rigid endoscope and gentle suction. When possible, the entirety of the nasal cavity including the inferior and middle meatuses, sphenoethmoidal recess, and nasopharynx should be visualized to exclude the possibility of multiple bleeding sites or the presence of a mass or lesion. The specific site of bleeding can often be clearly identified and subsequently controlled. The specific hemostatic technique used is highly dependent on the availability of equipment and the experience of the practitioner. These may include chemical cautery, mono or bipolar diathermy, or local application of absorbable hemostatic matrices. Monopolar cautery near the orbital apex, pterygopalatine fossa, or within the sphenoid proper should be used with great caution as neuropraxia can occur from propagation of current through the adjacent neurovascular structures. In the setting of HHT, laser-assisted cauterization is especially useful. This may be achieved with an argon or potassium titanyl phosphate (KTP) laser by first applying the laser energy to the periphery of the lesion prior to focusing on the lesion itself.

Silver nitrate application is a common method of chemical cautery, particularly for anterior bleeds. The stick should be applied precisely to the bleeding point and held for only a few seconds. The white coagulum that forms is thought to be due to protein denaturation. It is generally taught that cautery must not be applied bilaterally to the anterior nasal septum simultaneously to avoid the potential risk of septal perforation. While this is largely anecdotal and highly unlikely, the resultant perforation can be quite difficult to manage and thus bilateral cauterization is not recommended.

Absorbable Nasal Packing

If identification of a bleeding site is deemed ineffective or not possible, the practitioner should next proceed to nasal packing. Packing refers to the placement of any material within the nose in an effort to control or limit the egress of blood. While a wide variety of products exist, globally they may be divided into absorbable and nonabsorbable materials.

The development of biodegradable topical hemostatic agents has enabled a shift away from the exclusive use of nonabsorbable packing. These materials include oxidized cellulose, microfibrillar collagen, porcine or bovine gelatin, and human thrombin solutions. While these materials provide less mechanical tamponade, they are able to penetrate the interstices of the sinonasal labyrinth in order to achieve direct contact with the area of bleeding (Fig. 32.3A). In one Baxter-sponsored randomized nonblinded trial comparing the gelatin-based agent FloSeal (Baxter Biosurgery) to nonabsorbable nasal packing,

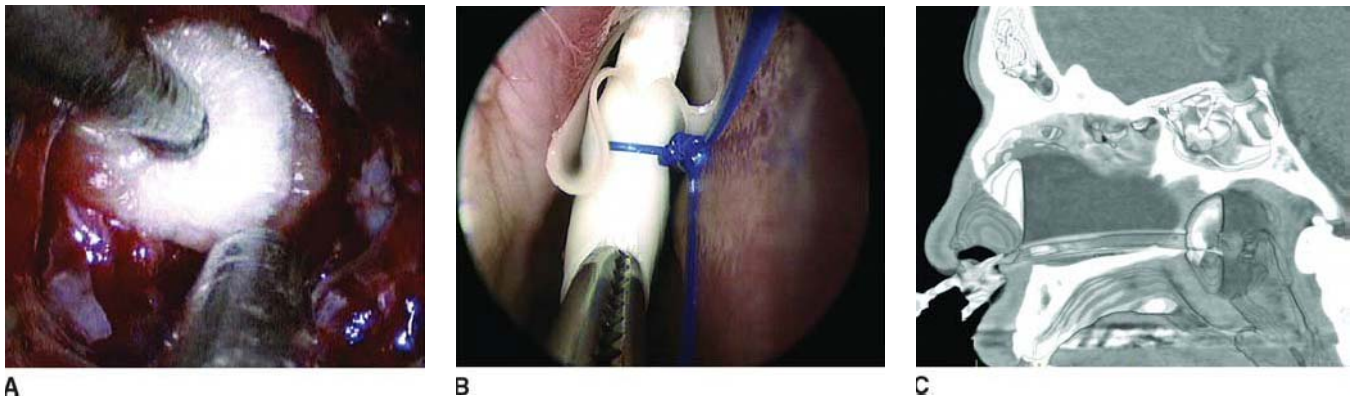


Figure 32.3 Application of absorbable and nonabsorbable packing materials. **A**: Placement of a hemostatic gelatin solution over site of bleeding during tumor removal. **B**: Insertion of a PVA sponge into the right nasal cavity. The sponge is wrapped in the finger of a nonlatex glove to prevent mucosal adhesions. **C**: Sagittal CT demonstrating proper positioning of an inflated balloon catheter within the nasopharynx.

FloSeal was found to significantly reduce the rate of rebleeding at 1 week (17). While patient satisfaction and comfort were also improved with the absorbable agent, it should be noted that these agents tend to be more expensive than traditional packing.

While multiple materials have been shown to promote hemostasis, most act in a similar manner to provide a stable platform for fibrin and platelet aggregation. An alternative mechanism for hemostasis has been exploited by a new class of aminopolysaccharide known as chitosan. Chitosan is a mucoadherent biocompatible polymer that has known tissue-adhesive and drug-eluting properties (18). Chitosan is also strongly cationic and is able to attract red blood cells at the site of a vascular injury thereby promoting hemostasis independent of the innate clotting cascade. A chitosan/dextran gel was studied by Valentine et al. (19) and found to be both hemostatic and capable of inhibiting adhesion formation following sinus surgery.

Nonabsorbable Nasal Packing

If absorbable packing is unavailable or ineffective, larger nonabsorbable packs may be considered. Traditionally this was achieved by using layered ribbon gauze; however, modern expandable polyvinyl acetate (PVA) polymer sponges have largely replaced this practice (Fig. 32.3B). No statistically significant difference has been demonstrated between the use of ribbon gauze and a PVA sponge, but the latter is much easier to insert and more comfortable for the patient (20). Nasal packing containing lipid materials such as petroleum should be used with caution as they have been shown to be associated with myospherulosis, which may lead to increased adhesion rates and poorer outcomes (21).

In massive posterior bleeds, sponge packs may fail to adequately control the epistaxis. In these cases, expandable devices may be required where balloons are inflated in the nasopharynx and nasal cavity in order to tamponade the entire nasal cavity (Fig. 32.3C). If nasal balloons are unavailable, a 14 Fr Foley catheter inflated with 15 mL of saline may also be used to tamponade the nasopharynx and provide a foundation against which anterior packing may be placed.

As with any acute intervention, nasal packing does carry several theoretical risks. Packing, particularly if placed bilaterally, may compress the septal mucosa resulting in ulceration and potential subsequent perforation. Bilateral posterior packs can also theoretically induce the nasopulmonary reflex leading to hypercarbia, hypoxia, and decreased lung volume (22,23), and thus hospital admission with telemetry monitoring is recommended. Toxic shock syndrome (TSS) is a rare possibility if packs are left *in situ* for several days. TSS results from a staphylococcal exotoxin and typically presents within the first 24 hours although it has been reported up to 5 weeks following sinus surgery. Of note, TSS is not associated with any particular type of packing and it can neither be predicted nor prevented by prophylactic antibiotics (24). Given that most packs are removed after 1 to 7 days, the need for antibiotics is controversial although they are still commonly used.

Management of Comorbid Systemic Factors

Once bleeding has been controlled, the systemic effects of blood loss should be considered. If the patient is hypovolemic fluids and plasma expanders may be administered. Blood transfusion should be considered following a significant loss of blood volume with associated hemodynamic derangement. In patients who are otherwise healthy, the risks associated with transfusion should be weighed against the patient's overall hemodynamic status and availability of alternative methods of fluid resuscitation.

Management of hypertension, thrombocytopenia, and coagulopathies will also aid in epistaxis management and

prevention of recurrence. Appropriate reversal of iatrogenic platelet or clotting factor dysfunction is beyond the scope of this chapter however specialist consultation with attention toward the risks of reversal in the setting of the underlying disorder is generally recommended.

SURGICAL MANAGEMENT

Surgical management of epistaxis is typically reserved for those patients whose bleeding is refractory to more conservative therapies, have chronic or recurrent episodes, or have had a single life-threatening bleed. The choice of procedure depends on a variety of preoperative factors including, most importantly, the suspected site of bleeding. The goal of these procedures is to isolate and ligate the offending arterial input while preventing disruption of adjacent structures and preserving normal sinonasal function.

Sphenopalatine Artery Ligation

The SPA can be exposed endoscopically by raising a posterolateral mucosal flap over the orbital process of the palatine bone. As the flap is elevated, the crista ethmoidalis and accessory posterolateral neurovascular bundles will be encountered (25). The SPA can then be identified and dissected from the surrounding tissue using a ball tipped probe. The artery may be occluded using clips, bipolar cautery, or some combination thereof. If bipolar cautery is to be used, it should precede clip application as tissue desiccation may shrink the tissue away from a previously applied clip (Fig. 32.4A). Dissection should be continued posteriorly toward the choanal arch to rule out the possibility of an additional posterior nasal branch that may enter the nose through a separate foramen posterior to the SPA. Alternatively, the artery may be traced laterally into the pterygopalatine fossa in order to ligate it prior to its terminal bifurcation. The mucosal flap may then be replaced that hastens remucosalization and often can avoid the need for nasal packing.

Ethmoidal Artery Ligation

The ethmoidal vessels may be accessed within the orbit using a limited medial canthal (Lynch) incision. This incision is often broken into a seagull shape to prevent linear contracture postoperatively. The anterior ethmoidal artery is identified running from the periorbita into its foramen at the frontoethmoidal suture (Fig. 32.4B). This suture line is typically located immediately superior to the medial canthus and care should be taken not to disrupt the canthal tendons during the periorbital dissection. The posterior ethmoidal artery may be found approximately 12 mm posterior to the anterior ethmoidal artery. Once exposed, the arteries can be clipped or divided following diathermy or suture ligature. Some authors have also described endoscopic identification and cauterization of the anterior ethmoid artery either within the ethmoid roof or intraorbitally following removal of the lamina papyracea (26).

Other Sources of Intranasal Bleeding

Experience with surgical management of epistaxis has also formed the basis of the principles of vascular control in sinonasal and skull base tumor resection. Previously described endoscopic landmarks may be used to identify the vascular supply of lesions in the setting of highly distorted anatomy providing the opportunity for directed arterial ligation using bipolar cautery, endoscopic vascular

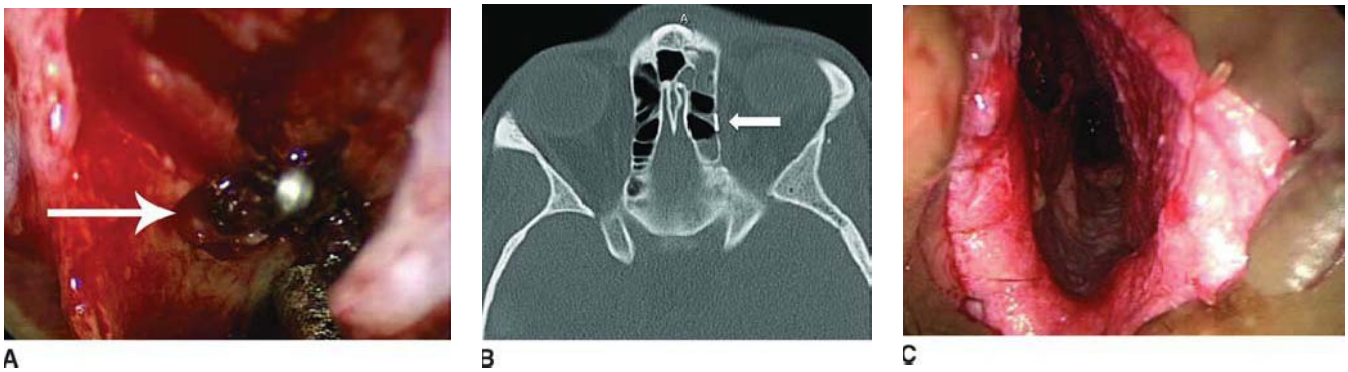


Figure 32.4 Examples of surgical management of epistaxis. **A**: Clip placed over the SPA after bipolar diathermy (*white arrow* indicates origin of vessel at sphenopalatine foramen following resection of the crista ethmoidalis). **B**: Axial CT image demonstrating proper placement of a clip over the intraorbital origin of the anterior ethmoid artery (*white arrow*). **C**: Endoscopic view of the right internal valve following septodermoplasty in an HHT patient with replacement of the mucosa using an allograft.

clips, or more recently ultrasound energy (27). High volume venous plexus bleeding may also be encountered during these procedures derived from the cavernous, basilar, or pterygoid plexuses depending on the site of surgery. Absorbable hemostatic agents have also been used successfully in the management of these areas as they are capable of permeating through the venous channels providing localized tamponade as well as scaffolding for clot formation.

Rarely, bleeding from the proximal internal carotid system may occur secondary to aneurysm/pseudoaneurysm, trauma, or iatrogenic injury. Endoluminal occlusion or stenting is typically required in these instances for definitive vascular control. However, the exposed endosphenoidal portion of the carotid must be also dealt with to prevent further complications related to exposure of the vessel to the sinonasal milieu. In these situations a wide sphenoidotomy may be performed with rotation of a pedicled nasoseptal flap to provide reliable and robust coverage of the dehiscent region.

Septodermoplasty

In the setting of HHT refractory to multiple prior attempts at monopolar, argon, or KTP laser cauterization, the affected mucosa may require wide resection via septodermoplasty. In this procedure, the nasal mucosa is excised in a supramucoperichondrial plane and replaced by an allograft or split thickness skin graft taken from another site such as the thigh. The graft is then sutured or fixed by mattress sutures (Fig. 32.4C). The operation can be performed bilaterally in a staged fashion. While good control is often achieved in the short term, eventually bleeding will often recur as new lesions develop in different sites of the nose (28).

ENDOVASCULAR EMBOLIZATION

In patients who are poor surgical candidates, selective endovascular embolization of the internal maxillary arborizations may be attempted via catheterization of the femoral artery. Embolization has been described using microcoils, polyvinyl alcohol particles, dextran microspheres, absorbable gelatin sponge, or detachable balloons and has reported success rates of 60% to 90% (29). However, the proximal location of the arterial occlusion relative to surgical ligation allows for the formation of collateral arterial inputs, which may result in recurrent epistaxis. Reported complications include facial pain, trismus, amaurosis, and ophthalmoplegia. This method also carries a significant risk of embolic stroke and ultimately, even death. The combination of increased risk, poorer long-term control rates, and inability to address the internal carotid system suggests that embolization should be utilized only after surgical arterial ligation has been attempted or ruled out as a possibility.

HIGHLIGHTS

- Epistaxis most commonly originates from the anterior septum and is self -limited in nature. It has a bimodal age distribution with posterior and more severe bleeding being more common in the sixth decade.
- Secondary causes of local epistaxis may frequently be identified on rigid endoscopy. The presence of a sinonasal tumor should be ruled out in patients presenting with unilateral epistaxis and concomitant nasal obstruction.
- Many over-the-counter and herbal therapies may result in systemic coagulopathies or platelet dysfunction. A complete patient history should always include a review of nonprescription medications.
- In patients with HHT, work up for the presence of AVMs and genetic testing of family members is currently recommended. These patients will often require multiple surgical interventions including repeated laser assisted cauterization and potential septodermoplasty.
- When treating a patient with acute epistaxis, adherence to universal precautions and management of the airway are paramount. The choice of intervention should escalate from conservative to more aggressive as the individual situation demands.
- Surgical management of epistaxis should be considered if more conservative measures have failed or in the setting of a single life-threatening bleed. The goal of surgery is to occlude the offending artery while preserving normal sinonasal function.
- Endovascular embolization may be less effective than surgery, carries increased associated risks, and is typically unavailable for bleeding derived from internal carotid artery arborizations. While this intervention is appropriate in many instances, it should always be weighed against the practicality and efficacy of endoscopic arterial ligation.

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Acute Rhinosinusitis

33

Elizabeth K. Hoddeson *Sarah K. Wise*

ABSTRACT

This chapter provides an in-depth discussion of acute rhinosinusitis, beginning with definitions of rhinosinusitis and its epidemiology and economic impact. The pathophysiology of acute viral rhinosinusitis and acute bacterial rhinosinusitis are reviewed. Next, a discussion of appropriate components of patient history and physical examination, as well as indications for radiologic imaging in the setting of acute rhinosinusitis, is undertaken. Finally, acute rhinosinusitis treatment modalities and complications are highlighted.

Sinusitis is defined as inflammation of the paranasal sinuses, and *rhinitis* as inflammation within the nasal cavity. In 1996, the Task Force on Rhinosinusitis, sponsored by the American Academy of Otolaryngology-Head and Neck Surgery, the American Rhinologic Society, and the American Academy of Otolaryngologic Allergy recommended the replacement of the term sinusitis with *rhinosinusitis*. This recommendation was based on rhinitis commonly preceding sinusitis, as well as the fact that sinusitis without rhinitis is extremely rare (1).

There are multiple potential contributors to the development of rhinosinusitis, including both host and environmental factors (Table 33.1). Examples of host characteristics that may contribute to rhinosinusitis include congenital conditions, such as cystic fibrosis or immotile cilia syndrome, allergic states or altered immune function, anatomic abnormalities, systemic diseases, and neural mechanisms. Some external factors that can result in rhinosinusitis are infectious agents, trauma, exposure to noxious chemicals or medications, and surgical changes.

In a given patient with rhinosinusitis, many host and environmental factors may be present simultaneously. For example, a patient with cystic fibrosis who has altered anatomy from prior surgery may present with an acute bacterial infection of the sinonasal cavities. Therefore, defining rhinosinusitis based on etiology could become very complicated. For this reason, the Task Force on Rhinosinusitis elected to classify this disorder based on temporal factors (1) (Table 33.2). *Acute rhinosinusitis* is defined by the presence of the condition for up to 4 weeks (1). *Chronic rhinosinusitis* can be diagnosed after the condition has been present for at least 3 months (1). The term *subacute rhinosinusitis* is used when the duration is between 4 and 12 weeks (2). When there are four or more episodes of acute bacterial rhinosinusitis (ABRS) in 1 year with resolution of symptoms in between episodes, the diagnosis is *recurrent acute rhinosinusitis* (2).

The Task Force on Rhinosinusitis examined the definition, diagnosis, management, and outcome analysis of rhinosinusitis in order to facilitate patient care and research (1,3). These efforts have been furthered by additional panels in 2004 (sponsored by the American Academy of Otolaryngology-Head and Neck Surgery, the American Rhinologic Society, the American Academy of Otolaryngologic Allergy, the American Academy of Allergy, Asthma, and Immunology, and the College of Allergy, Asthma, and Immunology) and in 2007 (sponsored by the Academy of Otolaryngology-Head and Neck Surgery Foundation) (2–4). The goal of this chapter is to utilize these resources in addition to current literature to review acute rhinosinusitis, including its epidemiology, pathophysiology, clinical presentation, the role of imaging, current treatment recommendations, and complications.

EPIDEMIOLOGY

Rhinosinusitis is a significant health care problem, believed to be increasing in both incidence and prevalence (1). According to the 2009 Summary Health Statistics for U.S. Adults

TABLE 33.1 PREDISPOSING FACTORS AND CONTRIBUTORS TO THE DEVELOPMENT OF RHINOSINUSITIS

Host Factors
- Congenital conditions
  - Examples: Cystic fibrosis; Immotile cilia syndrome
- Allergic or immune conditions
  - Examples: Environmental allergy; Human immunodeficiency virus; Immune suppressive agents (i.e., chemotherapy); Bone marrow transplant
- Paranasal sinus anatomic abnormalities
  - Examples: Middle turbinate concha bullosa; Obstructing frontal recess cells; Severe nasal septal deviation
- Systemic inflammatory conditions
  - Examples: Wegener granulomatosus; Sarcoidosis
- Presence of neoplasm

Environmental Factors
- Infectious agents
  - Examples: Viruses; Bacterial pathogens
- Trauma
  - Examples: Resultant mucosal edema and inflammation; Altered bony anatomy
- Exposure to noxious chemicals
- Iatrogenic
  - Examples: Medications; Surgery

National Health Interview Survey, over 29.3 million adults in the United States had been diagnosed with rhinosinusitis by a physician (5). This comprises approximately 12.6% of the United States population. It has been previously reported that the prevalence of rhinosinusitis is almost twice as common in women (20.9%) as in men (11.6%) (5,6). Other demographic factors, such as geography and race, may play a role as well. The frequency of rhinosinusitis is generally lower in the Western United States (12.1%), as compared to Southern regions (19.5%) (5). Non-Hispanic white persons (17.5%) and non-Hispanic black persons (15.7%) have approximately twice the prevalence of rhinosinusitis as Hispanics (8.6%) (5,6). While prior survey data have not demonstrated that poverty status is relevant to the frequency of rhinosinusitis, regional variation in the frequency of rhinosinusitis may potentially be attributable to differences in air quality, including presence of pollutants and allergens (5,6).

TABLE 33.2 TEMPORAL CLASSIFICATION OF RHINOSINUSITIS

Term	Duration of Symptoms
Acute rhinosinusitis	Up to 4 wk
Subacute rhinosinusitis	4–12 wk
Chronic rhinosinusitis	Longer than 12 wk
Recurrent acute rhinosinusitis	>4 acute episodes in 1 y with resolution between episodes

Economic Burden of Acute Rhinosinusitis

The economic impact of rhinosinusitis is staggering. Although references on this topic are few, thorough investigations were published in 1999 and in 2004, based on the 1996 and 1998 National Health Interview Surveys, respectively (6,7). The direct annual health care cost was estimated at $5.8 billion in 1996, of which about 30% was incurred to treat pediatric patients 12 years of age or younger (5,7). Nearly 90% of the expenditures were associated with ambulatory or emergency department visits (5,7). In 1996, there were 16.7 million outpatient physician, hospital office, and emergency department encounters attributed to the primary treatment of sinusitis (7). The majority of outpatient office-based physician care for sinusitis was delivered by primary care physicians (64.9% by family medicine and internal medicine doctors, and 15.4% by pediatricians) (7). Overall, outpatient visits with sinusitis as the primary diagnosis accounted for 36% of total medical expenditures in 1996, and medications to treat this condition added another 17% (7). In 1992, Americans spent $200 million on prescription medications and more than $2 billion on over-the-counter medications to treat sinusitis (8). The Integrated Health Interview Series for 1997 to 2006 shows that 55.8% of patients with sinusitis spend more than $500 annually on health care, higher than the amount spent by those suffering with chronic diseases such as chronic bronchitis, hay fever, ulcer disease, and asthma (9).

The indirect costs of rhinosinusitis are, as one would expect, not insignificant and are also increasing. The number of total restricted activity days due to rhinosinusitis rose from approximately 50 million per year in the period between 1986 to 1988 to 61.2 million per year between 1997 and 2006 (5,9,10). According to the 2007 estimates of workday productivity, this translates into $18.3 billion in lost opportunity cost (9). Based on the 2006 survey data, patients with sinusitis miss an average of 5.67 workdays due to illness annually, as opposed to 3.74 missed workdays for those without sinusitis (9). More difficult to quantitate, but certainly relevant within the realm of indirect costs, are the detrimental effects of rhinosinusitis on quality of life and the impairment of daily functioning due to the significant physical symptoms present when someone is suffering from rhinosinusitis (4).

PATHOPHYSIOLOGY AND MICROBIOLOGY

In order to fully understand the pathophysiology of rhinosinusitis, one must consider the concepts of *inflammation*

and *infection*. Inflammation is a cascade of processes and signals via which mediators, such as leukocytes, are enabled to eliminate foreign agents and repair damaged tissues (4,11). Acute inflammation is characterized by exudation of fluid and plasma proteins from blood vessels with emigration of leukocytes, predominantly neutrophils, as these cells gather to combat the offending entity (4,11). It can be identified within minutes to hours of an insult or trigger. Chronic inflammation develops as the condition persists over weeks to months. The hallmarks of chronic inflammation are the presence of lymphocytes, macrophages, eosinophils, and basophils, along with increased vascularity, fibrosis, and tissue necrosis (4,11). Subacute inflammation is described as the interval period when overlapping patterns of inflammation are observed (4). Infection is traditionally diagnosed when microorganisms present in a host, directly interacting with the host tissue and replicating. This results in expression of disease in the host organism (4). Bacterial infection is characterized by the presence of one or more bacteria per high density field, which correlates to at least 1,000 colony forming units per milliliter (4).

Histopathologically, acute rhinosinusitis is predominantly an exudative process (1,12). Examination of tissue specimens reveals a mixed inflammatory cell infiltrate in which neutrophils predominate. Hemorrhage, ulceration, and the presence of bacteria or fungi may also be seen (1,4,12).

Acute Viral Rhinosinusitis

The majority of acute rhinosinusitis is infectious in etiology (4) (Table 33.3). The leading pathogen is viral. A sinus puncture study in patients with acute community-acquired rhinosinusitis demonstrated the most common identifiable viral organisms in descending prevalence to be rhinovirus 15%, influenza virus 5%, parainfluenza virus 3%, and adenovirus 2% (4,13). The pathogenesis of infection by the most common of these, the rhinovirus, was very well delineated in the end of the twentieth century by Gwaltney's group at the University of Virginia. The rhinovirus enters the body through the nose, either by direct inoculation or by large airborne particles (4,14). Viral particles travel in the mucus stream to the adenoid region where they attach to a specialized receptor (rhinovirus receptor intercellular adhesion molecule 1) on lymphoepithelial cells overlying lymphoid follicles (4,15–17). An inflammatory reaction is thus incited, and common acute viral rhinosinusitis (AVRS) symptoms, including sore throat, nasal obstruction, and rhinorrhea develop within hours of exposure (4,18).

Although historically viruses were thought to cause predominantly rhinitis, involvement of the paranasal sinuses in the clinical setting of AVRS is well documented radiologically in both adults and children (19,20). These studies were performed predominantly in the late 1980s and early 1990s at a time when people were comparing the relatively new modalities of computed tomography (CT) and magnetic resonance imaging (MRI) against the standard imaging modality for rhinosinusitis, plain film radiography. Abnormalities, including air–fluid levels, aerosolized secretions, and thickened mucosa are seen most often in the maxillary sinuses 87%, but also in the ethmoid sinuses 65%, the frontal sinuses 32%, and the sphenoid sinuses in 39% (4,21). These findings are associated with exocytosis of large amounts of mucin by goblet cells in the paranasal sinus epithelium after they have been stimulated

TABLE 33.3 RELATIVE FREQUENCY OF INFECTIOUS ORGANISMS IN ACUTE RHINOSINUSITIS

Cause	Organism	Frequency
Virus	Proportion of total acute rhinosinusitis (ARS) cases	39%–87%[a]
	Proportion of viral pathogen recovered on sinus puncture:	
	Rhinovirus	
	Influenza virus	15%
	Parainfluenza virus	5%
	Adenovirus	3%
		2%
Bacteria	Proportion of total ARS cases	0.05%–2%
	Proportion of each bacterial species in acute bacterial	
	rhinosinusitis (ABRS):	20%–43%
	S. pneumoniae	22%–35%
	H. influenzae	2%–10%
	M. catarrhalis	2%–6%
	Anaerobes	<5%
	S. aureus and *Streptococcus pyogenes*	

[a]Percentages given are culture-proven viral infections. A proportion of acute rhinosinusitis is culture-negative, which is presumably due to difficulties in technicalities of viral culture. In the rhinosinusitis literature, culture-negative disease is presumably viral in origin.

by inflammatory mediators in the setting of acute viral infection (4).

Acute Bacterial Rhinosinusitis

ABRS classically occurs when a patient with AVRS develops a superimposed or secondary bacterial infection (2). Only about 0.5% to 2.0% of AVRS are complicated by a bacterial infection (2,13). Yet, there are still about 20 million cases of ABRS annually in the United States (2,22). AVRS can promote development of ABRS by several mechanisms. The inflamed, edematous mucosa can obstruct sinus ostia and impair mucus drainage (2,23,24). Mucociliary function and clearance is also directly affected by inflammation; this deficit is magnified in a setting of increased mucus production (24). Infection by bacterial pathogens that colonize the nose and nasopharynx is promoted by mucus stasis and enabled as the bacteria are deposited into the paranasal sinuses by nose-blowing (2,13,25).

This concept of the transition from AVRS to ABRS is critical as we discuss patient presentation and accurate evaluation of progression of symptoms for diagnostic purposes. An episode of AVRS can be complicated by a bacterial infection at any point, but early in the presentation the clinical distinction between the two is essentially impossible. The more specific diagnostic criteria pertaining to the timeline of the infection will be discussed later in this chapter, and are directly related to recommended management of acute rhinosinusitis.

Microbiology of Acute Bacterial Rhinosinusitis

Knowledge regarding the microbiology of acute community-acquired bacterial rhinosinusitis in adults has been predominantly delineated from cultures of maxillary sinus mucus, as these are the most accessible of the paranasal sinuses (4). The majority of ABRS infections are due to a single bacterial isolate, but about one-fourth of cases have polymicrobial infection, more commonly seen in pediatric cases (4,26). The most common bacterial species isolated from the maxillary sinuses of patients with uncomplicated ABRS are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* (2,27) (Table 33.3). The relative frequency of bacterial isolates in ABRS has proven to be a reproducible relationship; *S. pneumoniae* is identified in 20% to 43% of cases, *H. influenzae* in 22% to 35%, and *M. catarrhalis* in 2% to 10% (2,26–31). The *H. influenzae* identified are predominantly the nontypeable organisms (4). In the last several decades of the twentieth century there was a very large increase in the prevalence of β-lactamase-producing *H. influenzae* to greater than 50%; however, in the 21st century this appears to have stabilized at about 40% of the isolates (4,13,32,33). Macrolide-resistant *S. pneumonia* is an increasing concern, and has been associated with increased risk of treatment failure (34–36). Anaerobic bacteria account for only 2% to 6% of ABRS, some of which arise from primary dental pathology (4). *Staphylococcus aureus* and *S. pyogenes* play an interesting role in ABRS. Overall, they account for less than 5% of cases, although *S. aureus* is often overestimated based on culture from nasal swabs, as opposed to endoscopically-directed sinus cultures or direct sinus aspirates (4). Of note, *S. aureus* and *S. pyogenes* have a higher propensity to cause complications of acute rhinosinusitis, such as intracranial or orbital extension of the disease (4).

Special Scenarios—Microbiology of Nosocomial Acute Bacterial Rhinosinusitis

Nosocomial rhinosinusitis has a much higher prevalence of gram-negative organisms than community-acquired ABRS. Examples of organisms found in nosocomial infections include *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter* species, *Proteus mirabilis, Serratia marcescens,* and gram-positive cocci, such as streptococci and staphylococci (4). For many years we have known that patients at high risk for nosocomial rhinosinusitis are those who require extended periods of intensive care with prolonged endotracheal intubation or nasogastric tubing (4,37). Nasotracheal intubation has a higher risk for nosocomial sinusitis than orotracheal intubation (4,38). Nosocomial sinusitis develops in 25% of patients requiring nasotracheal intubation for longer than 5 days (4,39).

Special Scenarios—Acute Fulminant Invasive Fungal Sinusitis

Acute fulminant invasive fungal sinusitis is an aggressive disease characterized by the rapid spread of fungi from the sinonasal mucosa into the orbit, soft tissues, and brain parenchyma via direct and vascular invasion (40). Affected patients typically have a clinical condition associated with impaired neutrophil function, such as hematologic malignancies, aplastic anemia, diabetes, acquired immunodeficiency syndrome, organ transplant, or iatrogenic immunosuppression due to chemotherapy (40). The most common etiologic organisms are *Aspergillus* and *Mucormycosis* species. In this special patient population with decreased ability to mount an immune response to infectious organisms, the signs and symptoms of disease may be subtle. The most common physical finding on sinonasal endoscopy is an alteration in the mucosa of the nose and sinuses that suggest angioinvasion by the fungal organisms, with ultimate hypoperfusion of tissues. White discoloration may suggest tissue ischemia, whereas black discoloration is a late finding of tissue necrosis (40). Decreased mucosal bleeding and sensation of anesthetic regions of the face or oral cavity may be signs of this invasive process (40). The most common locations of mucosal abnormalities are middle or inferior turbinate, nasal septum, and palate (41). The gold standard for diagnosis of this disease is permanent section with Gomori methamine

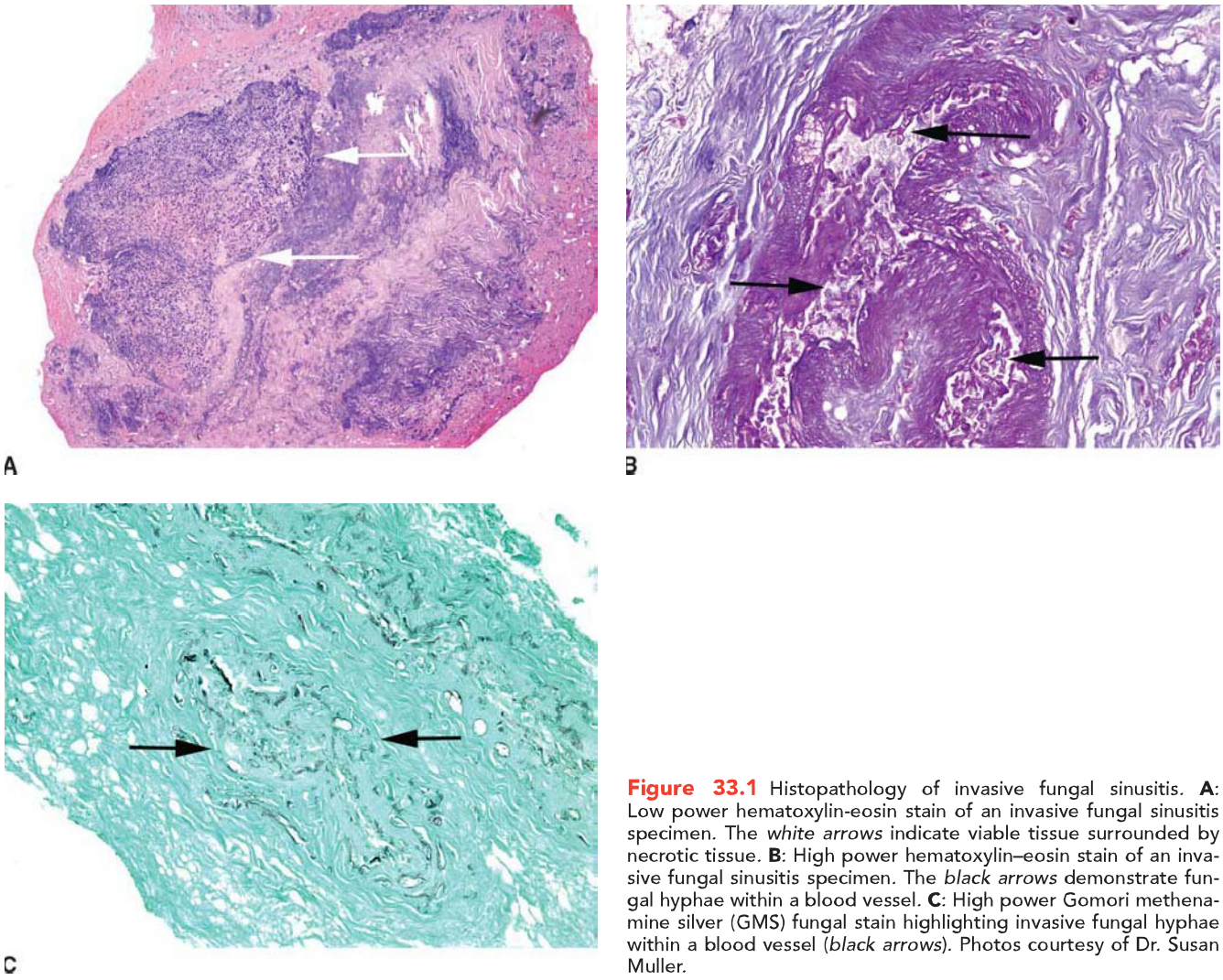


Figure 33.1 Histopathology of invasive fungal sinusitis. **A**: Low power hematoxylin-eosin stain of an invasive fungal sinusitis specimen. The *white arrows* indicate viable tissue surrounded by necrotic tissue. **B**: High power hematoxylin–eosin stain of an invasive fungal sinusitis specimen. The *black arrows* demonstrate fungal hyphae within a blood vessel. **C**: High power Gomori methenamine silver (GMS) fungal stain highlighting invasive fungal hyphae within a blood vessel (*black arrows*). Photos courtesy of Dr. Susan Muller.

silver stain showing "hyphal forms within the submucosa with or without angiocentric invasion and tissue necrosis with minimal host inflammatory infiltrate" (40) (Fig. 33.1A–C). Because prompt diagnosis is imperative with this condition, frozen section with histopathologic evaluation of any suspicious lesions is necessary to facilitate surgical resection and initiation of antifungal therapy without delay. The potassium hydroxide–calcofluor white method is an alternative rapid diagnostic technique in which potassium hydroxide is used to dissolve human material, and the calcofluor white is used as an optic brightener that binds to the cell wall of the hyphae and fluoresces when viewed with a fluorescent microscope (40).

CLINICAL PRESENTATION AND EVALUATION

Symptoms associated with rhinosinusitis are well recognized. The common symptoms include nasal obstruction, nasal discharge, nasal purulence, postnasal drip, facial pressure and pain, alteration in the sense of smell, cough, fever, halitosis, fatigue, dental pain, sore throat, aural fullness, otalgia, and headache.

Patient History

When a patient presents with a constellation of symptoms consistent with acute rhinosinusitis, the care provider should document all relevant symptoms. Clarification of the severity of symptoms and their time course is critical in establishing an accurate diagnosis and forming an appropriate treatment plan. Assessment of the patient's pain within this evaluation is strongly encouraged. Pain is one of the three cardinal symptoms described as the diagnostic criteria for ABRS, and pain is a major reason why patients seek medical care (4,42).

The early consensus report outlined by the Task Force on Rhinosinusitis in 1996 outlined a stratification of major and minor symptoms in order to facilitate appropriate diagnosis of ABRS and help emphasize its distinction from AVRS (1). Subsequent reports have replaced this model with a new concept, highlighting three cardinal

TABLE 33.4 THREE CARDINAL SYMPTOMS TO DIAGNOSE ABRS

1. Purulent nasal discharge
2. Nasal obstruction
3. Facial pain, pressure, or fullness

symptoms: purulent nasal discharge, nasal obstruction, and/or facial pain, pressure, or fullness (2,42) (Table 33.4). The logic behind this new slant in symptom interpretation for the diagnosis of ABRS is based upon the high sensitivity and relatively high specificity of these indicators for ABRS, especially when they are present for 10 days or longer (2,42–44). Presence of purulent nasal drainage, whether reported by the patient or seen on physical exam in the posterior pharynx or intranasally near the sinus ostia, correlates to the presence of bacteria on antral aspiration (2,45,46). Findings of purulence also correlate with radiographic evidence of ABRS (2,47). Nasal obstruction is associated with objective measures, such as rhinomanometry or nasal peak flow rate (2,48). Facial pain and dental pain are also predictive of ABRS according to culture results and to radiographic findings, but the location does not correlate with the specific sinuses involved (2,44,45,49).

After a thorough history of symptomatology is obtained, a physician can often distinguish ABRS from AVRS or from acute rhinosinusitis due to noninfectious etiologies (2). According to the 2007 guidelines, "ABRS is diagnosed when the three cardinal symptoms are present for 10 days or longer beyond the onset of upper respiratory symptoms, or when the symptoms or signs of acute rhinosinusitis worsen within 10 days after a period of initial improvement (double-worsening)" (2). In the first 3 to 4 days of illness, AVRS cannot be distinguished from an early transition to ABRS (2). Purulent discharge does not indicate the presence of bacteria within the mucus, but rather it demonstrates the presence of neutrophils, which is characteristic of acute inflammation regardless of the etiology. Clear rhinorrhea may be indicative of AVRS, allergic rhinosinusitis, or other causes of nonallergic rhinosinusitis, such as vasomotor rhinitis. At 10 days or more, inflammation and edema from AVRS may still be present; however, the condition should be improving. If the symptoms are progressing at the 10 day timeframe, a diagnosis of ABRS is suggested (2,42).

Fever is not included as a cardinal sign of ABRS because it only has a sensitivity and specificity of about 50% for this diagnosis (2,42–44). Patients with AVRS may have fever during the initial several days of illness, which does not necessarily implicate an evolving secondary bacterial infection. However, if a patient presents with the three cardinal symptoms, which seem to be particularly severe or with a high fever within the first 3 to 4 days of onset of illness, a diagnosis of ABRS may be considered early (2,4,42). Additionally, if there are symptoms suggesting progression beyond uncomplicated ABRS, despite the duration of symptoms, treatment should be initiated early.

In addition to the thorough disease-specific history outlined above, a care provider for a patient presenting with symptoms of acute rhinosinusitis should perform a thorough medical and social history. Presence of significant comorbid conditions, such as diabetes mellitus, immunocompromised status, pulmonary disease, or congenital conditions are important to recognize when delineating a treatment plan. A history of atopy or perennial allergic rhinitis is also relevant in treatment planning. Prior nasal or facial trauma, facial surgery, or sinonasal surgery may affect a patient's experience of symptoms and disease course. A thorough review of a patient's medications and medication allergies should be obtained prior to applying any decongestant or local anesthetic to facilitate examination in the clinic, and certainly prior to prescribing medications. Understanding the patient's social history, including tobacco exposure and conditions of their home and work environments is important for comprehensive patient counseling. These factors may also suggest underlying conditions that are capable of predisposing a patient to symptoms of rhinosinusitis and to the development of ABRS.

Physical Examination

Although a diagnosis of AVRS or ABRS can be accurately made with a patient history, a thorough physical exam is imperative. Vital signs should be recorded. Examination of the head and neck should begin with facial examination. Swelling, erythema, or edema localized over the involved cheek or periorbital edema may suggest complicated ABRS with extension into the soft tissues. Palpation and percussion over the face and maxillary dentition may assist in localizing pain. Examination of the eyes includes assessment of the appearance of the conjunctiva, visual status testing, extraocular muscle function evaluation, inspection for the presence of proptosis, and funduscopic or Tonopen exams if clinically indicated. Otoscopic exam may reveal serous otitis media or acute otitis media. Anterior rhinoscopy is the basic tool of the physical exam that most specifically relates to detecting pathology in the sinonasal passages (4). Typically, the nose is evaluated before and after topical decongestion. Prior to application of decongestant, such as oxymetazoline or neosynephrine, the anterior nasal passages and inferior turbinates are inspected. After the nose has been decongested, one is usually able to visualize the middle turbinate and inspect for pus in the region of the middle meatus as well as hyperemia, edema, or crusting. Enlarged turbinates, presence of nasal polyps or masses, and nasal septal deviations may limit the extent of this examination. Visualization of purulent postnasal drainage upon oropharyngeal examination is rather sensitive and specific for ABRS (1). Vocal analysis may reveal

TABLE 33.5 INDICATIONS FOR SINONASAL ENDOSCOPY IN ACUTE RHINOSINUSITIS

Failure to improve on empiric therapy
Unilateral disease
Severe symptoms
Suspicion of complications of ABRS
Recent sinonasal surgery
Immunocompromised status

a hyponasal quality, consistent with reduced resonance due to decreased aeration of the paranasal sinuses (2). Auscultation of the chest is especially important in any patients with history of pulmonary dysfunction given the potential of lower airway inflammation coincidentally with upper airway infection. A full neurologic evaluation including cranial nerve examination is indicated if there is any concern for complicated ABRS with intracranial extension.

Endoscopic Evaluation

Endoscopically-directed middle meatus cultures are well correlated with cultures obtained by direct maxillary sinus aspiration (2,50). Cultures of secretions from the nose or nasopharynx, however, are poorly representative of maxillary sinus cultures (2,50). Blind swabs of the nasal cavity are not recommended since they are likely to be contaminated by normal colonizing bacteria (51). Directed cultures are not necessary for the diagnosis or treatment of uncomplicated ABRS (2). Often the initial evaluation of a patient with ABRS is by a primary care provider not trained in sinonasal endoscopic techniques, which should not deleteriously affect delivery of appropriate care. The most important role of endoscopy is the assessment and treatment of patients with refractory or chronic symptoms and in patients who have impending or existing complications of rhinosinusitis (4). The indications for the consultation of an otolaryngologist for endoscopy are symptomatic patients who fail to improve on empiric therapy, patients with unilateral disease, patients with severe or disabling symptoms, patients in whom complications are suspected, patients who have had recent sinonasal surgery, or immunocompromised individuals (4) (Table 33.5). Sinonasal endoscopy can be performed with either a flexible or a rigid scope. Flexible fiberoptic endoscopy is more comfortable for the patient and facilitates access toward the sinuses in a nonoperated patient. Rigid sinonasal endoscopy provides superior image quality, allows one to obtain cultures and tissue samples if indicated, and provides the ability to control epistaxis if encountered. Cultures can be obtained with a sterile swab or utilizing suction into a sterile trap device.

IMAGING

Imaging modalities available to evaluate the nose and the paranasal sinuses are plain film radiography, CT, and MRI (Table 33.6). Ultrasound has been used for evaluation of maxillary sinus disease, but its sensitivity is poor (9,52). Ultrasound has limited capacity to accurately image the paranasal sinuses given that they are surrounded by bone and contain air. It is very important to understand the strengths and weaknesses of each of these imaging techniques in order to incorporate them into practice in a cost-effective and algorithm-based manner. Information gained from a test should provide relevant data that can be used to impact clinical decision making.

TABLE 33.6 IMAGING MODALITIES IN ACUTE RHINOSINUSITIS

Modality	Strengths	Weaknesses	Indications in the Setting of ARS
Ultrasound	Low cost No radiation exposure	Low sensitivity	Not recommended
X-ray	Low cost Low radiation dose Portable exam	Low sensitivity Low specificity	No longer used routinely
CT	Excellent bony anatomy High sensitivity (>90%)	Higher cost Higher radiation dose Poor soft tissue differentiation Cannot distinguish AVRS from ABRS Findings do not correlate well with localizing symptoms	Suspicion for a complication of ABRS Suspicion for alternative diagnosis, such as neoplasm Presence of comorbidities that may predispose to complications of ABRS
MRI	Excellent soft tissue differentiation Excellent intracranial diagnostic capacity	Higher cost Longer scan time Poor delineation of bony anatomy Cannot distinguish AVRS from ABRS	Suspicion of neoplasm Suspicion of intracranial involvement

Note: No imaging modality is recommended in the routine diagnosis of uncomplicated ABRS.

X-ray

Sinus plain film radiography series consist of three views: a lateral, Caldwell or posterior–anterior view (central ray angle 15 degrees), and Waters or occipitomental view (orbitomeatal line angled 37 degrees to horizontal plane) (2). Radiographs must be obtained with the patient in an upright position, as the primary feature that is used to diagnose ABRS by plain film is the presence of air–fluid levels. Other imaging findings consistent with a diagnosis of ABRS on plain film radiography are sinus opacification and mucosal thickening (2). Relative advantages of plain films of the sinuses are low cost, low radiation dosage (1.4 cGy per film), and possibility of a portable exam in an intensive care setting (53). A prospective study using antral puncture results as the gold standard for diagnosis of ABRS showed that complete opacification, air–fluid levels, or both on plain film radiography of the maxillary sinuses have a diagnostic sensitivity of 73% and specificity of 80% (2,53–55). A similar study evaluating plain radiography and using CT as the gold standard for diagnosis of acute maxillary sinusitis reported the sensitivity of radiography as 67% and specificity as 87% (53,55). The positive and negative predictive values were reported as 82.5% and 76.9%, respectively (53,55). The sensitivity of plain film radiography to diagnose ethmoid, frontal, and sphenoid sinusitis was worse at 0% to 58.9%, 1.9% to 54.0%, and 0% to 38%, respectively (53,55). A negative plain film does not rule out the presence of sinusitis. By now most agree that plain radiographs have limited value for acute rhinosinusitis (1,56).

Computed Tomography

CT is considered the gold standard for radiographic evaluation of the paranasal sinuses (1,2). Standard sinus CT without contrast with 3-mm coronal cuts provides appropriate information regarding bony anatomy, permitting understanding of the complex structure of the paranasal sinuses (53). Findings on CT that correlate with ABRS are "opacification of the sinus cavities, air–fluid levels, and moderate to severe mucosal thickening" (2). The most accepted objective staging system used to evaluate the paranasal sinuses on CT is the Lund-Mackay classification system, which quantitates sinus disease by number of sinuses with any degree of opacification in addition to evaluation for any anatomic variants (57). Some of the limitations of CT are increased cost and increased dose of radiation (5 to 6 cGy), which may reach values up to 10 times the dose of a radiograph (2). Multidetector CT is a technology that facilitates reduced total radiation in imaging of the sinuses because the patient is scanned in a single plane and the remaining triplanar images are reconstructed from the original data set (2). Additionally, although findings on CT may be consistent with a diagnosis of ABRS, they cannot accurately distinguish between AVRS and ABRS (2,21). Further, there is a lack of correlation between localizing symptoms and findings on CT (2,49,58).

Using the presence of an air–fluid level or total opacification of a sinus as diagnostic criteria, sinus CT has a 90% positive predictive value for diagnosis of ABRS when compared with culture of aspirated sinus secretions (9,59). Still, the use of CT in diagnosis of uncomplicated ABRS is not cost-effective and universally not recommended (49,60–62). The role of CT in acute sinusitis outlined in the literature is very specific and consistent. CT should only be performed when a complication of acute rhinosinusitis or an alternative diagnosis is suspected (1,2,42). The complications of acute rhinosinusitis include orbital, intracranial, or soft tissue involvement. Alternative diagnoses of facial pain may include neoplasm (2,42). CT may also be utilized when the patient has comorbidities or a clinical condition that predisposes him to complications, such as diabetes, immunocompromised state, or a past history of facial trauma or surgery (2). Iodine-contrast enhancement may help to identify extra-sinus extension of disease in clinical situations when this is suspected (2).

Magnetic Resonance Imaging

Gadolinium-enhanced MRI does not display bony anatomy as well as CT, but it provides excellent soft tissue differentiation (53). Bacterial and viral inflammation remains indistinguishable from one another on MRI, but they are easily differentiated from fungal concretions or neoplasm (4). MRI is the best modality for delineating extension of disease beyond the paranasal sinuses into the orbits or intracranial compartment (4). Drawbacks of MRI include longer acquisition time and higher cost (53). CT remains the diagnostic modality of choice when sinusitis with complications is suspected, but MRI is the gold standard for the diagnosis of intracranial complications (63).

TREATMENT

Antibiotics are the most frequently recommended medications for the treatment of acute rhinosinusitis, accounting for 21% of antibiotics prescribed for adults and 9% of antibiotics prescribed for children (64–66). One study showed that physicians ordered, supplied, administered, or continued at least 1 antibiotic in 82.74% of visits for acute rhinosinusitis (65). Antibiotics are prescribed far in excess of the predicted incidence of ABRS (65). Appropriate antimicrobial use for ABRS requires knowledge of the natural history of untreated illness and the incremental benefit of antimicrobials on clinical outcomes in different scenarios (64) (Table 33.7).

Medical Management of Acute Viral Rhinosinusitis

The management of AVRS should be focused on symptom control, as this is a self-limited condition and there is no evidence that use of medications will help to decrease the potential for conversion into ABRS (2,3). Analgesic and antipyretic medications will help with pain and fever, two major symptoms prompting a patient to seek medical care

TABLE 33.7 MEDICAL TREATMENT MODALITIES FOR ACUTE RHINOSINUSITIS

Class	Generic Example	Clinical Benefit	Recommended Use
Analgesic/antipyretic	Acetaminophen	Decreases pain and fever	Recommended for AVRS and ABRS
Saline irrigations		Thins mucus, enhances mucociliary clearance, decreases inflammation	Recommended for AVRS and ABRS; may consider hypertonic irrigations
Topical decongestant	Oxymetazoline	Reduces mucosal edema and nasal airway obstruction	Consider in AVRS and ABRS for 3 d duration only
Systemic decongestant	Pseudoephedrine	Limited reduction of mucosal edema	Not as effective as topical decongestant
Topical corticosteroid	Fluticasone propionate	Improved symptom control in ABRS	Consider in ABRS with allergic component
Systemic corticosteroid	Prednisone	Not supported in literature	No evidence supporting use in AVRS or ABRS
Nonsedating antihistamine	Loratadine	Dries secretions	Consider in AVRS or ABRS with allergic component
Mucolytic	Guaifenesin	Thins tenacious secretions and phlegm	Improves symptom control in AVRS, limited literature support in ABRS
Antibiotic—*penicillins*	Amoxicillin ± clavulanate	Bactericidal, inhibit peptidoglycan cross-linking in cell wall synthesis	First-line for severe ABRS or mild ABRS that fails to improve with observation
Antibiotic—*cephalosporins*	Cefpodoxime proxetil, cefuroxime axetil, cefdinir	Bactericidal, inhibit peptidoglycan cross-linking in cell wall synthesis	Second most efficacious class for ABRS
Antibiotic—*sulfonamides and trimethoprim*	Trimethoprim-sulfamethoxazole	Bacteriostatic, inhibit folate synthesis, thereby preventing DNA replication and transcription	Alternative for first-line for severe ABRS or mild ABRS that fails to improve with conservative management in patients with penicillin allergy
Antibiotic—*tetracyclines*	Doxycycline	Bactericidal, inhibits protein synthesis	Good efficacy for ABRS
Antibiotic—*erythromycin, lincosamides, and macrolides*	Azithromycin, clarithromycin, erythromycin	Bactericidal, inhibits protein synthesis	Least efficacious for ABRS; consider as alternative for patients with penicillin allergy

in this clinical scenario (2). Nasal irrigations with hypertonic saline solution have been shown to improve symptoms and reduce the use of pain medications in AVRS (3,67). They thin mucus and help with mucociliary clearance (42). Decongestant options include systemic and topical administration, although topical nasal decongestants offer increased symptom relief given increased potency (2). Although theoretically they may help to restore patency of sinus ostia, this has not been demonstrated (2). Prescribers must inform their patients of the potential for development of *rhinitis medicamentosa* with use prolonged beyond 3 days (2,42). Systemic steroid therapy has not been shown to be effective for AVRS, and carries a risk of behavioral changes, increased appetite, and weight gain, even with short courses (2). Topical nasal steroids have minimal systemic absorption and consequently carry a very low risk for systemic side-effects (2). Yet, there is only weak evidence supporting their use in AVRS (2). If an allergic component is identified in the clinical presentation, their use may be more beneficial (2). Antihistamines are another class of medications that may be beneficial if allergy is suspected to play a role in the disease process. Although the drying effect of antihistamines may be desirable in certain clinical scenarios, there are no studies demonstrating their capacity to decrease duration of illness or to decrease the potential of conversion to ABRS (2). Antihistamines, particularly first-generation, carry risks of drowsiness and behavioral effects. These side effects are seen less frequently with second-generation antihistamines (2,42). Mucolytics are used to thin mucus in an attempt to facilitate mucociliary clearance, and their use is shown to decrease symptom scores compared to placebo (42,65).

Medical Management for Acute Bacterial Rhinosinusitis

For patients presenting with uncomplicated ABRS who have mild illness with mild pain and fever less than 38.3°C (101°F) and in whom there is assurance for follow-up, physicians can limit management to symptomatic relief and defer antibiotic treatment for up to 7 days after diagnosis (2). The 2007 guidelines emphasize that, "this observation

option is only appropriate if a system is in place that permits reevaluation if the illness persists or worsens" (2). Antibiotics are initiated if the patient's condition fails to improve by 7 days or worsens at any point during the observation period (2). Although illness severity largely determines whether a patient is suitable for observation, the clinician must take into account the overall clinical picture, including the patient's age and comorbidities when determining a treatment plan (2).

In cases of uncomplicated mild ABRS, antibiotics can safely be deferred as randomized controlled trials (RCTs) show that there is a high percentage of spontaneous improvement when patients receive placebo with only a moderate incremental benefit from the addition of antibiotics (2). In an era of growing concern about the overuse of antibiotics and resultant problems, including drug resistance and increasingly virulent bacteria, adherence to these guidelines is encouraged (65). A meta-analysis of 13 RCTs in 2007 shows complete spontaneous clinical cure in 8% of patients at 3 to 5 days after diagnosis of ABRS (95% CI, 5% to 14%), in 35% at 7 to 12 days (95% CI, 24% to 48%), and 45% by 14 to 15 days (95% CI, 23% to 70%) (64). Rates of spontaneous clinical improvement were 30% at days 3 to 5 (95% CI, 0% to 99%) and 73% at days 7 to 12 (95% CI, 56% to 85%), which remained stable at days 14 to 15 (64). Antimicrobial therapy had no effect on clinical cure at 3 to 5 days after diagnosis of ABRS, increased absolute cure rates by 15% at days 7 to 12 (95% CI, 4% to 25%) with a number needed to treat of seven patients, and had no statistical benefit at days 14 to 15 (64). The effects of antibiotics on clinical improvement rates were very similar to its effects on cure rates (64). This data correlates well with prior systematic reviews, which showed spontaneous improvement in 62% to 69% of patients after 7 to 14 days after diagnosis of ABRS, spontaneous cure in 19% to 39%, and an absolute increase of 13% to 19% in favorable outcomes when antibiotics are used (2,64,68–70). Of course, antibiotics are also associated with side effects and adverse events, which must be taken into account when prescribing them. The number needed to harm is nine patients, with the most common side effects being gastrointestinal, but also including skin rash, vaginal discharge, headache, dizziness, and fatigue (64). One analysis estimates that antibiotics result in 15 days (best case) to 89 days (worst case) of diarrhea, nausea and vomiting, or both per 100 patients treated with antibiotics for ABRS versus only 8.5 days for those treated with placebo (2,71).

Symptomatic relief for ABRS is essentially the same as for AVRS. Although one may consider adjunctive treatments for ABRS including analgesics, antipyretics, nasal saline irrigations, decongestants, corticosteroids, antihistamines, and mucolytics, none of these therapies has been specifically approved by the Food and Drug Administration for use in acute rhinosinusitis. Buffered hypertonic saline (3% to 5%) irrigations have shown a modest benefit for ABRS with decreased symptoms and decreased medication use (2,3). Compared with isotonic saline, the use of hypertonic saline in sinonasal irrigations may have superior anti-inflammatory effects and better ability to thin mucus, thereby enhancing mucociliary clearance, although this issue remains controversial (2,3,72–75). While keeping in mind the risk of *rhinitis medicamentosa*, use of topical decongestants is recommended in the management of ABRS, given improvement in outcomes and reduction of congestion on sinonasal mucosa on MRI seen in studies (2,76,77). Further, the superior potency of topical decongestant over systemic is depicted by the decreased congestion appreciated on MRI after topical administration as compared to systemic administration (77). Trials support the use of topical corticosteroids for ABRS with improved symptom control in patients, but there is no evidence for the use of systemic glucocorticoids for this illness (2,78–80). The use of antihistamines in nonatopic patients with ABRS is not supported (2,65). In fact, there is concern that the cholinergic effects may actually worsen congestion and prolong the infectious process (2,65). Use of second-generation antihistamines should be limited to patients whose symptoms suggest an allergic component to their disease process (2,65). Although, in theory, the use of mucolytics would seem beneficial in airway infections characterized by phlegm and mucus, the literature does not provide evidence supporting their use in ABRS (2).

Patients who present with ABRS and moderate to severe pain or temperature greater than 38.3°C (101°F) are considered to have severe illness and should be treated initially with oral antibiotics. Ideally, the antibiotic should be efficacious, cost-effective, and result in minimal side effects (2). Amoxicillin is the first-line antibiotic recommended for most patients (2,3,42,64,65). Amoxicillin is safe, inexpensive, efficacious, and has a narrow microbiologic spectrum (2,42) Meta-analysis confirms that treatment with amoxicillin decreases the duration of symptoms (2,42,64). Comparison of treatment durations of 5 and 10 days does not show a difference in resolution of symptoms, but does show that longer durations of treatment are associated with an increase in adverse events (2,42,64). The recommended alternatives for patients with penicillin allergy are trimethoprim-sulfamethoxazole or a macrolide antibiotic (2,42,64,65). It is important to remember when prescribing antibiotics that a regimen with simple once daily dosing for a short duration will have the highest compliance rate (2). Counseling a patient about the natural history of acute rhinosinusitis, the importance of completing a prescribed antibiotic regimen, and additional adjunctive measures for symptom control, including hydration and analgesia, is an important part of treatment planning with your patient (2).

Certain clinical scenarios warrant particular attention in antibiotic selection. If a patient has been treated with antibiotics in the recent past (4 to 6 weeks), they are at increased likelihood for infection with a resistant bacterium, and a fluoroquinolone or high-dose amoxicillin-clavulanate (4 g/250 mg/d) should be used, according to the 2004 Sinus and Allergy Health Partnership (SAHP)

Antimicrobial Treatment Guidelines (2,42,81). In the SAHP Guidelines, amoxicillin-clavulanate had the highest calculated clinical efficacy in both the groups that had and those that had not recently received antibiotics (65). Patients with young children in daycare are at risk for penicillin-resistant *S. pneumoniae* infection, and high-dose amoxicillin should be considered in this group (42,65). The SAHP Guidelines show that, in decreasing order of efficacy, other antibiotics that can be used for treatment of ABRS are cefpodoxime proxetil, cefuroxime axetil, cefdinir, trimethoprim-sulfamethoxazole, doxycycline, and azithromycin, clarithromycin, or erythromycin (65,81). This is an important list, especially given that a study in 2002 showed the second most frequently prescribed class of antibiotics for ABRS behind penicillins (including amoxicillin and amoxicillin-clavulanate) was the group including erythromycins, lincosamides, and macrolides (65). An antibiotic from this group was prescribed in 24.32% of visits for ABRS, ahead of cephalosporins, sulfonamides and trimethoprim, and tetracyclines, which all have demonstrated increased efficacy for this illness (65).

Management for Patients Who Have Failed Primary Treatment of ABRS

The most recent treatment guidelines from 2007 recommend using 7 days as a cut-off point after initial diagnosis to assess for treatment failure (2). Treatment failure entails *worsening*, defined as progression of presenting signs or symptoms or onset of new symptoms or signs, and *failure to improve*, defined as lack of reduction in presenting signs or symptoms of ABRS (2). Failure to improve, therefore, would not be diagnosed in a patient undergoing treatment for ABRS who has persistent, but slowly resolving symptoms of ABRS. Seven days is chosen as the cut point based on studies showing that between 7 and 12 days after diagnosis 73% of patients randomized to placebo and 85% of patients receiving antibiotics have clinical improvement (2,64). At 3 to 5 days after diagnosis, only 30% of patients receiving placebo and 41% of patients taking antibiotics have clinical improvement, thus a cut point at 5 days would include many false positives (2,64). If a patient fails treatment at the 7-day mark, they should be reevaluated for complications of ABRS, drug-resistant bacteria, or nonbacterial cause (2). If the patient was initially managed with observation, the clinician should begin treatment with amoxicillin or an appropriate alternative in patients with penicillin allergy (trimethoprim-sulfamethoxazole or macrolide antibiotic) (2). Patients who have been taking an antibiotic, such as amoxicillin, and who have treatment failure are more likely to be infected with reduced susceptibility bacteria (2). Organisms that should be suspected, particularly in a patient with previous antibiotic therapy, are beta-lactamase producing *H. influenzae* or *M. catarrhalis* and *S. pneumoniae* with reduced susceptibility to beta-lactams, macrolides, tetracyclines, and trimethoprim-sulfamethoxazole (2). Optimal antibiotic therapy recommended by the 2007 Guidelines for ABRS treatment failures are high-dose amoxicillin-clavulanate (4 g/d) or a respiratory fluoroquinolone (levofloxacin, moxifloxacin, gemifloxacin) (2). Cephalosporins and macrolides are predicted to offer inadequate coverage (2).

Management of Acute Fulminant Invasive Fungal Sinusitis—Medical and Surgical

The management of acute fulminant invasive fungal sinusitis necessitates combined medical and surgical modalities with a multidisciplinary approach. Systemic antifungal therapy with amphotericin or voriconazole is necessary, but alone not sufficient to treat this condition (40). Early aggressive endoscopic sinonasal debridement of all involved tissue is necessary for any patient with biopsy-proven disease or in anyone in whom there is high clinical suspicion. The goals of debridement include reduction of the fungal load, slowing progression of disease, and obtaining a specimen for culture and sensitivity studies (40). Many patients affected by this disease will inherently have thrombocytopenia or coagulopathy as part of their underlying condition. This must be addressed with platelet and factor transfusion pre- and intraoperatively in order to minimize hemorrhage (40). Adjunctive measures to tackle this disease involve strategies to correct the underlying immune deficit, such as correction of diabetic ketoacidosis, transfusion of white blood cells, or administration of granulocyte colony-stimulating factor (40). The mortality rate for this condition approaches 100% if there is symptomatic intracranial involvement, but overall is about 20% (41,82). Mortality is also strongly related to the underlying condition, with diabetics having significantly higher mortality (40%) than patients with hematologic malignancy (11%) (82). This disparity is likely due to a greater incidence of *Mucormycosis* over *Aspergillus* in diabetic patients, with the reverse true in patients with hematologic malignancy, and a delay in diagnosis in diabetic patients resulting in more advanced disease at the time of diagnosis (82).

COMPLICATIONS

Acute rhinosinusitis has three possible clinical courses: resolution, development of sequelae, or development of chronic rhinosinusitis. Adverse sequelae of acute rhinosinusitis can be broadly classified as extracranial, which includes local complications, extension into the soft tissues, or extension into the orbit, and intracranial involvement. Despite widespread use of antibiotics and reactionary concerns about their overuse in ABRS, a small but significant percentage of patients still develop adverse sequelae of acute rhinosinusitis, and specifically of ABRS.

Several factors have been identified as risk factors for development of complications from ABRS. The majority

of patients admitted for complications secondary to ABRS present in the winter months, from January through March (83). This seasonal incidence is likely secondary to an increased incidence of viral infections in the fall and winter (83). In the pediatric population, the highest risk age group for hospital admission due to complications of ABRS is 3 to 6 years of age (83). However, among pediatric patients admitted with orbital complications of ABRS, those most at risk for intracranial extension are age 7 years or older (40). In adults, intracranial extension is more commonly seen in patients with a history of chronic rhinosinusitis (40,84,85). However, in the pediatric population, intracranial involvement almost exclusively occurs in the setting of ABRS (40,86–89). Overall, the highest risk group for intracranial complications are males during adolescence and young adulthood (10 to 29 years old) (40,86,90,91). It has been suggested that this age group is disproportionately affected because this is the age at which the valveless diploic system is at its most vascular, therefore providing a good conduit for propagation of bacterial infection (40,86,92). Additionally, it is thought that the maturing posterior table of the frontal sinus is a poor barrier to spread of organisms (86). Infants are at particular risk for the development of meningitis because, as opposed to the efficient barrier to infection provided by the mature arachnoid mater, bacteria are freely transmitted across the immature arachnoid layer (40,93). Additional information regarding Complications of Rhinosinusitis may be found in Chapter 38.

Extracranial Complications

A relatively benign sequela of acute rhinosinusitis is anosmia. Acute rhinosinusitis accounts for 18% to 36% of anosmia (94). While transient hyposmia is common in acute rhinosinusitis, permanent anosmia may also occur, though rarely (51). Women are disproportionately affected, comprising 67% of patients presenting with viral-induced olfactory loss in one study (51). Two recent studies show promising results with improvement in olfaction in over 80% of patients with sensorineural deficits in olfaction, including those related to acute rhinosinusitis, treated with systemic steroids (94,95).

Pott puffy tumor (PPT), first described by Sir Percivall Pott in 1775, is a subperiosteal abscess of the frontal bone associated with frontal osteomyelitis (40,96). The pathophysiology occurs as bacterial infection, most commonly *S. aureus*, nonenterococcal *streptococcus*, and oral anaerobes, often polymicrobial, spreading from the frontal sinuses into the frontal bone causing inflammation and suppuration of the valveless diploic veins, which propagates to the Haverian system of the inner and outer tables of the skull, resulting in localized demineralization and necrosis (40). This ultimately results in perforation of the frontal sinus anterior table, facilitating the subperiosteal pus collection and formation of granulation tissue that characterizes PPT (40). This entity is managed with a combined surgical and medical approach.

Orbital extension of acute rhinosinusitis is the most common complication in both pediatric and adult populations (40,83). In the preantibiotic era, 17% of patients with orbital infection died of meningitis and 20% became blind in the affected eye (83,97). By 1991, the incidence of blindness had fallen to 10.5%, and in a pediatric study from 2009 reviewing 157 orbital complications of ABRS, the incidence of subsequent blindness was 0.6% (83,98). The Chandler classification for orbital complications of rhinosinusitis was introduced in 1970 (97). The strength of this system is its organization as a progression of patterns that describes the pathogenesis of orbital extension of ABRS from preseptal cellulitis (I) to postseptal cellulitis (II), and ultimate progression to subperiosteal abscess (III) and finally orbital abscess (IV) (97). Preseptal or periorbital cellulitis (class I) is the most common of the orbital complications in all age groups (70%) (40). The drawback of this classification scheme is its omission of the most advanced stages of orbital inflammation, including orbital apex syndrome, retrobulbar phlegmon, retrobulbar abscess, and cavernous sinus thrombosis which may also develop as a result of complications of acute rhinosinusitis (83).

Management of secondary orbital involvement is determined according to the Chandler stage of disease. All patients need antibiotics. For patients with preseptal cellulitis over 3 years of age in whom there is assurance of follow-up, treatment may be with broad-spectrum oral antibiotics, head elevation, warm compresses, topical decongestant, and saline irrigations (40,83). For more advanced disease, empiric IV antibiotic management may begin with high-dose beta-lactamase antibiotics, with cognizance of possible resistance, or a third-generation cephalosporin (83). Most preseptal and postseptal cellulitis (grade I and II) can be successfully managed medically (83). Indications for surgical intervention include: in stage I or II disease if the patient's condition fails to improve significantly within 24 to 48 hours of appropriate antibiotic administration so that cultures may be obtained to direct antibiosis, immediately if visual acuity worsens, if the patient develops increasing proptosis and/or ophthalmoplegia, and if an abscess is demonstrated on CT (83). Subperiosteal abscesses must be evaluated individually, and the treatment plan should be tailored to the specific clinical situation. The recommended criteria for medical management of medial subperiosteal abscesses are normal vision, pupil, and retina, no ophthalmoplegia, intraocular pressure of less than 20 mm Hg, proptosis of 5 mm or less, and abscess width of 4 mm or less (40,99). These patients will need attentive monitoring, and if they have any deterioration or fail to improve clinically within 48 to 72 hours, they will likely require repeat imaging and surgical intervention (40,83,99,100). Surgical intervention for secondary orbital involvement includes endoscopic sinus surgery to drain the affected sinuses and obtain cultures.

The extent of surgery is dictated by the degree of sinus involvement (83). The approach to an abscess, if present, depends on its location within the orbit. Many subperiosteal abscesses, particularly in young children, are along the medial orbital wall due to extension from the ethmoid sinuses and can be drained at the time of endoscopic ethmoidectomy (83,101). The main limitation with an endoscopic approach in the acute setting is potential for increased bleeding, which could compromise visualization (40). If this is a concern, a traditional Lynch incision can be considered to approach the medial orbital abscess and to perform external ethmoidectomy (40). An abscess that is lateral, superior, or inferior within the orbit will likely require external orbitotomy for drainage (83). Although often involved in surgical intervention for lesser degrees of orbital infection, ophthalmologists are integral while addressing an intraconal abscess (40).

Intracranial Complications

Intracranial complications affect between 0.5% and 24% of patients admitted to the hospital with rhinosinusitis (86,102,103). The intracranial complications include meningitis, extradural abscess, subdural empyema, intracerebral abscess, and cavernous and superior sagittal sinus thrombosis (86) (Fig. 33.2A and B). Their relative frequencies have been disputed in the literature (86). Infection of the paranasal sinuses can spread to the intracranial compartment directly via osteomyelitis of the skull, by retrograde thrombophlebitis and septic emboli, or through a posttraumatic, congenital, or postsurgical defect that connects the sinuses with intracranial contents (86). The proportion of brain abscesses secondary to either an otologic or sinogenic origin has been estimated at nearly two-thirds, and although historically this predominantly comprised otologic etiology, literature suggests that sinogenic cause has become nearly as common (86,102,104–106). Despite advances in imaging techniques facilitating early detection as well as pharmaceutical and surgical developments, the morbidity and mortality of intracranial complications have remained stable since the 1980s at 5% to 21% and up to 40%, respectively (86,103–106). Morbidities include long-term neurologic deficits, cognitive impairment, cranial nerve palsy, aphasia, epilepsy, hydrocephalus, and visual and hearing loss (40).

SPECIAL CONSIDERATIONS IN THE PEDIATRIC POPULATION

Pediatric patients are particularly susceptible to all infections given their evolving and maturing immune system. They frequently experience six to eight episodes of upper respiratory infection annually, as compared to the average one to three for adults (30). Given an average conversion of AVRS into ABRS of 0.5% to 2%, they are statistically projected to have more ABRS than adults. A large retrospective review of 339 pediatric patients admitted to the hospital for treatment failure of ABRS identified the peak age-group

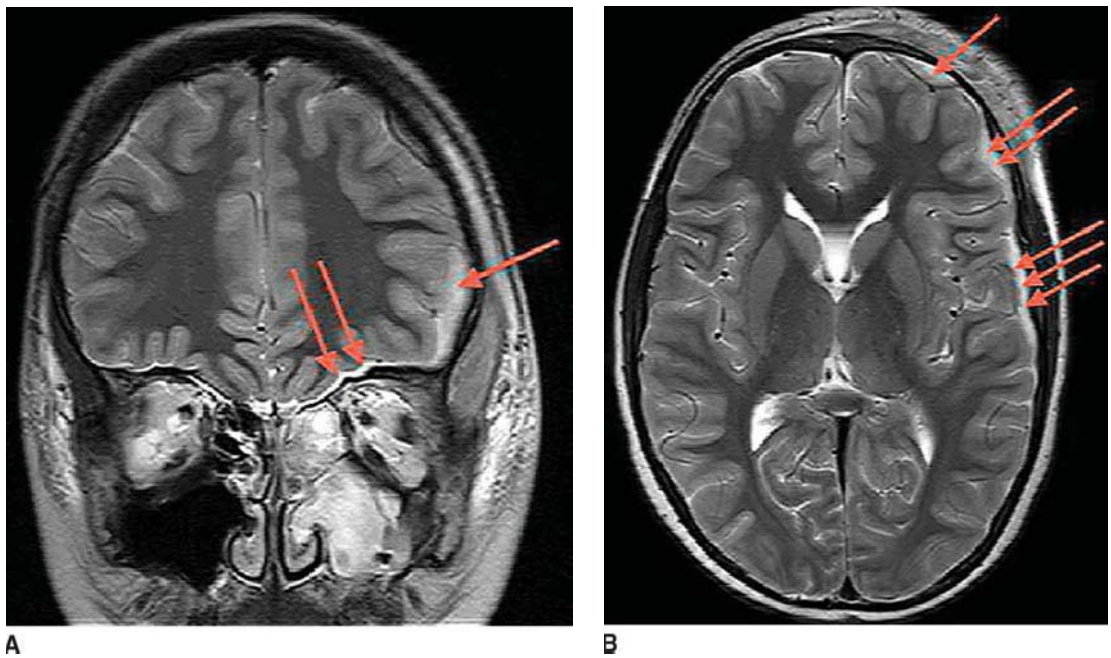


Figure 33.2 Intracranial abscess as a complication of acute rhinosinusitis. Coronal **(A)** and axial **(B)** T2-weighted MRI images of a child with epidural and subdural intracranial abscesses as a result of acute sinusitis. In the coronal image, opacification of the left maxillary and ethmoid sinus cavities can be appreciated. There is an intracranial fluid collection and meningeal enhancement along the floor and lateral aspect of the left temporal fossa (*arrows*). The axial image demonstrates epidural and subdural fluid collections along the left frontal and temporal aspects of the intracranial region (*arrows*).

for treatment failure between 3 and 6 years of age (83). This is potentially explained with a correlation to the age of first attendance at daycare, preschool, and kindergarten, with concomitant first exposure to pathogens that cause acute rhinosinusitis (83).

The patterns of complications from ABRS in the pediatric population are explained by sinus development and maturation during childhood. The maxillary sinus and ethmoid labyrinth are present at birth. Because orbital complications of sinusitis are frequently associated with ethmoid sinusitis, young children are particularly susceptible to orbital extension of disease (83). The sphenoid sinuses are frequently pneumatized by age 5, but the frontal sinuses don't appear until age 7 or 8. Over the next 5 or so years, the frontal sinuses pneumatize and mature, and accordingly intracranial complications, particularly related to the frontal sinuses, are seen most often in the preteen and adolescent years of life (83).

CONCLUSION

Although otolaryngologists are not frequently the ones providing care for uncomplicated AVRS and ABRS, it is important to be familiar with this disease process. Acute rhinosinusitis is common and has an associated tremendous economic impact. Adherence to guidelines in the treatment planning and follow-up evaluation of patients with acute rhinosinusitis will hopefully help to minimize the economic and quality of life burden associated with this disease, in addition to avoiding future patterns of multidrug resistant, increasingly virulent bacteria. Familiarity with the diagnosis and management of the life-threatening complications of ABRS is necessary as the otolaryngologist will certainly be involved in the care of the patient at that point.

HIGHLIGHTS

- Rhinosinusitis is a common illness with a large economic burden in the United States.
- The most common infectious cause of acute rhinosinusitis is viral illness. Less than 5% of viral illnesses transition into an ABRS. When ABRS does occur, the most common bacterial pathogens are *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae*.
- The three cardinal symptoms of ABRS are purulent nasal discharge, nasal obstruction, and/or facial pain, pressure, or fullness. ABRS is diagnosed when the three cardinal symptoms are present for 10 days or longer beyond the onset of upper respiratory symptoms or when there is a double-worsening of symptoms within 10 days of illness onset.
- Sinonasal endoscopy is indicated in ABRS for symptomatic patients who fail to improve on empiric therapy, who have unilateral disease, who have severe or disabling symptoms, in whom complications are suspected, or who are immunocompromised and consequently at risk for complications.
- CT of the sinuses is recommended when a complication of ABRS is suspected or an alternative diagnosis is considered. It may also be used when patients have comorbidities that predispose to complications. MRI is the gold standard imaging modality for diagnosis of intracranial extension of sinusitis.
- The recommended management for acute viral rhinosinusitis is analgesia and antipyretics, saline irrigations, and topical decongestants for 3 days or less. Topical corticosteroids can be used in addition to mucolytics or second-generation antihistamines if clinically indicated.
- The first-line antibiotic for ABRS is amoxicillin. For patients with penicillin allergy, first-line alternatives are trimethoprim–sulfamethoxazole or macrolides. Patients who have had antibiotics within 4 to 6 weeks prior or who have young children in daycare may be at increased risk for infection with resistant bacteria, and should receive high-dose amoxicillin, high-dose amoxicillin-clavulanate, or fluoroquinolone.
- The possible clinical outcomes for ABRS are resolution, development of complications, or development of chronic rhinosinusitis. The risk factors for development of sequelae of ABRS are male gender, age 10 to 29 years old, and illness during the winter months.
- The most common complication of ABRS in all age groups is orbital extension of disease, which includes the spectrum of illness from preseptal cellulitis through orbital abscess. There is a risk of blindness with extension of infection into the eye.
- Intracranial complications include meningitis, extradural abscess, subdural abscess, intraparenchymal abscess, and cavernous and superior sagittal sinus thrombosis. These have a high risk for associated morbidity and mortality and require aggressive multidisciplinary approach to management.

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Chronic Rhinosinusitis with Nasal Polyposis

34

Matthew W. Ryan

Nasal polyps (NPs) are among the oldest recorded ear nose and throat disorders, with historical references that date back to the ancient Egyptians of approximately 2000 BC. NP disease was later the subject of work by Hippocrates who gave these nasal masses their name "polypus." Today we recognize NPs to be benign nasal growths that usually arise as a result of paranasal sinus inflammation, that is, chronic rhinosinusitis (CRS). For this reason, NP disease is considered a subtype of CRS and is labeled chronic rhinosinusitis with nasal polyposis (CRSNP) (1). A variety of other terms have been applied to inflammatory sinonasal conditions with bilateral or diffuse polypoid inflammation: chronic hyperplastic sinusitis, nasal polyposis, or simply NP disease. However, NPs may also arise as isolated lesions in otherwise healthy paranasal sinuses; these solitary polyps are pathophysiologically distinct, and are not considered under the umbrella of CRSNP. Despite the fact that NP disease has been a matter of scientific interest for thousands of years, we do not yet have a widely accepted classification system for NP disorders, the diverse pathophysiologic mechanisms for NP formation are unsettled, and the ideal treatment approach continues to evolve. This chapter reviews the pathophysiology, diagnosis, and classification of NP disease. Treatment for NP disease is covered in Chapters 39 and 40.

The pathophysiology of CRSNPs may differ significantly from other forms of chronic rhinosinusitis without polyps. Thus chronic rhinosinusitis is generally subclassified as "polypoid" or : "nonpolypoid" (based upon the presence of polyps). Nevertheless, the clinical and pathologic presentation of these two entities often overlaps, resulting in a significant spectrum of inflammatory disease in the paranasal sinuses that defies distinct classification (2). Histopathologically, most NPs are noted to have pronounced eosinophilic inflammation. For this reason, allergic mechanisms were assumed to play a causative role in polyp formation. In contrast, chronic rhinosinusitis without nasal polyposis is more commonly found to have a neutrophilic inflammatory infiltrate, and bacterial infection was assumed to play a causative role. We now know that neither of these explanations is consistent or accurate. For example, CRSNP may arise as a result of disease processes that lead to chronic infection (e.g., ciliary dyskinesia, cystic fibrosis [CF]) and the inflammatory infiltrate may be either neutrophilic or eosinophilic. There are some cases in which nasal polyposis evolves out of an underlying CRS without polyps. While the distinction of polypoid and nonpolypoid CRS may be useful clinically, many studies consider them together. So our current classification system should be regarded as tentative, awaiting further clarification of the pathophysiology and appropriate subclassification of chronic rhinosinusitis (Table 34.1).

EPIDEMIOLOGY OF NASAL POLYP DISEASE

The epidemiology of NP disease is difficult to characterize because the diagnosis incorporates multiple syndromes and possible etiologies for NP formation. Questionnaire and survey studies are likely to be inaccurate, and nasal endoscopy is usually required for definitive diagnosis. Despite these limitations, data from a few well-designed studies reveal the prevalence of NP disease to be 1% to 4% (3). Autopsy studies report a higher prevalence but it is not clear that these polyps are clinically significant. NP disease appears to be more common in males and the incidence peaks in the fourth to sixth decades of life (3).

Ethnic and geographic differences may impact the incidence of the various forms of NP disease. Allergic fungal rhinosinusitis (AFRS), which may represent 5% to 10% of CRSNP cases taken to surgery, appears to be more common in warm or humid climates, and is predominantly a disease of teens and young adults. Noneosinophilic NP disease appears to be more common in Asian populations (4).

TABLE 34.1 CLASSIFICATION AND FEATURES OF VARIOUS FORMS OF NP DISEASE

Choanal polyp	Isolated, extends from site of origin (antrum, sphenoid, ethmoid, septum) to the posterior choana
CF	Children, neutrophilic infiltrate, sinus hypoplasia, or mucoceles
AFRS	mucocele formation with eosinophilic mucin, asymmetric sinus involvement, bone erosion, teens, and young adults
Eosinophilic mucin rhinosinusitis	eosinophilic mucin, symmetric sinus involvement, asthma, middle age, and older adults
AERD	asthma, history of asthma exacerbation after NSAID ingestion, symmetric sinus involvement
Churg-Strauss syndrome	asthma, peripheral eosinophilia >10%, vasculitis

TABLE 34.2 DIFFERENTIAL DIAGNOSIS OF NP DISEASE

Angiofibroma
Inverted papilloma
Encephalocele
Nasal glioma
Malignant tumor

Whether there is a difference in incidence of NP disease in Asian versus European peoples is unclear.

Age is an important factor in the incidence of various forms of NP disease. Nasal polyposis in childhood is very rare with an estimated incidence of 0.1% to 0.2%. For this reason, the discovery of an NP in a child should prompt an evaluation to secure an accurate diagnosis and rule out causative conditions such as CF. Antrochoanal polyps account for approximately 5% of polyp cases and present more commonly in young adults (3). AFRS, an important subtype of CRSNP (discussed further in Chapter 37), is also predominantly a disease of teenagers and young adults. Patients with other (non-AFRS) eosinophilic mucin rhinosinusitis tend to be middle aged (average age 48) (5).

Genetic predisposition quite plausibly accounts for at least some cases of NP disease, given the heritability of other eosinophilic inflammatory diseases such as allergic rhinitis and asthma. A genetic basis is also clearly established for diseases that are known to cause NPs, such as CF and Kartagener syndrome. While this topic has not been extensively investigated, one study found that 25% of NP patients had a first degree relative with NP disease (6). However, the majority of NP disease is not clearly heritable via Mendelian genetics.

CLINICAL PRESENTATION

NPs cause symptoms that are typical of other forms of chronic rhinosinusitis. Most patients will have months or years of progressively worsening sinonasal symptoms before they are diagnosed. In some cases, patients without a history of significant sinonasal symptomatology will present with continuous symptoms that can be traced back to an initial inciting event—usually a severe upper respiratory infection or flulike illness. Nasal obstruction, hyposmia, and rhinorrhea are common symptomatic complaints, but nasal congestion, facial pressure or headache, and postnasal drainage are also common. Symptoms alone are unreliable for the diagnosis of polypoid CRS, but smell dysfunction seems to be one feature that is more commonly encountered in CRSNP. This smell dysfunction may be a result of obstruction of airflow into the olfactory cleft or direct inflammation of the mucosa of the olfactory cleft.

The definitive diagnosis of NP disease requires histopathologic examination. A wide variety of tumors and other lesions can mimic NP disease (Table 34.2). These polyp mimics tend to be solitary and unilateral. A suspected polyp that is isolated or unilateral should be further evaluated with computed tomography (CT) imaging followed by biopsy. In most cases of CRSNP the polyps are present bilaterally, owing to their inflammatory etiology, and a clinical diagnosis can be made with information from the history and examination.

Large NPs may be visible on anterior rhinoscopy. Polyps appear as smooth rounded masses with a pale to yellow coloration, usually occurring in clusters (Fig. 34.1) The polyps may be almost translucent. However, there is a great variability in NP appearance with some having an erythematous or irregular mucosal covering. It must be noted that depending upon the degree and type of inflammation,

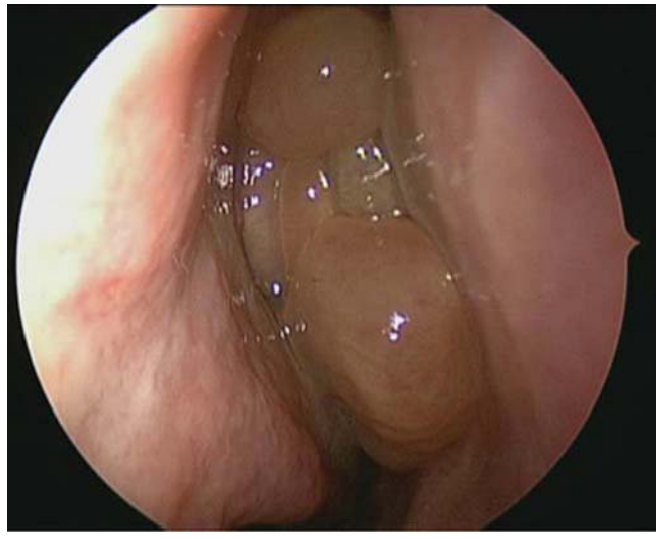


Figure 34.1 Endoscopic appearance of NPs in right nasal cavity, obscuring the middle turbinate.

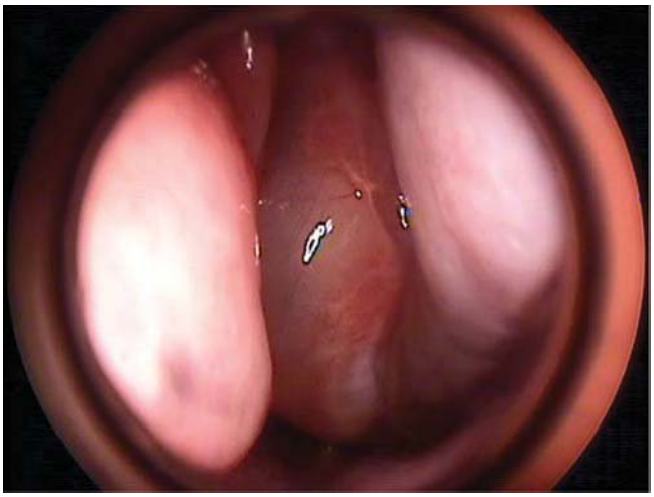


Figure 34.2 Endoscopic view of a smooth, rounded, pale, polypoid mass filling the left nasal cavity and extending almost to the nasal floor. Imaging revealed this mass to be a meningoencephalocele.



Figure 34.3 Endoscopic view of dense golden eosinophilic mucin in the right middle meatus with generalized nasal edema.

certain NPs may be indistinguishable from tumors. Likewise, some neoplastic lesions or encephaloceles may have an appearance very similar to an NP (Fig. 34.2). Thus in cases of suspected NP disease, imaging, biopsy, or close follow-up are indicated. Clinically significant NPs may not be visible on anterior rhinoscopy, however.

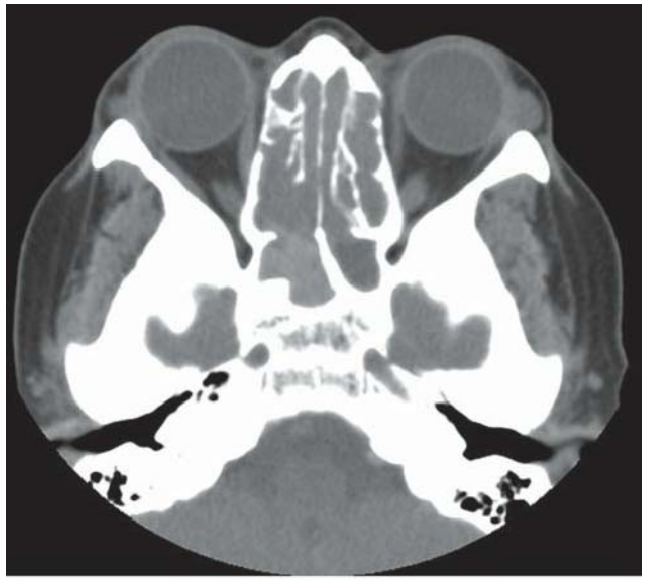
In most cases, NPs are only revealed with thorough nasal endoscopy. The development of office endoscopy has greatly improved our ability to diagnose and monitor the activity of NP disease. With the magnification and illumination of endoscopy it is possible to identify smaller polyps. Polyps usually arise from the lateral nasal wall in the middle meatus or sphenoethmoidal recess. Those polyps that originate lateral to the middle turbinate usually take their origin from the frontal, anterior ethmoid, or maxillary sinuses. Polyps medial to the middle turbinate are usually arising from the posterior ethmoid or sphenoid sinuses. In rare cases, polyps may originate on the nasal septum or from the olfactory cleft. In general, however, a nasal mass that appears to arise or take its origin from the nasal mucosa is less likely to be a benign polyp. NP disease may also be seen in conjunction with abnormal mucus secretions or purulent exudates. Eosinophilic mucin, which is a feature of eosinophilic mucin rhinosinusitis and AFRS, may sometimes be seen on endoscopy, especially in operated patients with an exacerbation of their inflammatory disease. Grossly, eosinophilic mucin is dense, gelatinous to clay-like with color that ranges from yellow to fluorescent green to brown (Fig. 34.3). The finding of eosinophilic mucin may point to one of these diagnoses but is not otherwise diagnostically useful.

As a clinical tool, nasal endoscopy is extremely helpful to monitor the disease burden in patients with CRSNP. Subjective symptoms are a notoriously poor predictor of polyp size or inflammatory disease burden. The treatment approach for CRSNP is discussed in Chapters 39 and 40. In general, while a patient with CRSNP is undergoing medical treatment or being followed up after sinus surgery, regular endoscopic examinations are warranted to evaluate the degree of sinus inflammation and polyp burden. Symptoms alone may not provide adequate warning of significant polyp recurrence until nasal airway obstruction or hyposmia recur. Accurate assessment of disease activity is best performed with surveillance endoscopic evaluations. Medical therapy can then be adjusted based upon the degree of sinonasal inflammation as well as the patient's symptom burden.

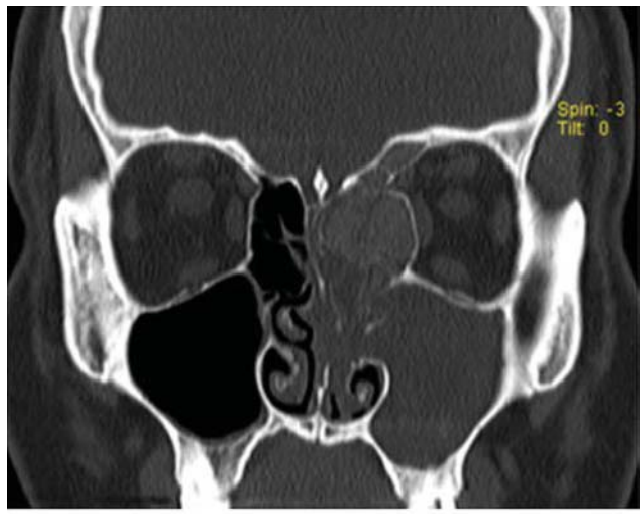
Imaging studies are an important component of the diagnostic workup of suspected NP disease. For sinonasal imaging, noncontrast CT is the study of choice. Imaging serves a variety of purposes in this setting. Nonpolyp lesions such as meningoencephalocele or nasal glioma can be distinguished from polyps based upon their location and associated skull base defects. Some tumors such as inverted papilloma and juvenile angiofibroma have characteristic imaging features. In CRSNP, CT enables a delineation of the involved sinuses, can reveal the presence of eosinophilic mucin, and can identify mucoceles, lamina disruption, or skull base erosion that may alter the treatment approach (Fig. 34.4). This imaging provides important anatomic information if surgery is performed. CRSNP causes a significant quality of life (QOL) burden, but is not usually a threat to life or bodily function. Imaging can identify those cases in which a conservative treatment approach is reasonable as well as cases in which more immediate surgical intervention is advisable (e.g., mucocele formation, intraorbital or intracranial expansion of disease). Magnetic resonance (MR) imaging is not usually necessary for the evaluation of NP disease. While MR can delineate polyp from retained secretions, establish a diagnosis of meningoencephalocele, and determine the extent of sinonasal neoplasms, the bony detail of the paranasal



A



B



C

Figure 34.4 Coronal CT images of three different phenotypes of NP disease, **(A)** chronic hyperplastic rhinosinusitis with nasal polyposis, **(B)** eosinophilic mucin rhinosinusitis with hyperdensity in the right sphenoid sinus corresponding to eosinophilic mucin, and **(C)** AFRS with left ethmoid mucoceles containing eosinophilic mucin, lamina papyracea displacement, and obvious asymmetric sinus involvement.

sinuses is lacking. Therefore MR imaging is reserved for special circumstances.

SEVERITY CLASSIFICATION IN NASAL POLYP DISEASE

The severity of NP disease can be measured along several different axes. Like many other chronic medical conditions, the symptom burden of CRSNP is only loosely correlated with objective measures of disease severity. From a patient's standpoint the symptom burden and QOL impairment are paramount. However, the treating physician must also use information from objective measures to formulate an appropriate treatment approach.

Symptomatic burden in CRSNP can be assessed with a variety of tools including nonvalidated symptom scales and validated disease-specific QOL instruments such as the sinonasal outcome test and rhinosinusitis outcome measure (7). These tools may be used during follow-up visits to assess patient symptom burden over time, and this information should be integrated with objective information to make appropriate adjustments in treatment.

Nasal endoscopy is the most useful objective tool for assessing the burden of inflammatory polyps in the nose and paranasal sinuses. Reliable estimation of polyp size is facilitated by the use of a grading system. One such method described by Lildholdt et al. (8) estimates the bulk of NPs in relation to fixed anatomical landmarks within the nose. A 0–3 grading system is used where 0, no polyps; 1, small polyps not reaching the upper edge of the inferior turbinate; 2, medium sized polyps reaching between the upper and lower edges of the inferior turbinate; and 3, large polyps reaching below the lower edge of the inferior turbinate. However, other similar grading systems have been devised with different scales (e.g., 1–4); therefore, it is important to describe the grading system used when reporting findings (8,9).

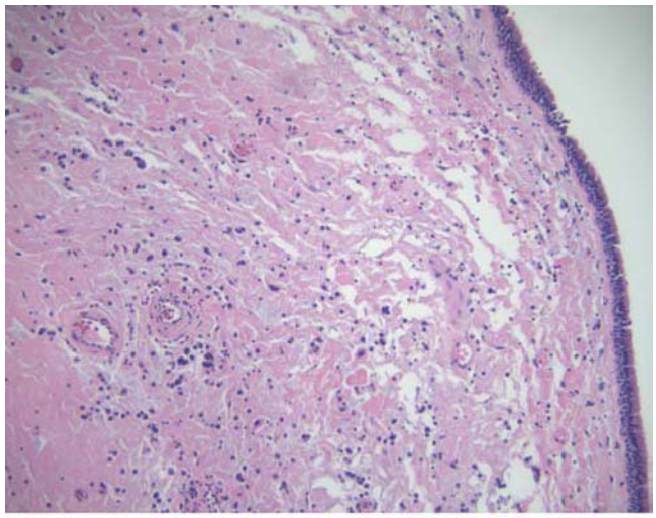
NATURAL HISTORY OF NASAL POLYP DISEASE

The clinical course of CRSNP is highly variable with some patients bothered only by nasal obstruction and others with a pattern of recurrent acute exacerbations that may represent episodes of obstructive bacterial sinusitis. In general, however, many patients with CRSNP will have functionally obstructed sinuses without associated bacterial sinusitis episodes. The natural history of most forms of NP disease is uncertain. Some NP diseases like antrochoanal polyp may be "cured" with a single surgery. Other individuals who develop NP disease in youth appear to "grow out of" their problem over a number of years. Yet others may develop the disease in middle age or later and appear to have an inexorable chronic disease that requires multiple surgeries and repeated courses of systemic steroids. Most CRSNP requires a disease management approach that incorporates current and future burdens of disease. The goals of treatment are to minimize the symptomatic burden over time, prevent rare complications, and minimize the impact of treatment—usually this means minimizing the number of surgeries required over time and minimizing the use of systemic steroid bursts.

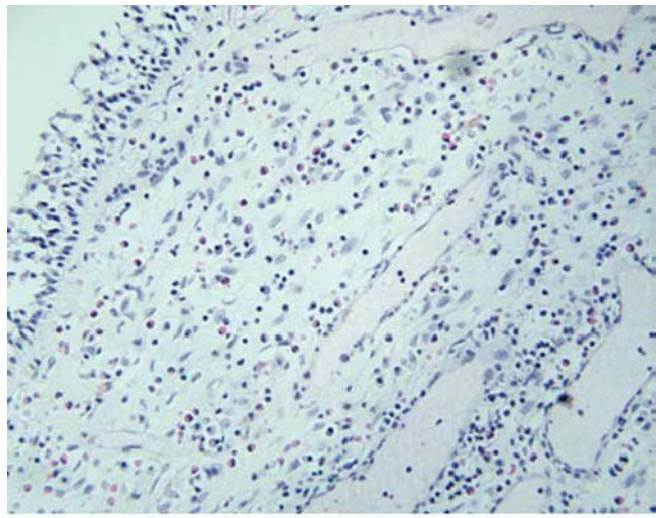
CRS with NP has a highly variable prognosis and we lack the tools to determine who will best respond to available therapies. For these reasons the etiopathogenesis of NP disease has generated considerable interest.

HISTOPATHOLOGY

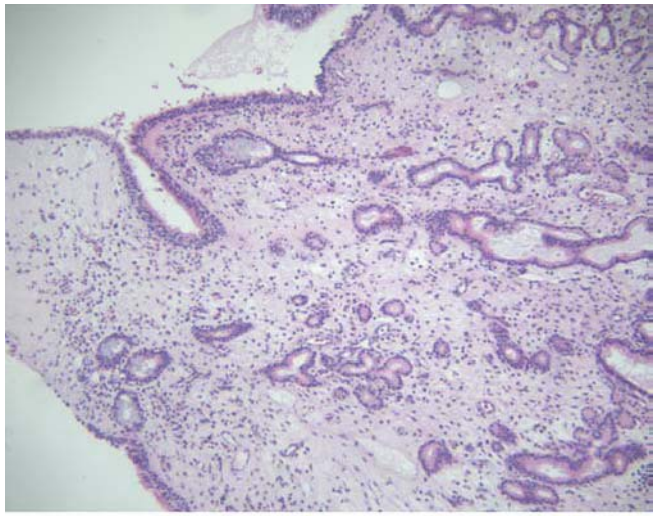
The grape-like masses of NPs are composed of respiratory epithelium with a variable degree of basement membrane thickening, encasing an underlying stroma that differs markedly from normal sinus submucosa. The histologic appearance of NPs is not specific for an underlying etiology of disease. The underlying stroma of NPs has historically been divided into three subtypes: (a) edematous, eosinophilic, (b) fibroinflammatory, and (c) glandular (Fig. 34.5). Of these, the edematous, eosinophilic polyps are the most common, representing up to 85% of polyp specimens. These consist of scattered fibroblasts with tissue edema and a variable infiltrate of mononuclear cells and other granulocytes such as



A



B



C

Figure 34.5 Histopathology of NPs. H&E stained photomicrographs, **(A)** fibroinflammatory polyp (40×), **(B)** edematous, eosinophilic polyp (100×), and **(C)** glandular polyp (40×).

neutrophils and mast cells. The overlying epithelium may have a variety of changes including ulceration, squamous metaplasia, epithelial hyperplasia, or goblet cell hyperplasia. This eosinophilic, edematous histopathology may be seen with a wide variety of conditions that are associated with NP disease including aspirin exacerbated respiratory disease (AERD), AFRS, Churg-Strauss syndrome, and CF. However, polyps in CF are more likely to have significant neutrophilia and therefore labeled "neutrophilic polyps." The fibroinflammatory polyp makes up 10% of NPs and is characterized by submucosal fibrosis with variable mixed inflammatory infiltrate. It is possible that fibroinflammatory polyps are "old" polyps that have undergone secondary fibrotic change. Glandular polyps are the rarest and share some histopathologic overlap with seromucinous hamartoma and respiratory epithelial hamartoma (10). Further examination of the histopathology of NPs with correlation to underlying pathophysiologic states and the clinical course of disease may one day provide the opportunity to more appropriately classify NP diseases and improve our prognostic capability. However, currently there do not appear to be histologic predictors of response to treatment or prognosis.

ETIOLOGY

A variety of theories have been offered over the millennia to explain the development of NPs including an imbalance of humors, obstruction of glandular ducts, lymphatic or vascular blockage, glandular neoplasia, and epithelial rupture with lamina propria prolapse. While it is now recognized that inflammation is an important feature of NP disease we still do not understand why only some patients with CRS develop NPs. Similarly, the anatomic events that lead to polyp formation are unclear. Polyps represent a common phenotypic endpoint that results from a variety of proinflammatory internal derangements of immunity or external triggers for inflammation (Table 34.3).

The inflammation in eosinophilic NPs (which makes up the majority of polyp types in Western populations) has been well characterized from a cellular and molecular standpoint. Inflammation in most CRSNP includes an infiltrate of chronic inflammatory cells with a predominance of eosinophils, lymphocytes, and increased expression of proeosinophilic cytokines (e.g., interleukin-5 [IL-5], granulocyte-macrophage colony stimulating factor) and chemokines (e.g., eotaxin, RANTES, MCP 3 and 4). Studies of NP inflammation have focused on mediators that regulate the recruitment, activation, and survival of eosinophils, and the effect of eosinophil products on polyp formation and growth.

Recent attention has also been directed toward the role of T cells as directors of NP inflammation. T cells are the predominant lymphocyte in NPs (11,12). The role of T lymphocytes in NP disease may depend on many factors including the phenotype (e.g., eosinophilic mucin rhinosinusitis), histology of the polyp (eosinophilic vs. neutrophilic), associated conditions such as allergy, asthma, and aspirin sensitivity, as well as genetic, racial, and ethnic differences (13–16).

Interest in T cells as important cellular actors in the inflammation in CRSNP has been fueled by the theory that superantigen stimulation of T cells drives the inflammation in NP disease. Bachert et al. (17) were the first to show that staphylococcal enterotoxins were potential contributors to the pathophysiology of CRSNP. The sinonasal cavities of CRSNP patients are frequently colonized by *Staphylococcus aureus*, which can secrete protein enterotoxin superantigens (18). Superantigens bind to the T-cell receptor/MHC class II receptor complex in a nonspecific manner and trigger cellular activation in up to 30% of the available lymphocyte pool. Mucus from CRSNP patients has been found to contain toxin producing *S. aureus* (18), and NP T cells show evidence of clonal expansion in response to stimulation by local staphylococcal enterotoxins (19–21). Additionally, staphylococcoal enterotoxins stimulate proinflammatory cytokine secretion by NP tissue *ex vivo*, with a reduction in immunomodulatory cytokines (IL-10, TGF-β1) (22). Regulatory T cells (Treg) are thought to suppress TH2 type inflammation, and defective or deficient Treg function may be partially responsible for the inflammation in eosinophilic airway diseases like CRSNP (23).

A variety of other mechanisms of disease are also being explored as potential causative factors in CRSNP. Chronic infection with biofilm forming bacteria, derangements of innate immunity, and dysfunctional IgE homeostasis are all potential mechanisms that may cause inflammation leading to NP formation. While our current understanding of the etiology of CRSNP is incomplete, clinicopathologic correlation is improving our differentiation of the several phenotypes of NP disease (24).

TABLE 34.3 CONDITIONS ASSOCIATED WITH NP DISEASE

Asthma
AERD
CF
Churg-Strauss syndrome
Ciliary dyskinesia
Allergy

NASAL POLYPS AND ALLERGY

For many years, allergy was presumed to be a causative factor in NP disease. This linkage is plausible given the eosinophilic inflammation in NPs, and the known role of allergy as a mechanism for the production of eosinophilic inflammation. Ample evidence links "allergic-type" inflammation, (i.e., the presence of eosinophils, IgE, and IL-4, IL-5, and IL-13) with CRSNP. A number of studies support this connection. For example, Newman et al. (25) showed

a correlation between severity of sinusitis on CT scan and asthma, allergy, and peripheral eosinophilia. However, detailed investigation has failed to consistently show that individuals with allergic rhinitis alone have an increased prevalence of NP disease (1). Approximately half of CRSNP patients have allergic sensitization (which is similar to the prevalence in the general population). Cross-sectional studies have not shown that skin test positivity correlates with severity of disease or responsiveness to treatment in CRS (26–28). Finally, there are no randomized controlled trials of immunotherapy for the treatment of NP disease.

The conflicting reports raise the possibility that atopic disease may only be important in a subset of patients with NP disease, or that systemic specific IgE does not relate to the local inflammatory milieu within the polyp. For many years it has been recognized that tissue IgE levels are elevated in NPs irrespective of allergy test results (2). Local IgE production within NP tissue may be involved in the pathophyisology of some polyp disease, even in the face of negative skin testing. For example, elevated, specific, and total IgE levels have been correlated with tissue eosinophilia in NP disease (17). Local nasal allergy without positive skin prick testing or serum specific IgE directed against allergens, what is now called "entopy," may explain in part the lower prevalence of "allergy" reported in some studies of NP disease (29). At present, allergy should be addressed as a comorbid condition with CRSNP and treated appropriately.

NASAL POLYPS AND ASTHMA

CRSNP and asthma are significantly linked. From an epidemiologic standpoint these two conditions frequently coexist. Approximately 7% of asthma patients have NPs, and it is estimated that 50% of NP patients have asthma. This relationship appears to be independent from allergic sensitivity (30). In addition to the long recognized clinical association of asthma and NP disease, histopathologic and molecular findings in asthma and NPs are similar. The similarity of these two conditions reinforces the concept of the "unified airway." That is, asthma and chronic rhinosinusitis may be separate clinical manifestations of a single systemic inflammatory disease. This linkage is further supported by the observation that treating upper airway inflammatory disease results in reduced burden of disease in the lower airway (30). Multiple uncontrolled cohort studies have shown that surgical treatment of chronic rhinosinusitis improves asthma. The relationship between CRS and asthma is further explored in Chapter 36.

FUNGI AND NASAL POLYP DISEASE

Fungi may be one extrinsic trigger for sinonasal inflammatory disease. The nasal cavities are commonly exposed to inhaled fungal spores, and it has been hypothesized that fungi serve as an extrinsic trigger for most eosinophilic chronic sinusitis, including NP disease.

In 1999 Ponikau et al. (31) proposed that the inflammation in chronic sinusitis may be a nonallergic immunologic response to fungi within nasal secretions. This theory, known as the "fungal hypothesis," generated significant interest because it offered an explanation for the extrinsic trigger of persistent inflammation in chronic sinusitis patients. This theory is supported by an *in vitro* study that demonstrated that peripheral blood mononuclear cells from chronic sinusitis patients exposed to Alternaria antigen secreted greater amounts of IL-5 than control subjects, suggesting that chronic sinusitis patients develop an inflammatory response to fungi that is not seen in normal subjects (32). The important corollary of the fungal hypothesis is that antifungal treatment administered either topically or systemically might be an effective treatment approach for chronic rhinosinusitis.

The inoculation of fungal spores into the nose is a daily event and multiple studies have shown that fungi can be cultured from most normal and "diseased" noses (31,33). Thus the presence of viable fungi within nasal secretions does not imply causation of disease. A more direct way to establish causation is to examine the clinical benefits of eradication of fungi. Indeed, initial uncontrolled cohort studies suggested that amphotericin B nasal irrigation improved symptoms and endoscopic findings in chronic sinusitis patients (34). However randomized controlled trials have failed to identify a benefit of antifungal treatment. A randomized trial showed that a 6-week course of oral terbinafine at 2.5 times the usual daily dosage did not improve symptoms or radiologic findings in chronic sinusitis patients (35). Multiple randomized trials of topically administered amphotericin B utilizing sprays and irrigations with different dosing schedules and treatment durations have also shown that this approach is not an effective treatment for chronic sinusitis (36–38).

While the fungal hypothesis has not be disproven, a study attempting to replicate the universal IL-5 response to Alternaria in PBMCs from patients with chronic sinusitis revealed a more heterogeneous response than that found by Shin et al. Specifically, this IL-5 response varied based upon disease state, allergic status, and geographic location of the patient (39). It remains to be determined whether antifungal treatment might be effective in certain subpopulations with chronic sinusitis. But current evidence suggests that identification and eradication of resident fungi within the sinonasal cavities may not be an effective approach for most forms of eosinophilic chronic sinusitis, and the role of fungi in triggering chronic sinus inflammation is unclear.

ASPIRIN EXACERBATED RESPIRATORY DISEASE

AERD, also known as aspirin-triad disease, or Samter triad, is an adult-onset disorder of rhinosinusitis, nasal polyposis, and asthma. Urticaria, angioedema, and anaphylaxis

are additional clinical manifestations in some individuals. Affected individuals can usually recount one or more episodes of an "asthma attack" after the ingestion of aspirin or other NSAID. A wide variety of other symptoms may be induced within an hour of NSAID ingestion including rhinorrhea and nasal congestion, conjunctivitis, urticaria, laryngospasm, and abdominal symptoms. The mechanism by which NSAIDs trigger these reactions is COX-1 inhibition. Selective COX-2 inhibitors are usually well tolerated in AERD (40). NSAID ingestion does not cause the condition; the reaction to aspirin is merely the means by which condition becomes manifest, and aspirin challenge in a controlled environment is the most definitive method of diagnosis. The prevalence of AERD depends upon the population under study. It is estimated that 1% to 4% of the population may have AERD. Among asthmatics who undergo aspirin challenge the prevalence rises to 10% to 20%, and in asthmatics with chronic rhinosinusitis/nasal polyposis 30% to 40%. Among asthmatics who report a prior NSAID reaction, challenge studies will be positive in 66% to 97% (40). AERD usually presents initially with symptoms of chronic rhinitis followed by the development of asthma and eventually nasal polyposis, but this sequence is by no means universal as some subjects have preexisting allergic rhinitis or asthma. About 20% of all patients with CRSNP have aspirin sensitivity (41). The condition appears to be more common in women with an onset in the 30s to 40s. The condition does not appear to be familial, with only 1% reporting a family history of the disease (40).

The pathogenetic mechanisms of aspirin sensitivity are incompletely understood but include an abnormal metabolism of arachidonic acid in the cyclooxygenase and lipoxygenase pathways. This results in an overproduction of proinflammatory cysteinyl leukotrienes and prostaglandin D_2 and reduction in the production of anti-inflammatory prostaglandin E_2. These aberrations lead to eosinophilic upper and lower airway inflammation (42). These alterations have been demonstrated in NPs. For example, leukotriene-forming enzyme genes are upregulated in NP tissue with a resulting increase in cysteinyl leukotriene concentrations (43).

While AERD has a spectrum of severity, these patients are generally felt to have a particularly severe form of disease that is difficult to manage (44). Aspirin-sensitive patients are more likely to require multiple endoscopic surgeries to manage their disease (45). Management consists of leukotriene modifiers (montelukast, zafirlukast, and zileuton), topical or systemic corticosteroids, endoscopic sinus surgery, and aspirin desensitization

CYSTIC FIBROSIS

CF is an autosomal recessive disease caused by mutations of the CFTR gene on chromosome 7q31. The molecular defect leads to defective chloride channels and increased mucus viscosity in the respiratory tract, and hyperviscosity of mucus leads to severe dysfunction of mucociliary clearance in the sinonasal cavities with secondary infection, inflammation, sinus blockage, and polyp formation. Infectious sinusitis, usually due to *Pseudomonas* and *S. aureus*, leads to accumulation of DNA from neutrophils recruited to the infected tissue further increasing the viscosity of secretions. Up to 5% of the Caucasian population carries the gene, and one in 20,000 infants are affected. Nasal polyposis is rare in children but may be present in 5% to 86% of CF children (gysin). Essentially all patients with CF have sinus inflammation whether they are symptomatic or not. Interestingly, the sinonasal consequences of the CF mutation may not be confined to homozygotes with two abnormal genes. In a case-control study, 7% of CRS patients had a CF mutation, while non-CRS controls had a 2% rate of mutation of one allele (46). In another study (47), 53% of CF carriers self-reported CRS. These findings suggest that in some patients, heterozygosity for a CF gene may be a contributing factor in the development of CRS.

The goals of medical and surgical management of CRSNP in CF patients are altered by the disease process. The sinonasal mucosa usually fails to normalize after appropriate medical and surgical treatment (48,49). Surgery in CF CRS is indicated for medically refractory polyposis with nasal obstruction, pulmonary exacerbations associated with sinusitis, to improve sinus health in anticipation of transplant, and for mucoceles. The pattern of rhinosinusitis also leads to frequent anatomic changes such as medial displacement of the lateral nasal wall, demineralization of the uncinate, frontal and sphenoid hypoplasia, and mucocele formation. Chronic sinusitis in CF is notorious for recurrence and refractoriness to treatment.

Surgical series have documented high rates of polyp recurrence and return to baseline symptoms within the first few years after surgery (50,51).

However no studies are available that compare CF to non-CF patients with CRSNP, with regard to symptom severity or polyp recurrence.

CONCLUSION

Rather than being a single disease, CRSNP is a clinical phenotype that results from a variety of pathologic conditions that cause sinonasal inflammation. The inflammation that leads to NP formation is heterogeneous though eosinophilic inflammation predominates. AERD, ciliary dyskinesia, and CF are clearly causative factors in NP formation, but most polyp disease remains idiopathic. A variety of external triggers or intrinsic derangements of immunity are likely involved in these cases. NPs are usually diagnosed on clinical grounds, but should be carefully differentiated from other sinonasal mass lesions with imaging or biopsy in select circumstances.

HIGHLIGHTS

- NPs are a common manifestation of a variety of pathologies including infection, mucociliary dysfunction, deregulated eosinophilic inflammation, atopy, and altered eicosanoid metabolism
- NPs should be clinically distinguished from other sinonasal masses through imaging, biopsy, or close follow-up
- While NP disease is commonly associated with atopy, the role of specific allergy as a causative or disease modifying factor is controversial
- Children with NPs should be evaluated for CF
- The histopathology of NPs is not predictive of treatment outcome or prognosis
- Eosinophilic mucin rhinosinusitis is a subtype of NP disease characterized by the accumulation of dense eosinophil-rich mucin in the paranasal sinuses. This condition may be confused with allergic fungal sinusitis.

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35 Nonpolypoid Rhinosinusitis: Pathogenesis, Diagnosis, Staging, and Treatment

Zara M. Patel *Peter H. Hwang*

Rhinosinusitis is one of the most common diseases diagnosed in the United States. Approximately 20 million cases of acute bacterial rhinosinusitis (ABRS) are diagnosed annually (1). In addition, more than 30 million people suffer from chronic rhinosinusitis (CRS). This corresponds to an annual prevalence of 13% to 16%, which has been increasing (2). CRS, therefore, is one the most common chronic conditions reported in the United States, more prevalent than asthma, heart disease, diabetes, or headache.

The costs associated with rhinosinusitis are substantial and are also increasing. Direct health care expenditures associated with acute rhinosinusitis are estimated at $3.5 billion annually, while those of CRS total $4.3 billion (1,3). These figures do not take into account indirect costs such as lost or restricted workdays or decreased productivity. For the individual CRS patient, this represents an approximate annual cost of $1,539 (4).

CRS can significantly worsen patients' quality of life. When compared to the general population, CRS patients report more pain, less vitality, and decreased social functioning. Outcomes studies have shown that patients with CRS have worse scores in several quality of life domains compared to patients with chronic obstructive pulmonary disease, diabetes, and congestive heart failure (5).

Our understanding of the pathophysiology of CRS has improved dramatically over the last decade, although these findings have inevitably led to even more questions about CRS etiologies. Progress in basic science coupled with technologic improvements in endoscopy, imaging, and surgical technique have progressively enhanced our ability to diagnose and treat rhinosinusitis.

PATHOPHYSIOLOGY

Acute Rhinosinusitis

The etiology of acute rhinosinusitis is thought to be more straightforward than that of CRS. In acute rhinosinusitis, the role of viral and bacterial pathogens has been well established (1,2). Acute viral rhinosinusitis is by far more common than acute bacterial rhinosinusitis (ABRS). Adults, on an average, have two to three acute viral upper respiratory tract infections annually, many of which involve the paranasal sinuses. Specific incidence rates are not known, but it is estimated that 39% to 87% of acute viral upper respiratory tract infections result in acute viral rhinosinusitis. Rhinovirus is responsible for approximately half of the cases, with other viruses such as coronavirus, influenza, parainfluenza, respiratory syncytial virus, adenovirus, and enterovirus accounting for the rest. Of all viral upper respiratory tract infections, approximately 0.5% to 2% will become complicated by a secondary ABRS (6).

During the acute viral infection, multiple inflammatory mediators are upregulated. Acute inflammation of the sinus mucosa, manifested by mucosal hypersecretion and edema, may cause obstruction of the sinus outflow tracts. The resulting mucus stasis may provide a rich environment for bacterial proliferation. Viruses may also damage or disrupt the nasal epithelium and impair mucociliary clearance, further predisposing the patient to a secondary bacterial infection. While acute viral infection is a primary etiology of ABRS, host factors such as odontogenic infection, atopy, systemic immunodeficiency, dysfunctional innate immunity, or anatomic obstruction may be secondary predisposing factors.

The most common pathogens associated with ABRS are *Streptococcus pneumoniae* (33%), *Haemophilus influenzae*

(32%), *Staphylococcus aureus* (10%), and *Moraxella catarrhalis* (9%) (7). Since the introduction of the 7-valent pneumococcal vaccine for children, there has been a trend toward decreasing prevalence of *S. pneumoniae* isolates and increasing prevalence of *H. influenzae* isolates derived from adults with acute maxillary sinusitis (8).

Chronic Rhinosinusitis

The pathophysiology of CRS has revealed itself to be much more complex than previously assumed, and the paradigm of treating rhinosinusitis simply as a prolonged infection is long past. The contribution of inflammation to CRS pathogenesis is increasingly appreciated, with multiple varied pathways potentially leading to a common endpoint of mucosal inflammation.

The categorization of CRS subtypes has evolved to reflect an improved understanding of varied pathophysiologies in CRS. Indeed, CRS subtypes may demonstrate differential clinical responses to treatment, likely due to differing pathophysiologies. The first branching point of classification is polypoid versus nonpolypoid rhinosinusitis; as another chapter in this book covers the polypoid type, we do not concentrate on it here. Further subcategories include eosinophilic versus noneosinophilic, and finally allergic fungal versus nonallergic fungal (Fig. 35.1). As another chapter in this text covers fungal rhinosinusitis, we only discuss fungus as it may relate to other forms of CRS (9).

Our understanding of underlying mechanisms of CRS has evolved beyond the local milieu of the nose and paranasal sinuses towards a greater appreciation of systemic pathophysiology. For example, the emerging concept of unified airway disease emphasizes the mutual influence and interplay between the upper and lower respiratory tracts, with shared inflammatory mediators such as T-cell cytokines IL-4, IL-5, and IL-13 and similar leukocytic profiles, especially eosinophils (10).

Paranasal sinus inflammation can be incited by the interaction of multiple etiologies, including microbial factors, environmental factors, and host factors such as abnormalities in structure, genetics, physiology, and innate immunity (Fig. 35.2).

Microbial Factors

Although antimicrobial agents are ubiquitously used to treat CRS, the actual role that infectious organisms play in CRS has been a controversial topic over the last decade. Bacteria have been cultured from the sinuses of patients with CRS but also from those of healthy normals. With the identification of bacterial superantigens and bacterial biofilms associated with CRS, it appears that bacteria may have a much more complex role in the etiology of CRS beyond the classic pathway of infection as is seen in ABRS.

Superantigens are exotoxins produced by a wide array of infectious microorganisms that have the ability to activate a much larger subpopulation of the T-lymphocyte pool (5% to 30% as opposed to less than 0.01% activated by traditional antigens). The activation of the T cell is able to occur without antigen–peptide receptor specificity due to cross-linking of both the outside portion of the major histocompatability class II complex on antigen presenting cells as well as the T-cell receptor in its variable beta portion.

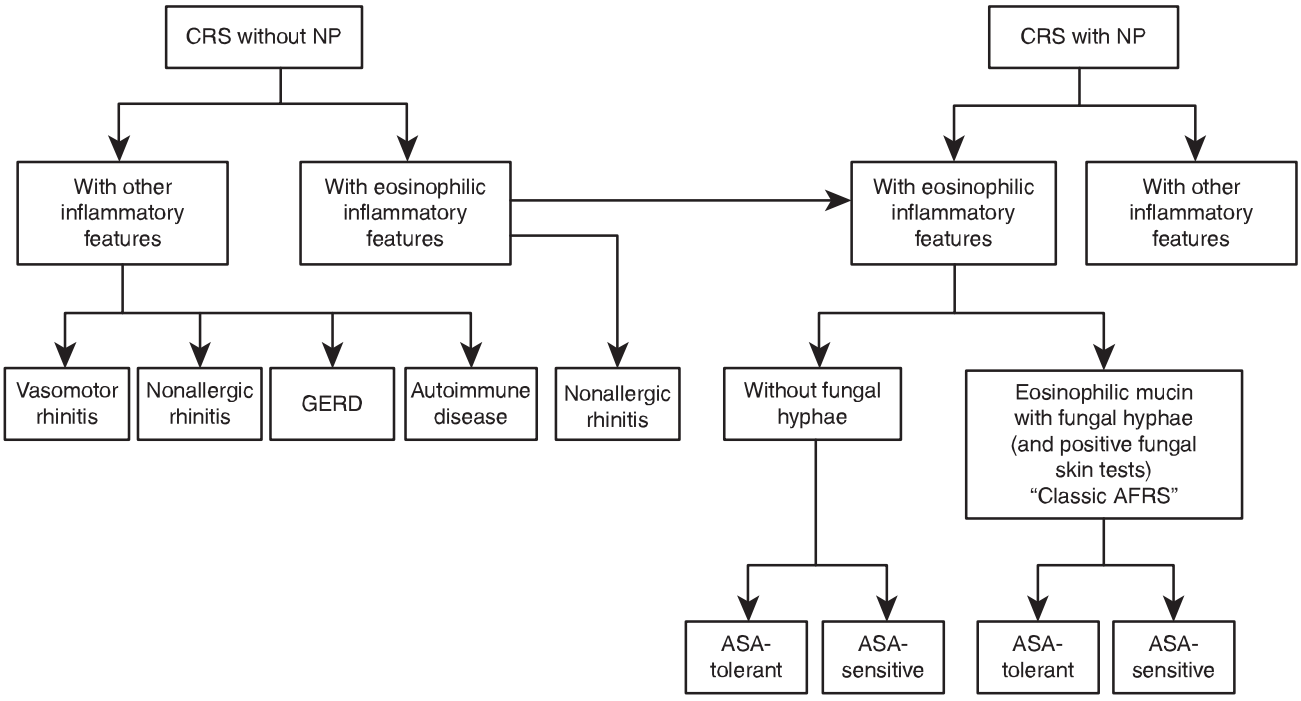


Figure 35.1 Classification for CRS.

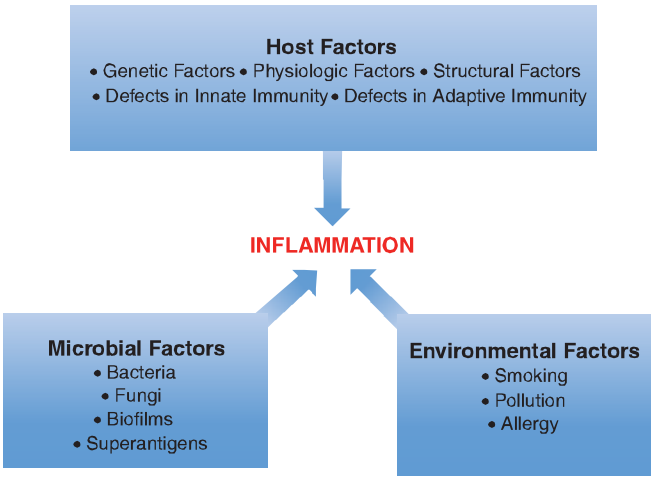


Figure 35.2 Underlying factors contributing to the pathophysiology of CRS.

Without requiring antigen specificity, T-cell–mediated inflammation may be propagated and magnified by the presence of bacterial exotoxins. Superantigens are not only linked to a dramatic upregulation in T-cell response, but have also been associated with increased eosinophils, increase in IL-5 and upregulation of PGE_2 (11).

Staphylococcus aureus is well recognized for its production of superantigens, synthesizing more than a dozen exotoxins associated with superantigen effects. Investigators have shown that patients with an elevated specific IgE to staphylococcal enterotoxins A and B had a higher incidence of asthma (12). Other investigators have expanded on these findings by identifying antibodies to other bacterial superantigens in CRS patients and by demonstrating altered steroid sensitivity in the presence of these superantigens (13,14).

Odontogenic infections are important to note as a potential etiology of CRS due to potential differences in microbial flora. The most common isolates in these cases are anaerobic streptococci, gram-negative bacilli, and enterobacteriaceae (15).

A biofilm is an organized community of bacteria adherent to an inert or living surface, embedded in a self-produced extracellular polymeric matrix. Biofilms appear to be the preferred form of bacterial existence, with only approximately 1% of bacteria existing in the free-floating planktonic form (16). The Center for Disease Control (CDC) estimates that around 65% of all human infections are caused or persist due to biofilms. Within the field of otolaryngology, biofilms have been implicated in varied diseases, including otitis media, chronic tonsillitis, adenoiditis, and device infections (such as in cochlear implants, tympanostomy tubes, and tracheostomy tubes) (17).

The extracellular matrix which constitutes biofilms is thought to protect against multiple defense systems such as antibodies, immune-system phagocytosis, and complement binding, making it up to 1,000 times more resistant to treatment when compared with the planktonic form (18). In addition, biofilms facilitate intermicrobial communication and exchange. Through quorum sensing, bacterial populations can redistribute densities to optimize utilization of nutrient resources. Biofilms also enable the interbacterial transfer of genetic information via plasmids to promote variability and adaptive mutations, such as antibiotic resistance. These factors, in addition to intrinsic nutrient gradients that are integral to the biofilm matrix, minimize the impact of environmental stressors and promote bacterial viability that can contribute to the persistence of infection in spite of prolonged therapy with antibiotics (19). Multiple studies have now shown the presence of both bacterial and fungal biofilms in patients with CRS, although the exact contribution of the biofilm to the pathogenesis of CRS remains to be clarified (20–22).

The pathogenicity of fungus in the paranasal sinuses has been well documented in cases of fungal ball, invasive fungal sinusitis, and allergic fungal sinusitis. However, the extent to which fungus may play a role in CRS at large remains a point of much debate (23).

In much the same way that bacteria can be found in the sinuses of both patients with CRS and healthy controls, fungus has also been found to be widely prevalent in the nose and sinuses of both CRS and normal populations (24). Thus the mere detection of fungus in the nose or sinuses of a patient with CRS does not indicate the pathogenicity of the fungus. The host response to fungus appears to be the differentiating factor between states of sinonasal disease and health. Shin et al. showed that by exposing peripheral blood mononuclear cells to fungal antigens *in vitro*, 89% of CRS patients showed increase in IL-5 and IL-13, but there was no such increase in controls. Interestingly, these results correlated with fungal-specific IgG, not IgE, implicating a nonallergic mechanism (25). However, Orlandi et al. found contradicting results when replicating the Shin study using CRS patients and controls from multiple geographic regions. Orlandi et al. (26) demonstrated elevated IL-5 and IL-13 production in both CRS patients as well as controls, and the IL-5 levels correlated to IgE response instead of IgG, directly contradicting the findings of the Shin study. It appears that more data is needed to make any conclusions about the extent of the association between fungus and CRS (27).

Environmental Factors

Smoking and exposure to secondhand smoke have been identified as morbid cofactors in CRS. Senior et al. found that the most significant risk factor for requiring revision sinus surgery was continued smoking. This was especially true for patients with more advanced disease. Briggs et al. (28) also demonstrated that persistent smoking is significantly associated with worse symptom outcomes after endoscopic sinus surgery. Cohen et al. (29) recently demonstrated decreased ciliary beat frequency as well as impaired transepithelial chloride secretion in both murine septal and human sinonasal epithelial cell (SNEC) cultures when exposed to cigarette smoke condensate. Two

case-control studies have now documented a significant independent association between secondhand smoke and CRS (30,31).

Other environmental pollutants can also have adverse effects on the upper respiratory tract predisposing to CRS. Longitudinal studies of clean-up workers at the World Trade Center disaster site show a clear correlation between environmental pollution exposure and disease in the upper respiratory tract, especially in patients with preexisting atopy (32).

Although there does appear to be a subset of patients with ABRS who have classic IgE-mediated allergic triggers, the association between allergy and CRS, in spite of the strong eosinophilic induction in both processes, is much less defined (33). While allergic rhinitis is a common comorbidity with CRS, the presence of allergy has not consistently been shown to affect the extent of radiographic disease, symptom severity, or the need for surgery (34).

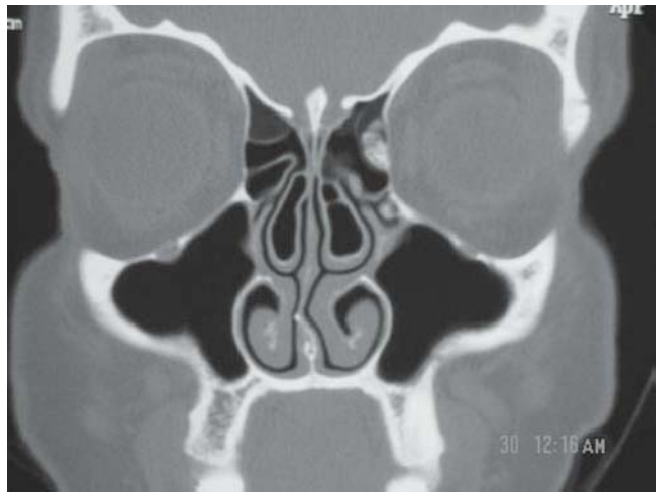


Figure 35.3 Coronal CT scan showing bilateral concha bullosa.

Structural Factors

Structural and anatomic factors were traditionally the main etiologic focus during the early years of endoscopic sinus surgery. Although multiple structural anomalies have been identified and associated with rhinosinusitis, we now know that the anatomic basis of the disease is only one of the categories of inciting factors, and these must be examined in light of other factors as described in this chapter. The term *ostiomeatal complex* (OMC) has been widely described and incorporated into our literature. It should be stressed that the OMC is a functional unit rather than an anatomic structure. It refers to the physiologic arrangement of structures into which the frontal, maxillary, and anterior ethmoid sinuses drain. Anatomically, this corresponds to the area of the ethmoid infundibulum, the middle meatus and its surrounding structures. Classic teaching suggested a pivotal role for the OMC in the establishment of CRS, and a recent study sought to test that hypothesis. Chandra et al. performed a retrospective review in which they found that more than 35% of patients meeting the definition of CRS did not manifest OMC obstruction radiologically. When present, however, OMC obstruction was associated with increased disease burden (35).

Patency of the pathways through which the sinuses drain is crucial for adequate mucociliary function and subsequent sinus drainage. The nasal and sinus mucosa produces approximately 1 L of mucus per day, which is cleared by mucociliary transport. Ostial obstruction may lead to fluid accumulation and stagnation, creating a moist, hypoxemic environment ideal for growth of pathogens.

Sinus obstruction may be caused by multiple anatomic variants, including septal deviation, concha bullosa, paradoxical middle turbinates, and infraorbital (Haller) cells (Fig. 35.3). Scarring from previous surgery or trauma can also anatomically impair sinus drainage. Craniofacial anomalies in which the anatomy of the sinuses is altered may predispose patients to rhinosinusitis. In children, foreign bodies should always be considered as another possible obstructive cause of sinusitis.

The underlying bone within the sinuses may itself also contribute to persistent inflammation or infection. Kennedy et al. demonstrated histologic changes in the ethmoid bone of CRS patients consistent with bony inflammation. Histomorphometry showed increased numbers of inflammatory cells and significantly increased bone turnover, comparable to the rate seen in osteomyelitis. Subsequently, Khalid et al. (36) found evidence of chronic osteomyelitis in the contralateral maxillary sinus of 52% of rabbits that had undergone induced unilateral maxillary rhinosinusitis. With these findings, the authors suggested that inflammation and possibly infectious agents may spread to distant sites through the bony Haversian system. Additional research is needed to determine whether these observed bony changes represent a primary causative phenomenon or a secondary reaction to the overlying inflammatory milieu.

Genetic Factors

The increased prevalence of CRS in patients with certain inherited disorders such as cystic fibrosis (CF) has led to the investigation of possible genetic mutations predisposing to CRS. A landmark study in 2000 showed that mutations in CF genes, in non-CF patients, were significantly more common in CRS patients than in controls (37). In confirmation, a recent genome-wide screen for CRS susceptibility identified a locus on 7q31.1–7q32.1, with the largest linkage signal near the CFTR gene (38). Polymorphisms in the TNF-α, MMP-9, IL-13, IL-33, and IL1A genes have been associated with increased susceptibility to CRS. Furthermore, alterations in the 6p22, 22q13, and 1q23 chromosomal regions have been demonstrated in both CRS and aspirin-sensitive asthma phenotypes, reinforcing concepts of a unified airway pathophysiology (39).

Physiologic Factors

Mucociliary dysfunction has often been cited as a precursor to CRS. Inherited disorders such as CF are associated with abnormal mucociliary clearance from the sinuses. The increased viscosity of nasal secretions in CF patients impedes adequate clearance and leads to ciliary injury, local mucosal edema, and further inflammation. Ciliary dysfunction is the hallmark of a group of disorders known as Primary Ciliary Dyskinesia. Morphologic ciliary defects, such as absent ATPase-containing dynein arms, result in ciliary dysmotility that predisposes patients to both acute and chronic rhinosinusitis. Kartagener syndrome, the most common form of Primary Ciliary Dyskinesia, is associated with a triad of chronic sinusitis, bronchiectasis, and situs inversus. The former term "immotile cilia syndrome" is no longer used in recognition of the fact that true ciliary immotility is far less common than motile but dyskinetic cilia.

Cytokines and other inflammatory mediators, along with respiratory pathogens and particulates released in patients with CRS, have been shown to impact ciliary function and propagate a cyclic loop of inflammation and ciliary dysfunction (40,41).

Acid reflux disease has long been noted by physicians in patients with CRS, but until recently, good data to support a correlation, let alone a causative association, have been lacking. DelGaudio et al. performed a prospective study looking at postsurgical patients with persistent CRS, looking for a possible role for nasopharyngeal reflux. The patients with persistent CRS had more reflux at the nasopharynx, the upper esophageal sphincter, and at the distal esophagus than controls, with the greatest difference at the nasopharynx (42). Wong et al. actively instilled acid into the esophagus of healthy volunteers, looking for a possible reflex arc to the nose. An increase in nasal mucus production occurred with instillation of both saline and hydrochloric acid into the esophagus. Although there was no clear difference between the test groups, the authors still concluded this may have demonstrated a reflex arc via the vagus nerve (43). A provocative study recently published in the gastroenterology literature was a placebo-controlled, double-blind trial in which 75 participants with symptoms of chronic postnasal drainage were randomized to treatment with 30 mg of lansoprazole twice daily or placebo (44). Patients did not have sinusitis or allergy, and they underwent ambulatory esophageal pH monitoring. After 16 weeks, the lansoprazole-treated group was 3.5 times more likely to have symptomatic improvement versus placebo, with absolute symptom improvements of 50% in the lansoprazole group versus 5% in the placebo group. Notably, the presence of heartburn symptoms or abnormal esophageal pH was not predictive of symptom improvement. While this study excluded patients with CRS, the demonstration of a therapeutic effect of proton pump inhibitors on the function of the nasal mucosa opens the door for further investigation.

CRS is a common finding in granulomatous disorders such as sarcoidosis and Wegener granulomatosis, but these are discussed elsewhere in this textbook so will not be expounded upon in this chapter. Briefly, in Wegener granulomatosis, nasal symptoms can be a presenting manifestation and often one of the most common complaints. Autoimmune disorders such as systemic lupus erythematosus, Sjogren syndrome, and relapsing polychondritis can also present with signs and symptoms of rhinosinusitis.

Immune deficiencies, whether inherited or acquired, can also contribute to sinusitis. In a retrospective review, Chee et al. (45) demonstrated immune deficiencies, which included low immunoglobulin levels and deficient T-cell function, in up to half of their patients with medically refractory sinusitis. Although IgG subclass deficiency is the most common deficiency identified, multiple entities including selective IgA deficiency, common variable immunodeficiency, and X-linked agammaglobulinemia can present with ABRS or CRS. In human immunodeficiency virus (HIV)-infected individuals, rhinosinusitis is one of the most common infections and can be more severe and treatment-resistant than in HIV-negative individuals. Hyperimmune states such as is seen in Churg-Strauss and Job syndromes can also predispose to rhinosinusitis. Even though most patients with rhinosinusitis are not immunodeficient, a history of persistent or recurrent infections despite adequate antimicrobial therapy should raise the suspicion of immune deficiency as a contributing factor.

Abnormalities in innate immunity are being increasingly well characterized and appreciated for their potential causative role in CRS. Early on in this past decade, CRS was thought to be mediated primarily by the adaptive immune system, with Th1 cells mediating neutrophilic nonpolypoid subtypes of CRS and Th2 cells driving the eosinophilic inflammatory response typified by polyposis. Recently, the interaction between innate immune functions within the SNEC and the adaptive immune system has come to light. The innate system recognizes certain pathogen-associated molecular patterns via transmembrane glycoproteins known as Toll-like receptors, which in turn switch on a signaling cascade, activating Th1, Th2 or type I interferon profile (46). Multiple antimicrobial peptides, such as lactoferrin, lysozyme, cathelecidins, defensins, SP-A and SP-D, and secretory leukocyte proteinase inhibitor are produced by the SNEC and are a major part of the innate immune system. Mucociliary clearance also plays a key role within the innate immune system, being the first defense against all inhaled particles (47).

DIAGNOSIS

In order to foster effective communication among physicians and researchers and to standardize the reporting of rhinosinusitis, the Task Force on Rhinosinusitis was created in 1996, sponsored by the American Academy of

TABLE 35.1 SIGNS AND SYMPTOMS ASSOCIATED WITH DIAGNOSIS OF RHINOSINUSITIS (1996 RHINOSINUSITIS TASK FORCE)

Major Factors	Minor Factors
Facial pain/pressure[a]	Headache
Nasal obstruction	Fever (all nonacute)
Nasal discharge/discolored postnasal discharge	Halitosis
	Dental pain
Hyposmia/anosmia	Fatigue
Purulence on examination	Cough
Fever (acute only)[b]	Ear pain/pressure/fullness

[a]Facial pain/pressure alone does not constitute a suggestive history for diagnosis in the absence of another major symptom or sign.
[b]Fever in acute sinusitis alone does not constitute a suggestive history for diagnosis in the absence of another major symptom or sign.
Adapted from Lanza, DC, Kennedy DW. Adult rhinosinusitis defined. *Otolaryngol Head Neck Surg* 1997;117:S1–S7.

Otolaryngology-Head and Neck Surgery (AAO-HNS). Their work resulted in the publishing of "working definitions" for rhinosinusitis in 1997 (48). The Task Force proposed a symptom-based format for the diagnosis of rhinosinusitis, with major and minor symptom categories (Table 35.1). According to the duration of the symptoms, rhinosinusitis was defined as *acute* when symptoms lasted 4 weeks or less, *subacute* when symptoms were present for 4 to 12 weeks, or *chronic* for symptoms lasting longer than 12 weeks. The term *recurrent acute* rhinosinusitis was reserved for patients with four or more episodes per year with disease-free intervals in between. An *acute exacerbation of CRS* was defined as a sudden worsening of symptoms in a patient already diagnosed with CRS, with return to baseline symptoms after treatment. A *strong* history consistent with rhinosinusitis would require the presence of either two major factors, or one major and two minor factors. When only one major factor or two or more minor factors were present, this constituted a *suggestive* history in which rhinosinusitis should be included in the differential diagnosis.

While these definitions have largely remained in use to the present day, there have been several efforts to further refine the working definitions of CRS. In 2003 a new task force, the Task Force for Defining Adult Chronic Rhinosinusitis, described objective criteria that must be present in addition to symptoms for a diagnosis of CRS (2). Once again in 2007, these criteria were further codified (49). These objective criteria may take the form of either physical exam findings or imaging studies (Table 35.2). Recently, consensus guidelines have been published jointly by five national societies including the AAO-HNS, the American

TABLE 35.2 DIAGNOSTIC CRITERIA FOR SINUSITIS FROM 2007 TASKFORCE

Acute Rhinosinusitis	Up to 4 wk of purulent nasal drainage (anterior, posterior, or both) accompanied by nasal obstruction, facial pain-pressure-fullness, or both: • Purulent nasal drainage is cloudy or colored, in contrast to the clear secretions that typically accompany viral upper respiratory infection, and may be reported by the patient or observed on physical examination. • Nasal obstruction may be reported by the patient as nasal obstruction, congestion, blockage, or stuffiness, or may be diagnosed by physical examination. • Facial pain-pressure-fullness may involve the anterior face, periorbital region, or manifest with headache that is localized or diffuse.
Acute Viral Rhinosinusitis	Acute Viral Rhinosinusitis (AVRS) that is caused by, or is presumed to be caused by, viral infection. A clinician should diagnose AVRS when symptoms or signs of acute rhinosinusitis are present <10 d and the symptoms are not worsening.
ABRS	Acute Viral Rhinosinusitis that is caused by, or is presumed to be caused by, bacterial infection. A clinician should diagnose ABRS when: a. Symptoms or signs of acute rhinosinusitis are present 10 d or more beyond the onset of upper respiratory symptoms, or b. Symptoms or signs of acute rhinosinusitis worsen within 10 d after an initial improvement (double worsening)
CRS	Twelve (12) weeks or longer of two or more of the following signs and symptoms: • Mucopurulent drainage (anterior, posterior, or both) • Nasal obstruction (congestion) • Facial pain-pressure-fullness • Decreased sense of smell AND inflammation is documented by one or more of the following findings: • Purulent (not clear) mucus or edema in the middle meatus or ethmoid region • Polyps in nasal cavity or the middle meatus • Radiographic imaging showing inflammation of the paranasal sinuses,
Recurrent Acute Rhinosinusitis	Four (4) or more episodes per year of ABRS without signs or symptoms of rhinosinusitis between episodes: • Each episode of ABRS should meet diagnostic criteria above

Adapted from Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg* 2007;137:S1–S31.

Rhinologic Society, the American Academy of Otolaryngic Allergy, the American Academy of Allergy, Asthma, and Immunology, and the American College of Allergy, Asthma, and Immunology (7). The guidelines address not only definitions of rhinosinusitis, but also suggest criteria for clinical research and clinical trial designs.

As with any other medical condition, the diagnosis of rhinosinusitis begins with a detailed patient history. Information that should be obtained in the initial history includes the presence of symptoms as outlined by the 1996 Task Force, duration and localization of symptoms, aggravating or relieving factors, and medications used. Any history of allergies or atopy should be addressed in depth. Details of any prior surgical interventions should be carefully elicited. Multiple, sinus-specific, validated symptom questionnaires exist, and have transitioned over the last decade from purely research-oriented tools to a helpful adjunct to patient care. Two of the more commonly used in recent publications have been the Sino-Nasal Outcomes Test-22 (SNOT-22) and the Rhinosinusitis Disability Index (50,51).

The initial portion of the physical exam consists of an anterior rhinoscopy performed with adequate lighting, either with a headlight, head mirror, or the endoscope itself. This should be performed in both the natural and decongested states to assess mucosal edema, turbinate hypertrophy, and response to topical decongestion. With fiberoptic endoscopy, our ability to examine the nasal cavity has been greatly improved (Fig. 35.4). Both rigid and flexible endoscopes may be used for nasal endoscopy, but the rigid scopes have the advantages of a wider field of vision, enhanced clarity, and the ability to use a second hand for instrumentation. In some situations, particularly in postoperative patients, a flexible endoscope may provide greater visualization of the floor of the maxillary sinus or the lateral recesses of the frontal sinus.

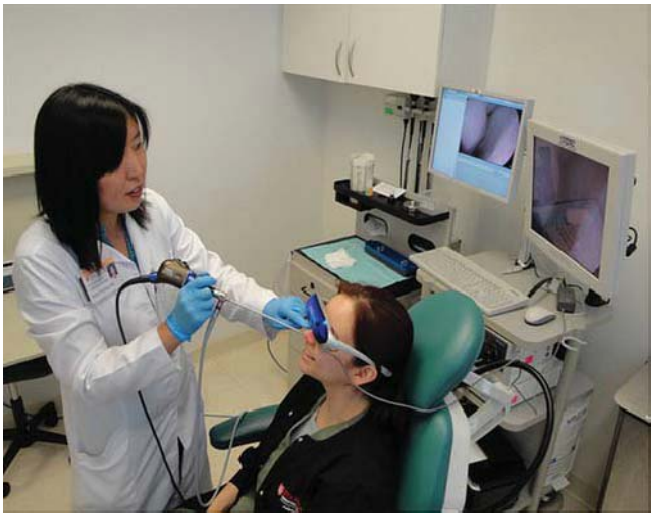


Figure 35.4 The setup for office endoscopy. While the examiner can see the endoscopic view on the monitor behind the patient, the patients themselves can watch along with specialized goggles.

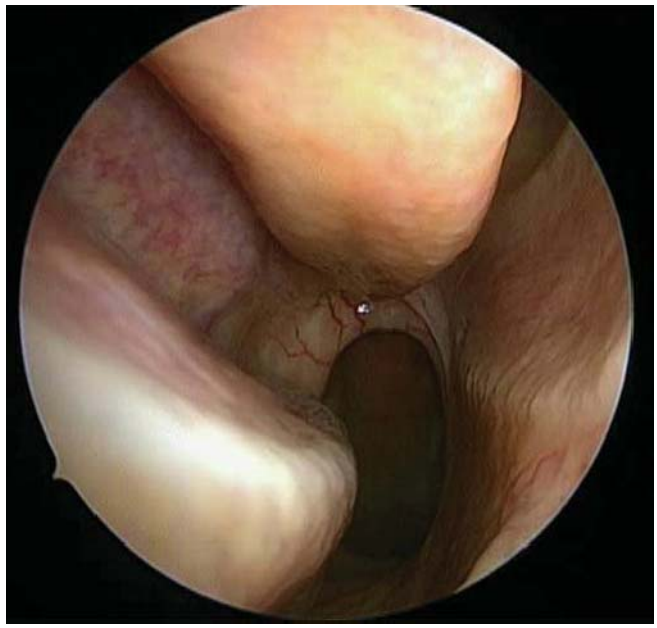


Figure 35.5 View of the inferior endoscopic pass. One can see the posterior aspect of the inferior turbinate, the postero-inferior septum and the choanae. If the endoscope were passed more posteriorly, the Eustachian tube and fossa of Rosenmuller could also be visualized.

Classically described, the nasal endoscopy is composed of three passes of the endoscope. After proper topical anesthesia and decongestion, the scope is first advanced medial to the inferior turbinate along the floor of the nasal cavity to the nasopharynx. Along the way, structures accessible for examination include the inferior septum and maxillary crest, inferior turbinate and inferior meatus, choana, eustachian tube orifice, fossa of Rosenmuller, and nasopharynx (Fig. 35.5). If an angled rigid scope or a flexible scope is used, the contralateral eustachian tube can also be examined. The second pass is performed above the inferior turbinate and medial to the middle turbinate in order to examine the superior septum, middle and superior turbinates, olfactory cleft, sphenoethmoid recess, and sphenoid sinus ostium (Fig. 35.6). The third pass is then directed into the middle meatus itself to examine the structures contained therein.

History and physical exam usually provide enough information to make the diagnosis of rhinosinusitis, especially in ABRS. However, radiologic imaging can be a useful adjunct in establishing objective evidence for the diagnosis of CRS. Plain films have no residual role in the contemporary work-up of CRS (7). Computed tomography (CT) scans are considered the standard for imaging the sinuses. CT scans provide excellent bony anatomic detail, readily depict anatomic variants, and provide a roadmap for presurgical planning (Fig. 35.7). Current multidetector CT protocols enable detailed coronal and sagittal reconstructions from thin section axial cuts. Triplanar imaging can be helpful in evaluating anatomic variations of the frontal recess or sphenoethmoid complex. Intravenous contrast is

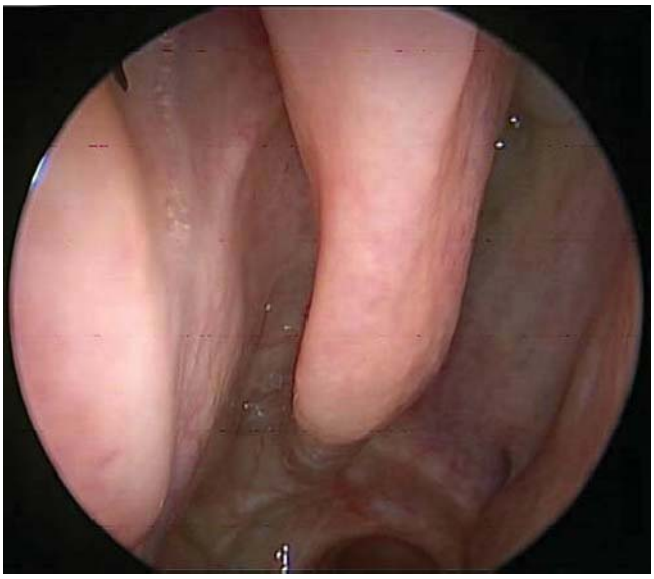


Figure 35.6 The superior pass. One can see the superior turbinate attachment to the face of the sphenoid sinus above the choana and if the endoscope were moved slightly superiorly and medially, the natural ostium of the sinus itself might be visible just medial to the superior turbinate. Sometimes the inferior third of the superior turbinate must first be removed before visualizing the natural ostium.

typically not required unless one is concerned about tumor or infectious complications involving the orbit or brain. Magnetic resonance imaging (MRI) can be a useful adjunct to CT for soft tissue and fluid delineation, but is inferior in imaging of bony detail. Due to recent concerns regarding excessive radiation exposure from radiologic studies, there has been renewed interest in the potential use of MRI as a primary diagnostic imaging tool in CRS (52). Lin and Bhattacharyya have performed the only study to date



Figure 35.7 CT scan demonstrating CRS. This is a coronal CT image showing the maxillary and ethmoid sinuses. Note the complete opacification of the right maxillary sinus and the fluid or mucosal thickening visualized within the left maxillary sinus with a small Haller cell present.

examining the diagnostic accuracy of MRI in CRS relative to CT. They found the results correlated strongly and suggested that MRI may be viable when used as the primary diagnostic tool, although more data need to be gathered and validated (53).

In patients with medically refractory ABRS and CRS, endoscopically obtained culture of purulent secretions with sensitivity profiles is an important tool in diagnosis (54). In a meta-analysis of 126 patients, the yield of endoscopic middle meatal cultures was assessed against the gold standard of maxillary sinus puncture and aspiration performed in the same patient; endoscopically derived cultures were shown to have a satisfactory yield and excellent correlation with sinus puncture (55). These may be performed with sterile suction traps or small wire swabs, as both have been shown to be equally efficacious. In both cases, however, care must be taken to minimize contamination from the nasal vestibule. Nonendoscopic swab cultures obtained from the vestibule or nasal cavity should be avoided, as these are not likely to be accurate and typically only demonstrate contaminant pathogens.

More specialized objective tests of nasal function that are less commonly utilized include olfactory testing, rhinomanometry, and acoustic rhinometry. The Smell Identification Test is a 40-item forced-choice scratch-and-sniff test of olfaction that provides comparative normative data for smell function by age and gender. The test is also designed to detect malingering and has sufficient sensitivity to assess longitudinal changes in olfactory function over time. Rhinomanometry and acoustic rhinometry measure airway resistance and volume, respectively, and are currently used primarily in clinical research.

STAGING

Over the years, multiple staging systems for CRS have been proposed to stratify patients according to severity of disease, but two have remained as the most accurate and widely used, not only in research protocols but in clinical practice as well.

The most widely used system for radiologic stratification is the Lund-Mackay CT staging system, owing to its simplicity as well as its excellent interobserver and intraobserver agreement. Scoring is based entirely on CT findings, and different anatomic regions are given a numeric score: 0, no opacification; 1, partial opacification; and 2, total opacification (Table 35.3). The frontal, maxillary, anterior ethmoid, posterior ethmoid, and sphenoid sinuses are graded separately, and the OMC is also scored, for a total possible score of 24 (56). In the recently published Task Force guidelines, a modification to the Lund-Mackay system is proposed, citing the need to substratify within grade I disease (47).

Soon after the publication of the Lund-McKay radiologic staging system, a modification was suggested, now known as the Lund-Kennedy grading system, which

TABLE 35.3 LUND-MACKAY CT STAGING SYSTEM

Sinus	Right	Left
Frontal	0–2/2	0–2/2
Maxillary	0–2/2	0–2/2
Anterior ethmoid	0–2/2	0–2/2
Posterior ethmoid	0–2/2	0–2/2
Sphenoid	0–2/2	0–2/2
OMC	0 or 2/2	0 or 2/2
Total	Total score/24	

Each individual sinus is scored: 0 = clear, 1 = partial opacification, 2 = total opacification. Scoring for the OMC: 0 = clear, 2 = occluded. Adapted from Lund VJ, Kennedy DW. Quantification for staging sinusitis. The staging and therapy group. *Ann Otol Rhinol Laryngol Suppl* 1995;167:17–21.

incorporates the presence of anatomic variants, type of surgery performed, symptom scores, and endoscopic scores in addition to the CT score (Table 35.4) (57).

DIAGNOSTIC CORRELATES

One of the conundrums in the decision-making process in patients with CRS has been the inability to correlate symptoms with more objective testing such as nasal endoscopy or CT scans. Many well-designed outcomes studies have consistently shown poor correlation between subjective and objective findings in CRS. This discrepancy is often highlighted when evaluating patients for surgery, as surgical decisions are frequently made on a combination of subjective and objective criteria that are not necessarily in agreement.

Multiple studies have attempted to correlate nasal endoscopy findings with the symptom-based diagnostic criteria for CRS. Stankiewicz and Chow (58) analyzed 78 patients prospectively who met the 1997 subjective criteria for CRS with same-day nasal endoscopy and CT scanning. They found that nearly 70% of patients had normal endoscopies. Notably, they found that endoscopy was a good predictor of CT scan findings, with almost 80% of patients with a normal CT scan having a normal endoscopic evaluation. Abnormal endoscopy had a positive predictive value of 74% in predicting positive CT scans, with polyps, purulence, and mucosal edema being the most significant signs seen on endoscopy. Casiano et al. analyzed the correlation between nasal endoscopic findings and CT scans in 247 patients who were undergoing endoscopic sinus surgery. They developed an endoscopic staging system to evaluate their patients and found a relatively high degree of correlation between endoscopy and CT. The sensitivity was 84% and the specificity 74%. When polyps were present, the correlation with CT increased to 94% (59).

Other authors have sought to correlate patient symptoms with CT scan findings. Hwang et al. (60) examined 125 patients prospectively with symptom questionnaires and sinus CT scans. They found that 35% of patients who met symptom-based criteria for CRS had negative CT scans, while 9 out of 10 patients who did not meet the criteria had positive scans. Overall, the subjective criteria had a high sensitivity of 89%, but a very low specificity of 2%. Other authors have confirmed these findings. In one study, up to 53% patients who met the CRS subjective criteria had normal CT scans, with no difference in symptom severity between patients with positive and negative CT scans (61). It was recently demonstrated that there is no better correlation in postsurgical patients. Ryan et al. found that symptoms did not correlate well with either CT findings or endoscopy score. Although endoscopy and CT scores correlated well, a normal endoscopy could not assure a normal CT scan (62). All of these studies together confirm that symptomatology, nasal endoscopy, and CT evaluation are complementary in the evaluation of the patient with CRS.

TABLE 35.4 KENNEDY STAGING SYSTEM FOR CHRONIC SINUSITIS

Stage	Findings
I	Anatomic abnormalities All unilateral sinus disease Bilateral disease limited to ethmoid sinuses
II	Bilateral ethmoid disease with involvement of one dependent sinus
III	Bilateral ethmoid disease with involvement of two or more dependent sinuses on each side
IV	Diffuse sinonasal polyposis

Adapted from Kennedy DW. Prognostic factors, outcomes and staging in ethmoid sinus surgery. *Laryngoscope* 1992;102(12 Suppl):1–18.

TREATMENT

Acute Rhinosinusitis

The overprescribing of antibiotics is an issue affecting primary care providers and otolaryngologists alike. High rates of drug resistant infections have made the judicious, evidence-based use of antibiotics an imperative.

The first determinant in treatment of acute rhinosinusitis is whether the infection is likely viral or bacterial. Clinical guidelines have proposed that acute viral and bacterial sinusitis generally cannot be differentiated until day 10 of symptoms, beyond which the infection is likely to be bacterial (48). At day 10, antibiotic treatment is appropriate, but reliable patients may also be observed, since the rate of spontaneous improvement in ABRS is 40% to 60%. Antibiotic treatment before day 10 of symptoms may be appropriate in patients who have a relapse of symptoms after initial improvement ("double worsening") or in patients with severe symptoms.

Clinical trials for acute rhinosinusitis are difficult to interpret because of highly variable diagnostic inclusion

criteria. Systematic reviews suggest that antibiotics shorten the duration of illness and may increase the rate of cure by 15% compared with placebo. Antibiotics may also decrease the need for concomitant supportive medication (63–66).

If antibiotic therapy is chosen, the treatment regimen should begin with a narrow spectrum antibiotic, broadening coverage in the face of immunocompromise, failure to respond to initial therapy, or specific culture results showing resistance. The 2007 guidelines recommend amoxicillin as an appropriate first line therapy. If patients fail to respond, fluoroquinolones or high-dose amoxicillin-clavulanate (4 g/day) are recommended (1). Regional resistance rates should be considered when prescribing. The duration of therapy is generally recommended to be 10 days, although this is based simply on the duration used in most clinical trials, and has not been validated definitively (53).

As with trials examining antibiotics, studies of intranasal steroid use in ABRS have used broad inclusion criteria, and may not truly reflect the patient population defined by our Task Force guidelines. However, a Cochrane review in 2007 performed a meta-analysis of four double-blind placebo-controlled trials and recommended use of intranasal steroids in ABRS as monotherapy or as an adjunct to antibiotics (67).

Buffered normal saline irrigation can be used via high pressure or low pressure delivery systems to rinse the nasal cavity. Decongestants and mucolytics can also be used as supportive therapy, although care must be taken in patients with high blood pressure when administering oral decongestants, and patients must be counseled to avoid prolonged use of topical nasal decongestants to avoid developing rhinitis medicamentosa. Decongestants and normal saline irrigation are both listed as optional under the 2007 guidelines.

Complications of acute sinusitis are rare (estimated 1 in 1,000 cases of ABRS) but carry the potential for serious morbidity and require urgent treatment. Severe headache, altered mental status, high fever, and prostration should alert the clinician to the possibility of intracranial extension of infection. Meningitis, epidural abscess, cavernous sinus thrombosis, or even frank brain abscess are potential adverse sequelae. The presence of periorbital edema, erythema, impaired extraocular motility, or diminished visual acuity may indicate orbital extension of infection. Prompt imaging with contrast is indicated to characterize the presence and extent of extrasinus spread of infection, and consideration must be given to urgent administration of intravenous antibiotics and surgical treatment.

Chronic Rhinosinusitis

Antimicrobial Therapy

The 2007 guidelines actually offered no specific treatment recommendations for CRS, instead focusing on minimizing symptoms with preventive strategies such as normal saline irrigation, good hand-washing habits, and treatment of underlying exacerbating factors. They also recommended evaluating refractory patients with CRS for contributory factors or disease states such as CF, ciliary dyskinesia, or anatomic variations (48). In keeping with the multifactorial pathophysiology of CRS, the treatment options are equally varied; as in ABRS, the relative lack of published trials comparing treatments in CRS is a barrier to providing truly validated evidence-based care. As discussed above, the role for a microbial effect on inflammation is more likely mediated through superantigens and biofilm formation rather than solely a planktonic infection. Nevertheless, oral antibiotics are the most commonly prescribed agents for CRS. Because of increased prevalence of Staphylococcus species, gram-negative bacilli, and anaerobes in CRS (especially after sinus surgery), broader spectrum antibiotics may be necessary if given empirically (68). Antibiotic selection should be guided by appropriately obtained cultures whenever possible, especially in postoperative patients and those who have failed an initial trial of first-line antimicrobials. Culture-directed therapy may reduce drift toward highly resistant organisms over time, and sinus cultures have been shown to direct a change in therapy in 51.4% patients with CRS (69,70). Parenteral antibiotics have a limited role in the treatment of CRS and are not indicated for routine treatment. Intravenous antibiotics may be indicated in unusual cases of severe or complicated infections, highly resistant organisms, or patient intolerance of other therapies.

The optimal duration of antibiotic therapy for CRS has not been clearly established. Most authors recommend a prolonged course of 4 to 6 weeks of antibiotics; however, the only randomized controlled clinical trial looking at antibiotic therapy in CRS compared macrolide treatment (roxithromycin) to placebo for 3 months (71). The authors found statistically significant improvements in SNOT-20 score, nasal endoscopy, saccharine transit time, and IL-8 levels in lavage fluid in the macrolide group. This study was published in 2006, and by the time a Cochrane review was performed in 2011, it was still the only randomized clinical trial evaluating an antibiotic versus placebo in the literature (72).

Interestingly, it is not the antibiotic effect of macrolides that led to this study, but rather the anti-inflammatory effects of macrolides. Studies have shown that 14- and 15-membered ring macrolides inhibit multiple aspects of neutrophilic inflammation. Not only do they interfere with neutrophil migration and adherence to sites of inflammation, but they also reduce the neutrophil oxidative burst and increase the rate of programmed cell death. They also inhibit IL-1b, IL-8, nuclear factor kB, transforming growth factor B, and granulocyte-macrophage colony stimulating factor, all inflammatory cytokines (73). Multiple studies have demonstrated that macrolides may also inhibit formation of Pseudomonal biofilms, reduce the thickness of airway mucus secretions, and even have a reparative effect on inflamed upper and lower airway mucosa (74).

TABLE 35.5 TRIALS EVALUATING TOPICAL ANTIBACTERIAL THERAPY

Antibacterial Therapy for CRS: Summary of Presented Clinical Studies

Study	Sample Size	Antibacterial/Delivery System	Dose	Duration of Treatment	Placebo Treatment	Conclusions of Study
Desrosiers et al. (80)	20	Tobramycin-saline via large particle nebulizer	240 mg/d	1 mo	Saline-only solution	Few additional benefits when compared with control
Scheinberg and Otsuji (78)	41	One of the following antibiotics via nebulizer: cefuroxime, ciprofloxacin, levofloxacin, or tobramycin	cefuroxime, 285 mg t.i.d.; ciprofloxacin, 90 mg b.i.d.; levofloxacin, 70 mg b.i.d.; tobramycin, 95 mg b.i.d.	3–6 wk	None	Nebulized antibiotics were superior to oral therapies
Vaughan and Carvalho (79)	42	One of the following culture-directed antibiotic via nebulizer: ceftazidine, ciprofloxacin, levofloxacin, ofloxacin, tobramycin, or gentamicin	Information not provided	At least 3 wk	None	Nebulized antibiotics were safe and effective
Uren et al. (81)	16	Mupirocin via nasal lavages	200 mg/d	3 wk	None	Mupirocin was effective in treating patients with *S. aureus* infection

b.i.d., twice daily; t.i.d., three times daily.
Adapted from Comstock RH III, Lam K, Mikula S. Topical antibiotic therapy of chronic rhinosinusitis. *Curr Infect Dis Rep* 2010;12(2):88–95.

Most other published data on antimicrobials in the setting of CRS surrounds their use in topical application (Table 35.5). As discussed above, biofilms are thought to be an important causative factor in CRS, and high concentrations of antibiotic are known to be necessary for eradication. The appeal of topical antibiotic therapy is the ability to achieve high concentrations at the level of the sinonasal mucosa with minimal systemic absorption and adverse side effects. Ha et al. (75) evaluated topical mupirocin, ciprofloxacin, and vancomycin for the treatment of *S. aureus* biofilms *in vitro*, and determined that mupirocin was the only suitable choice for intranasal delivery because of its efficacy and lack of potential side effects. Ciprofloxacin was ineffective even at high concentrations, and vancomycin was only effective at concentrations so high that any absorption would lead to serum levels in the toxic range. Chiu et al. (76) found disappointing results when trying to apply topical tobramycin to eradicate *Pseudomonas* biofilms in the sinuses of rabbits, eradicating only planktonic bacteria with increasing concentrations, but not the biofilms themselves.

Topical therapies are less likely to be beneficial in treating unoperated sinuses, and the efficacy of distribution (nebulizer vs. irrigation) should be considered when assessing antimicrobial efficacy (77). Although early nonrandomized and uncontrolled clinical studies examining nebulized antibiotic therapy suggested it was safe and effective, the only study with a placebo comparison group showed no difference in outcomes between nebulized tobramycin versus nebulized saline alone (78–80). Studies of medicated irrigations have shown greater promise, perhaps related to better efficacy of large volume rinses in reaching the sinuses. Uren et al. (81) studied twice-daily irrigations of mupirocin at 500 μg/mL in sixteen patients with surgically recalcitrant CRS and endoscopic cultures positive for *S. aureus*. Fifteen of the sixteen patients had improved endoscopic findings, 12 of 16 noted improvement in overall symptoms, and 15 of 16 had negative post-treatment cultures for *S. aureus*. Although the current level of evidence is low for the use of topical antimicrobial therapy, promising results from pilot studies will hopefully be validated by larger scale controlled clinical trials.

Research interest in potential fungal etiologies of CRS has led to multiple studies examining topical antifungal therapy as a possible treatment option for CRS. Ponikau et al. (82) first published a prospective open-label trial using topical amphotericin B twice a day for 3 months and found it to be safe and effective. Criticisms of this study included lack of placebo control and randomization. This study was then followed by prospective randomized placebo-controlled studies using topical amphotericin B which failed to show any benefit, although notably these studies used nasal spray as the delivery method in lieu of irrigation (83,84). Ponikau et al. published a follow up randomized, blinded placebo-controlled study of amphotericin nasal lavage. Although the authors claimed beneficial effects of amphotericin B, there was no significant difference in

quality of life improvement between the treatment and control groups, and the study suffered from small sample size. Improvement in the endoscopic exam and a slight radiologic improvement were observed in the treatment group versus control (85). Finally, a definitive multicenter, placebo-controlled, double-blinded study was conducted, using multiple subjective and objective outcome measures, and no difference was demonstrated between the treatment and control arms (86). Recently this same group published a follow up "part two" to the multicenter trial, again examining topical amphotericin B compared with placebo; there was no significant effect on the levels of multiple pro-inflammatory cytokines, chemokines, and growth factors in CRS nasal lavage samples (87). It appears there is not sufficient evidence at this time to recommend topical antifungal therapy.

Multiple studies have been performed on adjunctive topical therapies targeting biofilms. Naturopathic treatments including tea tree oil and manuka honey have proven effective against biofilms through *in vitro* testing, but have yet to show their efficacy in clinical trials (88,89). Surfactants have recently held the most focus in the literature, with the goal of disruption of the biofilm matrix itself. Although neither 1% baby shampoo in saline irrigation or citric acid zwitterionic surfactant (CAZS) have been evaluated in randomized trials, both have shown clinical efficacy in disruption of biofilms on the paranasal sinus mucosa. Studies evaluating baby shampoo have shown symptomatic improvement in greater than half the patient population, but approximately 10% were forced to stop using it due to side effects (90). CAZS disrupted biofilms but at the same time caused ciliary dysfunction, with almost 85% of the cilia denuded compared to the saline controls (91).

Anti-Inflammatory Therapy

Topical steroid therapy is generally accepted as part of the treatment regimen for CRS in the form of nasal spray, with strong evidence supporting its use (92). Topical steroid irrigation has become a commonplace practice among rhinologists, particularly in the treatment of CRS with nasal polyposis, but also it can be used in CRS without polyposis. Uncontrolled case series have been published demonstrating efficacy in CRS patients refractory to more traditional treatments (93,94). Although there have not been any randomized trials looking at efficacy, budesonide irrigation is used frequently enough that studies examining the safety profile have emerged. Two articles to date have published no significant suppression of the adrenal axis in patients using budesonide, at 1 month and 2 month endpoints, respectively (95,96).

As with topical antimicrobial therapy, the efficacy of topical steroid therapy is related to the vehicle of delivery as well as the successful reach of medication to the target site. Saline irrigation alone has been shown to be beneficial in management of CRS symptoms, though the magnitude of the symptomatic improvement was not as large as that observed with topical nasal steroids (97). High volume irrigation in the head-down position appears to be most effective for delivery into the paranasal sinuses.

Systemic steroids have proven valuable in a variety of chronic inflammatory diseases, and their use in CRS is well established, especially in treating CRS patients with nasal polyposis. Although oral steroids are also commonly used by otolaryngologists for CRS without polyposis, a recent systematic review has revealed that the level of published evidence for their use is primarily level 4 and 5 (98). The use of oral steroids may be limited by well known side effects such as insomnia and weight gain, and may be contraindicated in patients with osteoporosis, diabetes, glaucoma, or psychiatric illness.

Other immunomodulating agents have been of increasing interest in management of the inflammatory aspects of CRS. Leukotriene receptor antagonists such as zafirlukast and montelukast have been anecdotally reported to have therapeutic effects in patients with nasal polyps who are being treated concurrently for lower airway disease, but there are no randomized clinical trials supporting its use in nonpolypoid CRS (99). Zileuton, a 5-lipoxygenase inhibitor, has been shown to be effective in nasal polyposis associated with aspirin exacerbated respiratory disease, but no studies have been conducted in nonpolypoid CRS (100).

That same understanding is what has spurred the study of omalizumab, an anti-IgE monoclonal antibody, in CRS. This antibody has had success in treating both asthma and allergic rhinitis (101). Pinto et al. (102) recently published a randomized, double-blind, placebo-controlled trial of omalizumab for patients with CRS, and while improvements were seen on the SNOT-20 at 3, 5 and 6 months compared to controls and reduced inflammation was seen on imaging in these patients, there were multiple other endpoints which showed no statistical difference. The authors concluded that IgE may play a small role in CRS, but that studies with larger enrollment were necessary to determine the clinical significance of these differences.

A number of other candidate therapeutic agents are being evaluated for their potential immunomodulatory effects in CRS. Vitamin D is one such agent, and there appear to be immunomodulatory interactions with the innate and adaptive immune systems (103). Treatment of CRS with vitamin D analogues remains to be studied. Statin drugs have also recently shown promise in decreasing inflammation in the upper and lower airways. Wang et al. recently performed an analysis of sinus tissues collected from patients with CRS. Suppression of highly expressed inflammatory mediators CCL5, CCL11, and IL13RA was found in patients who were on statins, suggesting that statins may induce anti-inflammatory effects (104). *In vitro* studies of cultured primary human airway epithelial cells exposed to ambient air pollution confirmed that expression of these mediators was suppressed by pretreatment with statins. Other compounds being investigated include retinoic acid, L-ascorbate, resveratrol, and bioflavanoids (105–108).

Although medical therapy is always considered first line, endoscopic sinus surgery is the final treatment pathway for many patients with CRS. There have been multiple studies showing that endoscopic sinus surgery improves patient symptoms, quality of life, and nasal endoscopic exam in cases of CRS refractory to medical therapy (109,110). Surgical indications, perioperative management, and surgical technique are discussed in another chapter.

HIGHLIGHTS

- Rhinosinusitis is one of the most common health care complaints with a significant impact on patients' quality of life.
- The pathophysiology of CRS is multifactorial and predisposing factors can be subdivided into microbial factors, environmental factors, and host factors such as genetics, physiology, anatomic structure, and innate immunity. These all interact to produce the endpoint of chronic inflammation.
- The diagnosis of CRS entails a combination of subjective and objective criteria. Nasal endoscopy and CT scanning offer distinct clinical advantages in the evaluation of CRS, and there is poor correlation between subjective and objective parameters in the assessment of CRS.
- The treatment of rhinosinusitis should address the predisposing factors leading to inflammation. This may involve the use of appropriately selected oral or topical antimicrobials, oral or topical steroids, saline irrigations, immunomodulators, and surgical intervention.

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36 The Unified Airway

Jeb M. Justice *Richard R. Orlandi*

Otolaryngologists frequently encounter patients with diseases of the upper airways. Patients with upper airway disease present a unique challenge. In addition to having diseases like allergic rhinitis (AR) or chronic rhinosinusitis (CRS) that negatively impact their quality of life, they are at risk of concurrently having or subsequently developing lower airway disease, such as asthma. Although upper airway disease has significant cost and morbidity in and of itself, asthma may have even more associated morbidity and socioeconomic burden. As such, recognition of concomitant lower airway disease and effective management of upper and lower airway disease is paramount.

Recent evidence has shown that the upper and lower airways behave as a single functional unit, with similar histologic characteristics and concurrent inflammation. Worsening of disease in one part of the airway negatively impacts other parts of the airway. Furthermore, effectively managing disease in one part of the airway seems to improve disease in other parts of the airway. This has led to the concept of the unified airway and it has revolutionized the understanding of the relationship between the upper and lower airways.

The concept of unified airway has solidified the need for multidisciplinary care for these patients involving primary care physicians, otolaryngologist, allergists, immunologists, and pulmonologists. Historically, otolaryngologists have less experience in recognizing and managing lower airway disease. Thus it is important for otolaryngologists to understand the concept of the unified airway and apply this to their practice to best manage these patients.

The concept of a unified airway is based on a century-old observation that patients with lower airway disease had a high incidence of upper airway disease as well. In the last 15 years, interest has increased in the relationship between the lower and the upper airways and the shared inflammation between the two. Krouse has proposed three criteria in support of the theory of the unified airway and they are as follows:

1. Patients with upper airway disease such as rhinitis and rhinosinusitis should have a higher prevalence of lower respiratory diseases such as asthma; the corollary, increased prevalence of upper respiratory disease among patients with lower respiratory diseases, also should be present.
2. Interrelated pathophysiologic mechanisms between upper and lower airway diseases should exist to explain the interaction of these two disease processes.
3. Treatment of one portion of the unified airway should improve symptoms in a separate portion of the respiratory system (1).

Asthma may represent the most important aspect of this concept insofar as it carries the most morbidity of all the airway diseases. The presence of AR and CRS are clues to the development of asthma, and effective management of these diseases can positively impact the management of asthma. In this chapter, the evidence and literature that has helped support the concept of a unified airway is reviewed. Furthermore, the disease processes that affect the upper and lower airways are discussed. Finally, treatment modalities and the impact of treatment of one part of the airway on the rest of the airway are reviewed.

ALLERGIC RHINITIS

AR is a common disease affecting 20% of adults and up to 40% children in United States. Its importance lies in its direct and indirect costs to society and its negative impact on quality of life (2,3). AR is characterized by an immunoglobulinE (IgE)-mediated, type 1 hypersensitivity reaction that is triggered by an inhaled antigen. The immunologic response to this inhaled antigen produces

TABLE 36.1 NASAL AND NONNASAL SYMPTOMS OF ALLERGIC RHINITIS

Nasal
Sneezing
Rhinorrhea
Pruritus
Congestion
Smell impairment
Postnasal drip
Eustachian tube dysfunction
Nonnasal
Lacrimation
Conjunctivitis
Itching eyes
Fatigue
Sleep disturbances
Depression
Headache
• Palatal pruritus
• Ear fullness/otalgia
• Midface pressure
• Cognitive impairment

Reprinted from Ahmad N, Zacharek MA. Allergic rhinitis and rhinosinusitis. *Otolaryngol Clin North Am* 2008;41:267–281.

the classic symptoms of AR, which are characterized in Table 36.1 (4).

With regards to the underlying mechanisms of AR, the first phase is known as the priming phase during which one's mast cells are sensitized to a specific antigen. The first exposure to an antigen leads to processing by an antigen presenting cell (APC) or a macrophage. After processing the antigen, the APC interacts with a CD4+ Th2 helper T cell, leading to release of Th2 type cytokines like interleukin (IL)-4 and IL-13, as well as inducing B cells of the immune system to differentiate into plasma cells. The plasma cells produce IgE specific to the initial inciting antigen and attach them to the surface of mast cells rendering the mast cells sensitized. The patient is now primed to have a mast cell degranulation of inflammatory mediators upon subsequent allergen exposure.

The next exposure to the specific allergen will result in the degranulation of the mast cell and release of preformed mediators such as histamine, kinins, and proteases, which lead to the classic symptoms of AR, listed in Table 36.1. This "early phase response" takes place 10 to 30 minutes after exposure to the allergen. This is in contrast with the late phase of the allergic response, which occurs 4 to 8 hours after exposure. This delayed reaction is the result of chemotaxis and migration of neutrophils, basophils, eosinophils, T-lymphocytes, and macrophages across the mucosal endothelium into the nasal submucosa (4).

Supporting the concept of a unified airway, there is a clear relationship between AR and asthma. Over 80% of asthmatics have rhinitis and 10% to 40% of patients with rhinitis have asthma (5). Although there are distinct differences between the two diseases, there are many similarities, especially the hallmark inflammatory response. Later in this chapter, more evidence supporting the link between AR and asthma and how treating AR can retard the progression to asthma is reviewed. The link between AR and CRS is controversial and is examined later in this chapter.

CHRONIC RHINOSINUSITIS

Adult CRS has been defined as a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 weeks duration. It affects more than 30 million Americans and has a significant burden on society from a cost and quality of life standpoint (6). Symptoms of CRS have been divided into major and minor symptoms and are listed in Table 36.2.

For over 70 years, there has been a recognized coexistence and suspected association between asthma and sinusitis (7–9). Much like asthma and AR, the hallmark of CRS is inflammation. Patients who have CRS have a 20% prevalence of asthma, approximately three to four times greater than the 5% to 8% prevalence of asthma in the general population. Multiple mechanisms have been proposed to explain this link. The nasobronchial reflex, the pharyngobronchial reflex, and posterior nasal drainage of inflammatory mediators have been postulated to link CRS with asthma and a lower airway inflammatory response, but none of these hypotheses provides a complete explanation of the relationship between CRS and asthma (10). Multiple studies have demonstrated that a local inflammatory reaction in one portion of the airway can reach the systemic circulation and potentially affect distant airway sites. These are discussed in more detail below.

TABLE 36.2 SIGNS AND SYMPTOMS IN CRS

Major
Nasal obstruction
Facial pressure
Nasal discharge/postnasal drainage
Purulence
Anosmia/hyposmia
Minor
Cough
Headache
Dental pain
Ear pressure
Fatigue
Halitosis

Reprinted from Joe SA, Thakkar K. Chronic rhinosinusitis and asthma. *Otolaryngol Clin North Am* 2008;41:297–309. Original data from Lanza DC, Kennedy DW. Adult rhinosinusitis defined. *Otolaryngol Head Neck Surg* 1997;117:S1–S7.

TABLE 36.3 CLASSIFICATION OF ASTHMA SEVERITY FOR PATIENTS ≥ 12 OF AGE

Components of Severity		Classification of Asthma Severity (Youths ≥ 12 y of age and adults)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 d/wk	>2 d/wk but not daily	Daily	Throughout the day
	Nighttime awakenings	Less than or equal to two times per month	Three to four times per month	Less than one time per week but not nightly	Often seven times per week
	Short-acting $beta_2$-against use for symptom control (not prevention of EIB)	≤2 d/wk	>2 d/wk but not greater than one time per day	Daily	Several times per day
Normal FEV_1/FVC: 8–19 y (85%) 20–39 y (80%) 40–59 y (75%) 60–80 y (70%)	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 ≥80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 >60% predicted • FEV_1/FVC reduced > 5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/y (see note)	2/y (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbation may be related to FEV_1			

Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute, Aug 2007.

ASTHMA

Despite the marked heterogeneity of the asthma phenotype, a consensus definition for asthma has been developed that recognizes this condition to be a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells. The classic symptoms of asthma are recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and/or in the early morning. These episodes are typically characterized by widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. It is the association of asthma with AR and CRS that is one of the central points to the idea of the unified airway, as effective management of AR and CRS may prevent the development of asthma or beneficially impact the severity of asthma and its resultant morbidity.

Diagnostic tests for asthma include pulmonary function tests, such as forced expiratory volume (FEV), peak expiratory flow, and the methacholine challenge test, which provokes bronchial hyperresponsiveness. Furthermore, a diagnosis of asthma is established when a reversible airflow obstruction is confirmed with the above-mentioned tests as well as a response to an inhaled beta-agonist. Asthma severity can be classified clinically as mild intermittent, mild persistent, moderate persistent, and severe persistent. This classification scheme is detailed in Table 36.3, and is useful in guiding management. Management typically consists of anti-inflammatory modulators such as inhaled or systemic corticosteroids as well as short or long acting beta-agonist bronchodilator agents. Other options include leukotriene-inhibitors, methylxanthines like theophylline, and mast cell stabilizers like cromolyn or nedocromil. Anti-IgE monoclonal antibodies are available but reserved for severe cases due to their significant cost (11). Furthermore, pulmonary function tests may be repeated to assess response to therapy, and treatments can be adjusted based on these results.

The impact of asthma on society is substantial. In 2005, roughly 23 million (7.8%) Americans reported having asthma, 6.2 million of whom were under the age of 18. African-Americans are disproportionately affected. The prevalence of asthma under the age of 14 in the African-American population is 13.6%, followed by Hispanics (9.2%) and Caucasians (7.5%) (12). Asthma leads to a significant impact on school and workdays lost, outpatient physician visits, hospitalizations, emergency department visits, and use of newer, more expensive asthma

medications. In 1994, the total direct and indirect costs attributed to asthma were 12 billion dollars (13). If one considers the above statistics in addition to the relationship that asthma has with AR and CRS, one begins to understand the importance of recognizing multiple airway diseases in patients. Otolaryngologists historically may not have considered the diagnosis of asthma in patients with AR or CRS, but with new knowledge of the unified airway, it is imperative to consider this fact in order to effectively manage these patients.

OTHER UNIFIED AIRWAY CONDITIONS

The unified airway model can be extended to include the middle ear cleft and possibly the larynx. Histologically, the middle ear mucosa is lined with the same pseudostratified, ciliated columnar epithelium as found in the upper and lower airways. Furthermore, cellular and cytokine analysis of middle ear effusions from atopic patients with chronic otitis media with effusion (COME) demonstrates findings consistent with a Th2-mediated immune response. This realization has important implications as atopic patients with COME may benefit from new treatment approaches (14). Allergic laryngitis has been described in the literature but insufficient evidence exists to demonstrate a causal relationship between allergen exposure and the subsequent development of laryngitis (15).

EVIDENCE FOR THE UNIFIED AIRWAY

Previous Hypotheses

Several hypotheses previously attempted to explain the link between the upper and lower airways. The first was the nasobronchial reflex, which postulated that there was a direct reflex arc between the upper and lower airways that led to immediate changes in the lower airways after stimulation of the upper airways. Initial studies demonstrated increased lower airway resistance in nonasthmatic patients immediately after application of silica particles to their nasal mucosa. These studies showed that atropine and section of the trigeminal nerve could blunt this effect (16,17). However, more recent studies have not been able to replicate similar findings, that is, immediate changes in the lungs after nasal provocation. In fact, the more recent studies showed delayed changes in the lower airways supporting a different mechanism of cross-talk, and these studies will be detailed below. There is potentially a reflex link between the upper and lower airways but this hypothesis does not provide a comprehensive explanation of the unified airway (1,18).

Others have postulated that the loss of nasal protection of the lower airway could explain the worsening of the lower airways in patients with AR and CRS. Earlier studies demonstrated that mouth breathing led to increased bronchospasm compared to nasal breathing, perhaps because of the loss of the filtering role of the nasal airway. Again, however, subsequent studies have failed to confirm this relationship. Lastly, posterior drainage or aspiration of nasal secretions have been postulated to incite inflammation in the lower airways. Studies looking at this phenomenon do not support it as playing a significant role in the unified airway (1,18).

Allergic Rhinitis and Asthma

The idea that AR and asthma are related originates from the late 19th century (19). Only recently have we begun to develop an understanding of this link. As Krouse (1) has stated, asthma and AR are linked from the standpoint of epidemiology, pathophysiology, and treatment. As such, studies have shown that asthma patients who also have AR tend to have more severe disease with higher treatment costs; treatment of rhinitis may improve asthma control; and early treatment of AR may prevent the development of asthma. In fact, the World Health Organization's Allergic Rhinitis and its Impact on Asthma update in 2008 recommends that "Patients with persistent AR should be evaluated for asthma by history, chest examination, and if possible and when necessary, the assessment of airflow obstruction before and after bronchodilator." Furthermore, their guidelines recommended that all patients with AR be screened by history and questioning for asthma, and that any patient who had concerning history as well as any patient with severe or persistent AR, be sent for formal evaluation with pulmonary function testing (20). Fokkens and Braunstahl (21) stated that AR and asthma may be "manifestations of the same airway disease, rather than two distinct disease of the nose and lung."

As stated previously, over 80% of asthmatics have rhinitis and 10% to 40% of patients with rhinitis have asthma. Furthermore, there may be a temporal relationship in the onset of AR and asthma as suggested by a large Danish study from 1983. In this study, both AR and asthma presented for the first time within the same year in 25% of patients and within 2 years of each other in 75% of patients (22). Going a step further from merely establishing an association between these two conditions, multiple studies, including the Finnish Twin Cohort Study, which followed 11,000 patients for 15 years, suggests that AR is a risk factor for the development of asthma. In these studies, AR typically occurs prior to the onset of asthma, and this progression has been referred to as the "allergic march" (23,24).

AR and asthma have similar pathophysiologic mechanisms. As stated previously, the ciliated pseudostratified columnar epithelium in the nasal cavity is similar to that of the respiratory mucosa. The inflammatory process in both areas is similar. Both sites involve eosinophils, lymphocytes, and mononuclear cells as well as similar cytokines, such as IL-4, 5, and 13, which are typical of Th2 type allergic response. However, there are differences in that the

nasal airway mucosa lacks smooth muscle and therefore does not exhibit the smooth muscle hypertrophy and remodeling that is characteristic of long-term asthma (18).

There is evidence to support that patients who have only asthma or only AR have eosinophilic inflammation in the other uninvolved airway site. For example, Gaga et al. (25) found that asthmatic patients had significant amounts of eosinophils in the nasal mucosa in the absence of a diagnosis of AR. The reverse is also true. Djukanovic et al. (26) demonstrated via bronchial biopsies that atopic nonasthmatics (patient with AR but without the diagnosis of asthma) had basement membrane thickening and eosinophilic inflammation in their lower airways. Other studies have shown that nonasthmatics with AR are prone to bronchial hyperreactivity (27,28). According to Ryan (18), "the finding that patients who have rhinitis without an asthma diagnosis or asthma symptoms have bronchial hyperreactivity lends further support to the notion that asthma and rhinitis are different manifestations of a single respiratory disease".

Several studies by Braunstahl et al. have helped elucidate the common pathophysiology and inflammation shared by AR and asthma. Two studies, in which eight AR patients without asthma were compared to eight normal controls, showed bronchial provocation with allergen-induced nasal inflammation. Specifically, they found that eosinophils, IL-5, and eotaxin were increased in the nasal mucosa after bronchial provocation. Furthermore, mast cell numbers decreased in the nasal mucosa secondary to increased degranulation after provocation, as well as increases in peripheral blood IL-5 (29,30). Another study, with similar groups of patients, showed that nasal allergen provocation in allergic nonasthmatic patients induced increased eosinophilia in the bronchial mucosa as well as increased expression of cellular adhesion molecules, signifying increased inflammatory cell migration (31). These studies demonstrate that inflammation in one part of the airway can lead to inflammation in another site, and based on increased eosinophilia in the blood, it seems as though these inflammatory mediators are disseminated hematogenously.

Treatment of AR helps improve asthma control. Several studies have demonstrated that inhaled topical nasal corticosteroids in asthmatics with AR help reduce bronchial hyperresponsiveness (32–34). Another large retrospective review found that medical treatment of AR in asthmatic patients significantly reduced the risk of asthma-related hospitalization and emergency department visits (35). Conversely, treatment of asthma may improve symptoms of AR. One study of nonasthmatics with AR showed that orally inhaled steroids improved allergic symptoms, blood eosinophil levels, and FEV1 levels. This study also suggests that nonasthmatic patients with AR have some degree of bronchial inflammation when exposed to allergens, as expected in the model of "one airway, one disease" (21,36).

One potentially exciting development is the role of specific immunotherapy for AR and preventing the development of asthma. A study of 205 children aged 6 to 14 without a diagnosis of asthma were randomized to treatment of a birch or grass pollen allergy versus an open control group and followed. At 3, 5, and 7 years, approximately 45% of the control group had developed asthma, while only 26% of the treatment group had developed asthma (37). More studies are needed to confirm this finding, yet the possibility of preventing the development of asthma is important and is one way that understanding the unified airway can lead to better patient care.

Chronic Rhinosinusitis and Asthma

As stated above, there is an epidemiologic connection between asthma and CRS, specifically one of the eosinophilic forms of CRS with nasal polyps. There is also a shared pathophysiology between the two from the standpoint of a similar inflammatory milieu. Both diseases are characterized by a Th2 type immunologic response with increase in mast cells, eosinophils, T lymphocytes, IL4, IL5, IL13, and similar cell adhesion molecules. The underlying mechanism that links CRS and asthma is not completely clear, but seems to involve shared inflammation or systemic signaling where inflammation in one location of the unified airway leads to increased inflammation in another site of the unified airway.

Several studies support the relation of CRS to asthma. Asthmatic patients with CRS have a correlation between the extent of disease on sinus computed tomography scanning and increased sputum and blood eosinophil counts (38). Furthermore, Bresciani et al. (39) found that the severity of sinus symptom scores and the extent of sinus disease were directly correlated with asthma severity. With regards to treatment, Ragab et al. (40) concluded that effective medical management of chronic sinus disease improved asthma symptoms and markers of inflammation. Two different studies reported a decreased need for asthma medications, improved pulmonary function, and fewer asthma exacerbations after sinus surgery in asthmatic patients with CRS (41,42). Therefore, it seems prudent to consider lower airway disease burden when deciding about treatment for CRS. Medical and surgical treatment of CRS seem to improve lower airway disease. Ehnhage et al. (43) recommended considering endoscopic sinus surgery early in the natural course of nasal polyposis in patients with asthma, as their prospective study showed a significant improvement in mean asthma symptom scores as well as mean daily peak expiratory flow rate. This link may also be true in children as a review article by Lai et al. (44) concluded that aggressive treatment of sinusitis can significantly improve asthma symptoms and quality of life in children with CRS and asthma. One should also consider medical therapies that improve CRS and asthma, such as corticosteroids and macrolide antibiotics (45).

Two unique diagnoses that warrant mention are Samter triad and cystic fibrosis (CF). These diseases are additional examples of the upper and lower airways functioning as a

unit, and how lower airway disease burden can be impacted by medical and surgical treatment for CRS. Samter triad (aspirin triad, triad asthma) classically is described as aspirin sensitivity, asthma, and sinonasal polyposis. More recently, Samter triad has also been termed aspirin-exacerbated respiratory disease. It typically starts with rhinitis-like symptoms that eventually progress to persistent rhinosinusitis with polyps, followed later by asthma and aspirin sensitivity. Ingestion of aspirin by these patients leads to exacerbation of asthma symptoms within hours, accompanied by rhinorrhea, orbital edema, conjunctival injection, and cervicofacial flushing. Along with avoidance of aspirin, a combination of medical treatment for the asthma and surgical treatment for the polyps is necessary. Like nontriad asthmatics, sinus surgery leads to improvement in asthma symptoms; however, it should be noted that polyps in these patients tend to recur and often multiple polyp-surgeries are needed. Aspirin desensitization therapy is another option for these patients, but is sometimes limited by gastritis. Intranasal lysine-aspirin or ketorolac may prove to be effective alternatives to oral aspirin desensitization therapy (46,47).

CF is a genetic defect in a chloride-transporting channel that leads to multisystem exocrine dysfunction, most notably in the gastrointestinal and pulmonary systems. It also may have a significant impact on the sinonasal tract, causing mucosal edema, chronic sinusitis, and nasal polyps. Over 90% of CF patients show radiologic evidence of sinus disease, and studies have shown that sinonasal involvement leads to significant morbidity in these patients. 20% to 25% of CF patients require sinus surgery, and surgery is often recommended in CF patients awaiting or preparing for lung transplantation. *Pseudomonas aeruginosa* pulmonary infections in CF patients are often recalcitrant to medical therapy and are a significant cause of morbidity and even mortality (48). Studies have shown that these pulmonary infections likely start in the sinuses and ultimately infect the lungs (49). Therefore, it seems prudent to optimize management of sinonasal disease in CF patients. Multiple studies have shown sinus surgery to be safe and effective in CF patients with sinus involvement. Some patients will have persistent disease, however, and endoscopic maxillary mega-antrostomy is an option in CF patients with recalcitrant maxillary sinus disease as this procedure avoids mucosal stripping yet facilitates mucus clearance and topical sinus irrigation (50).

CONCLUSIONS

Although a link between the upper and lower airways has been suspected for decades, recent evidence has helped establish the concept of the unified airway, that is, "one airway, one disease." AR, CRS, and asthma are similar from an epidemiologic, pathophysiologic, and therapeutic standpoint. Managing disease of the upper airway improves asthma symptoms in patients with asthma, and may retard development of asthma in some patients. It is important that otolaryngologists recognize this association and apply it to patient care, as this may have a significant impact on morbidity and quality of life.

HIGHLIGHTS

- The upper and lower airways function as a single unit, the unified airway.
- Otolaryngologists frequently encounter and manage patients with diseases of the upper airway.
- Because of the shared inflammation between the upper and lower airways, patients with upper airway disease have a higher risk of concurrently having or subsequently developing lower airway disease, namely asthma.
- AR is related to and is an independent risk factor for development of asthma and for increased severity of asthma.
- Treatment of AR improves asthma control in asthmatics, and may delay or prevent the development of asthma in nonasthmatics.
- CRS is related to asthma. Successful treatment of CRS improves subjective and objective measures of asthma.
- Otolaryngologists should consider the diagnosis of asthma in patients with AR and CRS.

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Fungal Rhinosinusitis

37

Robert T. Adelson *Bradley F. Marple* *Matthew W. Ryan*

FUNGAL RHINOSINUSITIS

Introduction

Fungi are increasingly recognized as etiologic agents in a diversity of disease states in the nose and paranasal sinuses. Over the past 30 years our enhanced understanding of the role of fungi in sinus disease and the complex interactions between host and pathogen has led to a logical classification of fungal rhinosinusitis with improvements in treatment outcomes. At the same time, the development of endoscopic surgical techniques has improved our diagnosis and treatment of all forms of rhinosinusitis. One distinction between fungal rhinosinusitis and other forms of rhinosinusitis is that all forms of fungal rhinosinusitis require some level of endoscopic assessment or surgery.

Basic Mycology

Fungi are eukaryotic organisms ubiquitous in our environment. Scientists estimate the total number of these different fungal species to be between 20,000 and 1.5 million, of which only a fraction of a percent are responsible for human illnesses, perhaps with only a few dozen species responsible for over 90% of infections (1,2). Fungi can exist either as yeast or molds. Characteristically, molds produce *hyphae*, multicellular, branching tubular extensions (2 to 10 µm in diameter), which coalesce as a colony known as a *mycelium*. Yeast are unicellular, from 3 to 15 µm in diameter, and reproduce asexually via budding. Failure of buds to detach can result in a characteristic chain of fungal cells known as *pseudohyphae*. The *spore* represents an evolutionary solution to fungal survival problems posed by unfavorable conditions. These derivatives of sexual or asexual fungal reproduction disperse easily into the environment, can withstand adverse surroundings, and retain their germinative abilities until a more receptive milieu is encountered. Inhalation of spores is thought to be the most common route by which fungal rhinosinusitis is initiated (3). Once the nasal mucosa has been accessed, development of a pathologic condition is determined not only by the inherent characteristics of the fungus, but by the host's immune system and the complex host–pathogen interaction that ensues.

Classification of Fungal Rhinosinusitis

Fungal disease of the nose and paranasal sinuses can be classified based on the clinical, radiologic, and histologic manifestations of the host–pathogen relationship. Most classification schemes divide fungal rhinosinusitis into invasive and noninvasive diseases based on histopathologic evidence of fungus penetrating host tissue (4) (Table 37.1). Recent adjustments to the nomenclature regarding fungal rhinosinusitis reflect the evolving knowledge in this area of Rhinology (5). The full spectrum of invasive and noninvasive fungal rhinosinusitis is considered below.

Invasive Fungal Sinusitis

The unchecked incursion of omnipresent fungal pathogens are among the most impressive infections to which humans are susceptible. While an intact immune system provides sufficient defense against the development of invasive fungal disease, the proliferation of organ transplant procedures and the greater prevalence of diabetes mellitus have led to significant increases in the incidence of invasive fungal infections reported over the last 10 years (6). The growing population of patients with conditions that predispose them to invasive fungal disease, in combination with dramatic disease velocity and considerable morbidity and mortality, has made invasive fungal sinusitis (IFS) a topic of particular interest within the Otolaryngology literature. Previously, tissue-invasive fungal disease was commonly

TABLE 37.1 CLASSIFICATION OF FUNGAL RHINOSINUSITIS

IFS	AIFR
	GIFR
	CIFR
Non-IFS	Localized Fungal Colonization of the Nasal or Paranasal Sinus Mucosa
	Sinus FB
	AFRS

Modified from Chakrabarti A, Das A, Panda NK. Controversies surrounding the categorization of fungal sinusitis. *Med Mycol* 2009;47:S299–S308; Chakrabarti A, Denning DW, Ferguson BJ, et al. Fungal rhinosinusitis: a categorization and definitional schema addressing current controversies. *Laryngoscope* 2009;119:1809–1818.

referred to by a variety of terms including "zygomycosis," "mucormycosis" and "invasive aspergillosis," which encompassed almost all of the pathogens associated with human-invasive fungal disease. Revisions of the phylogenetic classification within the kingdom Fungi have eliminated the phylum Zygomycota and therefore the pathologic term Zygomycosis has been made obsolete (7). *Mucor*, *Rhizopus*, and many of the organisms responsible for invasive disease of the Order Mucorales are instead assigned to the subphylum Mucoromycotina until further study better delineates the relationship between these organisms (8). Finally, it has become clear that the various forms of fungal rhinosinusitis are primarily determined by host factors; thus the current classification scheme does not include the names of the organism.

General Description of IFS

IFS is defined by fungal elements invading host sinonasal tissue. A diagnosis of IFS hinges upon histopathologic evidence of fungi invading nasal tissue: hyphal forms within sinus mucosa, submucosa, blood vessel, or bone. Specific histopathologic features, immunocompetence of the host, and disease progression allow further classification of invasive fungal sinus disease into three forms: acute invasive fungal rhinosinusitis (AIFR), chronic invasive fungal rhinosinusitis (CIFR), and granulomatous invasive fungal rhinosinusitis (GIFR) (see Table 37.1). In brief summary, a time course of 4 weeks separates acute from chronic disease, AIFR and CIFR typically occur in patients with some degree of immunocompromise while GIFR is limited to the apparently immunocompetent (see Table 37.2). Accurate classification of these different disease entities is an important step in discussing each with regard to their clinical presentation, pathogenesis, diagnosis, and treatment.

ACUTE INVASIVE FUNGAL RHINOSINUSITIS

Clinical Presentation and Diagnosis

AIFR is almost always seen in patients with some degree of compromised immune function, especially defective neutrophil numbers or function, though it has been reported rarely in patients with normal immune function (9). Ailments associated with impaired neutrophil numbers or function, such as hematologic malignancies, aplastic anemia, hemochromatosis, insulin-dependent diabetes, AIDS, organ transplantation, or those undergoing iatrogenic immunosuppression with systemic steroids

TABLE 37.2 FEATURES OF INVASIVE FUNGAL RHINOSINUSITIS

Syndrome	Histopathology	Immunocompetence
Granulomatous	– Invasive fungal hyphae are sparse and found within noncaseating granulomas	– Immunocompetent
Invasive	– Dense fibrosis and mild inflammatory cell infiltrate in surrounding tissue	– Diabetic cases reported rarely
Fungal Rhinosinusitis	– *A. flavus* is most common	
Chronic Invasive	– Invasive fungal hyphae and necrotic tissue with mixed acute and chronic inflammatory cellular response.	– Diabetes Mellitus
Fungal Rhinosinusitis	– Matted hyphae can resemble sinus FB	
	– *A. fumigatus*, many others	
AIFR	– Invasive fungal hyphae with prominent angioinvasion, thrombosed vessels, and necrotic tissue.	– Immunocompromised as a result of hematologic malignancies, therapeutic immunosuppression, diabetes mellitus
	– Moderate inflammatory cell infiltrate (predominantly neutrophils)	
	– *Aspergillus* and Family Mucoraceae are common	– Immunocompetent cases reported rarely

Modified from Chakrabarti A, Das A, Panda NK. Controversies surrounding the categorization of fungal sinusitis. *Med Mycol* 2009;47:S299–S308; Das A, Bal A. Chakrabarti A, et al. Spectrum of fungal rhinosinusitis: histopathologist's perspective. *Histopathology* 2009;54:854–859; DeShazo RD. Syndromes of invasive fungal sinusitis. *Med Mycol* 2009;47:S309–S314.

or chemotherapeutic agents, are particularly prone to development of AIFR (4,10). A high index of suspicion for invasive disease should be maintained in the immunocompromised patient with symptoms of rhinosinusitis, as early findings are often subtle.

The presenting signs and symptoms of AIFR are not distinctly different from those associated with acute bacterial rhinosinusitis. Patients may complain of rhinorrhea, headache, nasal congestion, or facial pain; however, a fever is the most frequent finding, present in 50% to 90% of patients in the days prior to establishing a diagnosis of AIFR (11). The progression of AIFR leads to extrasinus extension by direct erosion through bone, perineural spread, or perivascular extension through communicating vessels in the surrounding bone (Figs. 37.1 and 37.2). Resultant nasal and/or palate mucosa necrosis, densely anesthetic regions of the face, proptosis, cranial nerve deficits, ophthalmoplegia, decreased vision, and mental status changes are ominous indications of aggressive vascular and neural invasion (12).

Several authors have examined the signs and symptoms of AIFR to better determine which patients will benefit from more aggressive diagnostic investigation. Within the immunocompromised patient population, the presence of a fever in combination with one additional symptom of sinonasal inflammation should prompt both imaging studies and nasal endoscopy (11). DelGaudio reported the success of a multidisciplinary approach for the early diagnosis and intervention for AIFR in neutropenic patients (13). Such patients presenting with fever of unknown origin or symptoms consistent with rhinosinusitis underwent sinus computed tomography (CT) scan and nasal endoscopy with appropriate biopsies in an effort to identify AIFR at an early stage. This surveillance protocol significantly reduced the number of surgical procedures required as

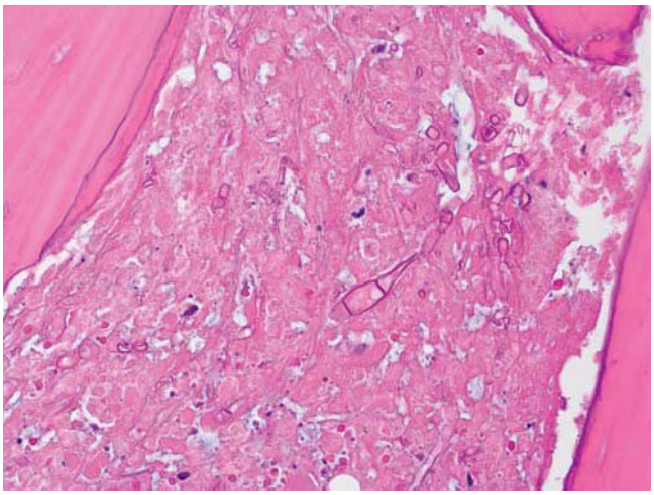


Figure 37.1 AIFR High Magnification (1200×) H&E stained section demonstrates necrotic material between trabeculae of bone removed from the ethmoid sinuses. Invasive septated fungal hyphae are seen penetrating the tissue. Image and Caption: Anthony T. Yachnis, MD; Department of Pathology, University of Florida College of Medicine, Gainesville, FL.

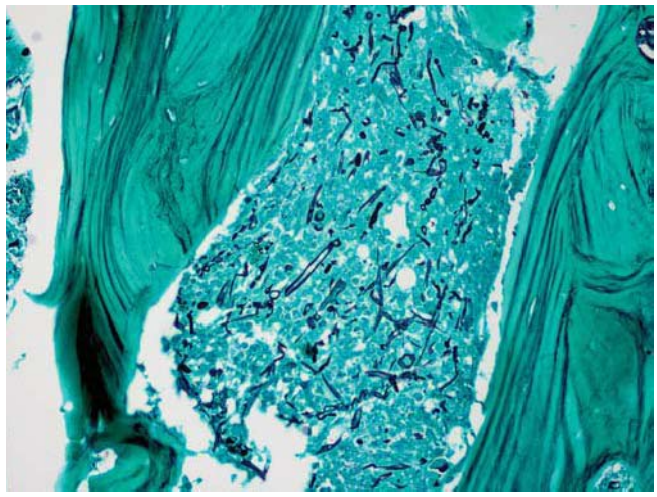


Figure 37.2 AIFR Low Magnification (600×) Gomori Methenamine Stain (GMS) section demonstrates an abundance of invasive fungal hyphae penetrating the bony sinus trabeculae. Image and Caption: Anthony T. Yachnis, MD; Department of Pathology, University of Florida College of Medicine, Gainesville, FL.

well as the long-term morbidity of AIFR (13). Endoscopic findings will change dramatically as the disease progresses. Alterations in the visualized nasal mucosa are subtle early in the course of AIFR; however, nasal mucosal changes are the most consistent physical findings and should always be investigated by thorough endoscopy and biopsy in high-risk patients (13,14).

If biopsy of obvious mucosal abnormalities fail to confirm the expected diagnosis, then directed biopsies should be obtained from sites commonly involved in AIFR, such as the middle turbinate (62%) and nasal septum (24%), as well as any other areas of mucosal edema (11). Pale mucosa that does not bleed normally or elicit painful reactions upon biopsy is indicative of tissue ischemia and incipient fungal angioinvasion. The risks of nasal biopsy are small and several authors emphasize the role of early nasal biopsy in the absence of specific mucosal abnormalities as one method of initiating treatment at the earliest stages of disease (14). The risk of hemorrhage from nasal biopsy can be diminished in patients with an underlying bleeding diathesis by replacing any deficient coagulation factors and correcting the thrombocytopenia to a platelet count of greater than 60×10^9/L. Cutting biopsy forceps will limit the resultant mucosal defect and allow the surgeon to accurately sample the leading edges of ischemic or necrotic mucosal lesions, as biopsies from areas of frank necrosis are less likely to provide a histopathologic diagnosis. Middle turbinate biopsy has been shown to have an overall sensitivity of 75% and a specificity of 100% in diagnosing AIFR on frozen section, and this lower-than-desired sensitivity may reflect the inherent difficulties with frozen section studies of fungal disease processes (15).

The utility of frozen section studies in surgery is twofold: to establish a diagnosis and to guide surgical decision making. Management of AIFR with frozen sections has been

studied by several authors, yet a clear consensus is lacking for the role of this type of histopathologic analysis in intraoperative management. Ghadiali et al. report the largest series to date for frozen section analysis in AIFR with an overall sensitivity of 84% for frozen section studies of biopsies to establish disease with no significant difference between the sensitivities of frozen section identification for *Mucor* when compared to that for *Aspergillus* (16). However, the use of histopathologic controls for surgical margins can be misleading and probably does not offer any additional assurance of disease eradication greater than the clinical appreciation of freely bleeding tissue margins (16). Tissue processing during preparation of the frozen section can be compromised by necrosis, hemorrhage, and distortion of the fungi such that even in cases where invasive fungi are identified, morphologic features that allow speciation cannot be appreciated (16,17). While fungal culture remains the gold standard for identifying the culprit fungi and guiding the choice of antifungal therapy, such cultures remain negative in 30% to 50% of cases (18,19), and prior or concomitant administration of antifungal agents also decrease yield on fungal culture. Newer methods such as *in situ* hybridization technology with oligonucleotide probes to identify fungus-specific ribosomal RNA sequences hold promise. This technique has advantages over traditional fungal culture of both greater speed and higher sensitivity in determining the involved fungal species, allowing more rapid institution of targeted antifungal therapy (20).

Radiology

Diagnostic imaging of the paranasal sinuses is often performed in the workup of patients with presumed or proven AIFR. Although no radiographic imaging findings have been found to be pathognomonic for AIFR, such studies assist in the differential diagnosis, treatment planning, and monitoring of the condition. CT images will document the presence of radiographic changes consistent with sinus disease and define the sinonasal anatomy both for surgery and as a baseline exam for future comparison. Fine-cut, noncontrasted CT scans of the sinuses in axial and coronal planes can detect paranasal sinus bony erosion and screen for extrasinus soft tissue involvement. Magnetic resonance imaging (MRI) (with or without gadolinium) delineates the degree of orbital involvement and/or intracranial spread. These findings provide key information regarding the feasibility of surgery and ultimately patient prognosis.

Although bone erosion and extrasinus extension are often cited as classic radiographic findings of AIFR, these results are not typically found in the incipient case of AIFR but instead are ominous signs of advanced disease. The radiographic findings with the greatest positive predictive values are also those that are indicative of late and often irreversible disease: osseous erosion, facial soft tissue thickening, extrasinus involvement. Soft tissue infiltration with loss of the fat planes anterior and posterior to the maxillary sinus is considered an early indicator of AIFR (21). Another subtle finding, severe sinonasal edema without evidence of bone erosion, is emerging as a consistent and early radiographic finding amongst many cases of invasive disease (16,22). Severe unilateral thickening of nasal cavity mucosa is the most consistent CT characteristic suggestive of early IFS, albeit nonspecific for invasive fungal disease (23) (Fig. 37.3).

Physicians should not become overly dependent upon radiographic information alone when considering the diagnosis of AIFR. AIFR may present without significant radiographic evidence of sinusitis and there is poor correlation between surgical specimens and radiographic demonstration of the extent of disease (23). While some studies report a normal CT scan in 12% of patients with histopathologic evidence of IFS, other reviews found no patient afflicted with the disease to have a normal CT scan (11,16). Care should be taken in the interpretation of CT scans in cases suspicious for AIFR as imaging studies are supportive, but not diagnostic, of AIFR.

Pathology

Aspergillus and the members of the Subphylum Mucoromycotina (*Mucor, Rhizomucor, Absidia*) are the fungi most frequently implicated in AIFR, though unusual cases involving *Candida, Bipolaris, Cunninghamella, Conidiobolus, Scytalidium, Fusarium,* and *Exserohilum* have been reported (2,12).

The clinical manifestations of AIFR develop as a result of the propagation of angioinvasive and neuroinvasive fungi within the sinonasal cavity and facial tissues. AIFR

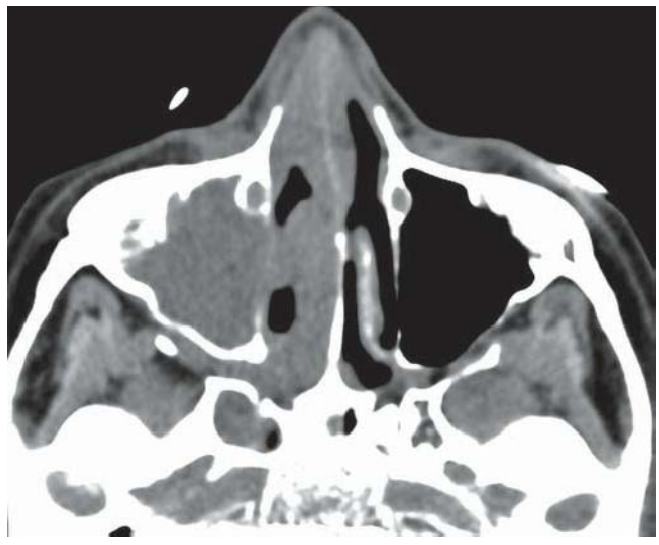


Figure 37.3 AIFR Axial on contrast CT scan shows right maxillary sinus opacification and right nasal cavity mucosal thickening. There is loss of normal fat planes within the pterygopalatine fossa, a sign of invasive disease. Image and caption: Jeffrey Bennett, MD. Department of Radiology, University of Florida College of Medicine, Gainesville, FL.

is defined by fungal forms invading into the submucosal tissue, often associated with angioinvasion resulting in vascular thrombosis, infarction, and necrosis. Areas of coagulative tissue necrosis are extensive and the total numbers of hyphae can be relatively sparse at times, with an associated neutrophilic infiltration (9). The acidotic environment of tissue ischemia and necrosis provide an ideal medium for fungal growth and further propagation of the fungal infestation (12).

Treatment

AIFR is a condition specific to a well-defined patient population, and as such, a high index of suspicion for disease and preventive measures constitute the first step in management in the at-risk population. The most closely monitored of the high-risk population, those with hematologic malignancies or post-transplant patients (AIFR incidence rates from 1.7% to 2.6%), are also most amenable to methods of decreasing environmental exposure to fungi, administration of prophylactic antifungal drugs, and hospital-based screening protocols for IFS. Hospital rooms equipped with high-efficiency particulate air filtration have been shown to reduce fungal burdens, thereby intervening at the initial stage of fungal inhalation (10,14).

Prophylaxis with antifungal medications in high-risk patients should be used with caution, as their side effect profiles, toxicity, and the potential for augmenting drug resistance remain important concerns (10). Nevertheless, prophylaxis is frequently initiated in high-risk patients undergoing additional immunosuppressive therapy. Similarly, prophylactic antifungal medications are indicated for patients with a known history of invasive fungal disease who will require further immunosuppressive therapy (7,10,24).

While secondary prophylaxis with amphotericin B deoxycholate (ABD) is well established and demonstrates a reduction in the rate of recurrent infection, newer, less toxic antifungal agents have supplanted ABD in this role (10). Posaconazole, a second-generation extended spectrum triazole, has been shown to be superior to standard azole therapy in preventing invasive fungal infections in immunocompromised hosts and may soon play a primary antifungal role in the treatment of AIFR (25). While there are no studies that compare prophylaxis regimens with regard solely to AIFR, there is evidence that severely immunocompromised patients, with neutropenia have improved outcomes with posaconazole over earlier generation azoles in the prevention of fungal infections (26). AIFR treatment is most successful when aggressive multimodality therapy can be instituted in the earliest stages of disease. Some hospital-based protocols initiate CT scans of the sinuses in high-risk patients with sinonasal symptoms or unexplained fever, followed by endoscopic examination and intranasal biopsy of all patients with radiographic abnormalities (14,22,23).

Treatment of AIFR relies on medical and surgical therapy directed against the offending fungal pathogen in addition to reversal of the patient's underlying state of immunocompromise. Systemic antifungal medication is instituted immediately while treatment of diabetic ketoacidosis (DKA) or restoration of neutropenia is undertaken. Correction of acidosis and underlying dehydration is associated with an 80% survival rate in AIFR with concomitant DKA (7,9). In transplant patients or those with hematologic malignancies, an absolute neutrophil count (ANC) less than 1,000/mm^3 has been associated with both the onset of disease and reduced survival. White blood cell transfusions and administration of granulocyte colony-stimulating factor that increase the ANC above 1,000 mm^3 have been shown to improve survival in neutropenic patients (14,18).

Systemic antifungal therapy is routinely employed in AIFR. ABD, a polyene macrolide, has been the drug of choice for the systemic treatment of invasive and disseminated fungal infections since its introduction into clinical practice in the 1960s (27). Amphotericin B exhibits fungicidal activity against a wide spectrum of pathogenic fungi; however, its side effects are multiple, serious, and can limit both dosage and duration of therapy in critically ill patients (27). Infusion-related symptoms including fever, chills, headache, nausea, vomiting, thrombophlebitis, and hyperkalemia are seen in 50% of patients and can be managed acutely; however, long-term myelosuppression, ototoxicity, and nephrotoxicity are more problematic (18,27,28). Nephrotoxicity, which occurs in 80% of patients treated with amphotericin B, and the resultant azotemia and electrolyte disturbances (hypokalemia) ultimately mandates halting therapy or switching antifungal agents (27). The negative impact of ABD on the general medical condition of these typically compromised patients has increasingly favored the use of lipid formulations of amphotericin B in lieu of the older and more harmful deoxycholate preparation.

Lipid-based formulations of amphotericin B have improved safety profiles, less renal toxicity, and are effective in treating AIFR (18,27). Though randomized clinical trials of invasive fungal infections in the treatment of AIFR comparing lipid-based formulations with the deoxycholate preparation are not available, evidence derived from treatment of other disseminated and invasive fungal infections favors equal if not greater efficacy and reduced complications in patients receiving the lipid formulation (7). Recently, small case series specifically addressing paranasal sinus disease demonstrate significantly greater survival rates in patients receiving lipid amphotericin B than in those managed with ABD (28,29). The ability to deliver higher total doses (5 to 7.5 mg/kg/day) with reduced toxicity highlights the issue of higher drug cost as the lone remaining obstacle to more widespread utilization of lipid-based formulations of amphotericin B (7,28).

The introduction of extended spectrum azoles, voriconazole, and posaconazole, has expanded the available options both for antifungal therapy of acute disease as

well as prophylaxis of recurrent invasive fungal infections in immunocompromised populations. Voriconazole produces survival advantages with fewer side effects than amphotericin B in the treatment of systemic invasive aspergillosis (30), while posaconazole demonstrates both survival benefits and reduced drug costs over standard therapy with amphotericin B in the management of the same invasive fungal condition (31). Posaconazole is active against the mucoracea while voriconazole is not. Posaconazole has been shown to be a cost-effective medication in the prevention of invasive fungal disease in neutropenic patients (25). The efficacy of posaconazole and voriconazole in treating *Aspergillus* AIFR has been reported. Baumann reported the successful use of voriconazole following sphenoidotomy in four cases of AIFR resulting from *Aspergillus*, while Chirch reported a successful case of combination therapy with caspofungin and voriconazole for *Aspergillus* AIFR in the absence of surgery (32,33). The reduced side effects of these agents may prompt their use both in treatment and prophylaxis within the medically compromised patient population at risk for AIFR. At the present time, however, clinicians should institute voriconazole therapy without hesitancy when either *Pseudoallescheria boydii* or Aspergillosis is identified. *P. boydii* is typically resistant to amphotericin, yet remains susceptible to azole therapy (9,18). While data specific to sinusitis is not available, initial therapy of pulmonary aspergillosis and systemic invasive *Aspergillus* infections with voriconazole (6 mg/kg IV b.i.d. then 4 mg/kg b.i.d. for 7 days, then oral dosage of 200 mg b.i.d.) resulted in significantly greater survival and fewer adverse events than in those treated with ABD (30). Visual disturbances and skin reactions are the most common adverse events in patients treated with voriconazole. While hepatic function abnormality is the most common serious adverse effect in patients treated with voriconazole, significantly fewer serious side effects were experienced in contrast to the group treated with ABD (30). The need for improvements in the medical management of invasive fungal disease is obvious, and a number of therapies including echinocandins, statins, iron-chelating agents, granulocyte transfusions, granulocyte-macrophage colony–stimulating factor, and hyperbaric oxygen have been considered (7,34). Echinocandins are a drug class of large lipopeptides with fungicidal activity against *Candida* and fungistatic activity against *Aspergillus*, suggesting a potential role in the combination therapy of invasive fungal disease. Though clinical trials in AIFR are lacking, a retrospective review comparing liposomal amphotericin B to combination therapy with caspofungin demonstrated a significant survival benefit in the AIFR cases treated with combination therapy (35). The lack of a mammalian cell target for echinocandins endows this therapy with a very favorable safety profile (7,34). Further clinical trials examining the role of eichinocandins in combination therapy for IFS should be forthcoming.

Antifungal medications can be administered through an intranasal route with the potential for greater local activity and fewer systemic toxicities. Intranasal routes have been explored as methods of IFS prophylaxis with varied success; however, as nasal irrigations, nebulizer treatments, and amphotericin B-soaked surgical dressings are of minimal risk and possibly of great benefit, they deserve consideration as adjunctive measures in the management of AIFR (12,14,24).

Surgery plays multiple roles in the management of invasive fungal rhinosinusitis. The first and most important is to secure a diagnosis through tissue biopsy. The second main role of surgery in AIFR is to debride tissue that is obviously involved with fungus, remove devitalized tissue, and establish pathways for sinus drainage and postoperative monitoring of the affected sites. Surgery interrupts the progression of disease by gross removal of the pathogen along with the necrotic tissue in which fungi thrive (12). Debridement is extended until healthy bleeding tissue is encountered. Resection back to vascularized margins favors the host defenses that are required to clear such infections: well-perfused tissue that can deliver systemic antifungal medications, restore a normal tissue pH, and augment local neutrophil numbers (36). There is no demonstrable difference in survivorship between endoscopic and open operations, and therefore open surgical procedures should be limited to those cases where diseased tissue cannot be removed endoscopically, for example orbital, facial, palatal, and intracranial fungal disease (37). The extent of surgery employed needs to be tempered by the patient's overall prognosis and the likelihood of reversing the underlying disease process that led to invasive fungal disease. Surgery facilitates effective antifungal treatment, but is ultimately less important than intact immunity and appropriate medical therapy.

PROGNOSIS OF AIFR

The mortality of AIFR has been cited traditionally as 50% to 80%; however, recent series report mortality rates as low as 18%, perhaps due to earlier recognition and treatment (13,14). Many authors have examined traits of both the host and pathogen to identify elements of prognostic significance. Anatomic extensions of disease with intracranial and/or intraorbital involvement are clinically obvious predictors of poor outcomes, borne out by large case series (17,36,37). The importance of host immune function is highlighted in studies that demonstrate recovery of ANC to be the single feature most predictive of survival in AIFR (9,11,14,18,23).

Chronic Invasive Fungal Rhinosinusitis

Some IFS progresses gradually over time. These cases, labeled CIFR and GIFR, are uncommon conditions with similar clinical presentations and relatively favorable prognosis in comparison to AIFR (38). The sharpest distinction between the two conditions can be made on the

basis of histopathologic features and typical causative organisms (4,5,9). At the present time, CIFR and GIFR are considered distinct disease processes, despite their similar clinical courses and treatment (5). CIFR and GIFR will be addressed separately in the discussion that follows, with particular attention to their distinguishing features.

CLINICAL PRESENTATION

CIFR, formerly known as chronic indolent IFS, was first identified by McGillin in 1980, and is now considered a slowly progressive form of invasive fungal disease (4,9). Symptoms of CIFR are nonspecific and mirror those of chronic rhinosinusitis (CRS): facial pain, headache, nasal congestion. Unilateral blood streaks within nasal drainage have been reported as the most common symptom in a large case series of CIFR (in which a few GIFR cases were included as well) (38). Ocular symptoms are common and are an indication of the extent and aggressiveness of the disease. While proptosis is common both to CIFR and GIFR, orbital apex syndrome with its attendant symptoms of disturbed visual acuity and impaired motion of the extraocular muscles is more particularly associated with CIFR (9).

Typical presentations of CIFR includes nonspecific rhinosinusitis symptoms made remarkable by their long duration, slow progression, and refractoriness to standard antibiotic therapy (39). Cases occur in immunocompetent patients, yet diabetes mellitus remains the comorbidity with which CIFR is most closely associated. Diagnosis of this uncommon infection in a well-controlled diabetic patient may be delayed until the development of vision changes, proptosis, facial deformity, seizures, or altered mental status mandate that the physician consider more ominous possibilities (38).

DIAGNOSIS

The clinical presentation of CIFR is nonspecific. Diagnosis is made by tissue biopsy. CIFR provokes modest sinonasal inflammation and endoscopic exam typically identifies nasal polyps and thick mucus without the eschar or necrosis characteristic of AIFR (39). A diagnosis of IFS can be established only by identification of submucosal invasion of fungal elements on histopathologic examination of tissue specimens, though imaging can narrow the differential diagnosis and better direct surgical biopsies. CIFR evolves over a time course of greater than 4 weeks and may affect normal populations or those with mild immunocompromise (cortico steroid treatment, diabetes mellitus, HIV) (39).

IMAGING

There are no pathognomonic imaging findings of CIFR (40,41). There are, however, radiologic features that are characteristic of CIFR and these are useful when drawing distinctions between an IFS and the less concerning allergic fungal rhinosinusitis (AFRS). In CIFR, paranasal sinus involvement is usually unilateral with a homogenous opacification on CT scan and bone erosion limited to sites of extrasinus extension (40). Neurologic or ophthalmologic deficits warrant a contrast-enhanced MRI of the 1 to delineate involvement of the dura or orbital contents, as intracranial or intraorbital disease significantly impacts treatment planning and prognosis (39). MRI findings particular to CIFR include a T1 intermediate signal intensity with T2 low to very low signal intensity with a homogenous and intense enhancement with contrast, yet these findings are not alone diagnostic of CIFR (40).

Pathology

Histopathologic features of CIFR help distinguish this entity from both AIFR and GIFR. CIFR has been attributed to a wide assortment of fungi; yet *Aspergillus fumigatus* remains the most commonly cultured pathogen across multiple independent case series (38,40). Plentiful submucosal fungal elements are found invading sinonasal mucosa, with only occasional angioinvasion and rare infarction of the surrounding tissue. A paucity of inflammatory cells are recruited and, importantly, fibrotic reactions or giant cell granulomas are absent (4,5,9,42). Dense collections of fungal hyphae and lesser degrees of necrosis distinguish CIFR from both GIFR and AIFR (4,5) (Table 37.2). Nasal polyposis is routinely associated with CIFR as is the recovery of especially viscid mucus within the affected paranasal sinuses (5).

TREATMENT AND PROGNOSIS

The relative rarity of CIFR and lack of controlled treatment trials obliges physicians to base their therapeutic interventions on published case reports and personal experience with cases of IFS. Surgery is required in every case to obtain a diagnostic biopsy and to debride the remaining involved tissue. The need for antifungal therapy in CIFR is less certain. Cure rates of nearly 90% have been reported in a series of surgically managed CIFR for which ABD followed by oral itraconazole was administered (38). Newer generations of antifungal medication with reduced side effect profiles tilt the risk:benefit ratio in favor of their more liberal use in CIFR (7,34,43). Extensive operations that are expected to result in adverse neurologic, functional, or aesthetic impairments are not supported in CIFR (38,39). Surgical debridement should remove all involved tissue and maintain intact natural barriers to infection (dura and periorbita), keeping in mind the more indolent disease course (39). Reexploration in the operating room and further resection of tissue is determined on an individual basis. The general consensus among recent authors recognizes that while surgery alone can successfully treat cases of CIFR, combined therapy using newer, less toxic, systemic antifungal chemotherapy agents is preferred (38,43).



Figure 37.4 **A,B**: GIFR Axial and Coronal CT scans show expansion of the involved right frontal sinus with long-standing invasive fungal infection. Bone of the skull base has become dehiscent and there is direct extension of GIFR into the brain. Image and caption: Jeffrey Bennett, MD. Department of Radiology, University of Florida College of Medicine, Gainesville, FL.

Prognostic features of CIFR are not well characterized; therefore, careful long-term follow-up is recommended. The prognosis for CIFR is far better than what can be expected in other IFS entities. The duration for antifungal therapy for CIFR is not uniformly established. Duration of therapy can be individualized to the severity of the patient's disease process and follow-up examinations. Asymptomatic recurrences of CIFR are not rare and should be treated early in order to prevent intracranial and intraorbital complications. Routine scheduled postoperative CT scans coupled with planned endoscopic surveillance with tissue biopsies as needed are the most effective methods for detection of recurrent invasive disease.

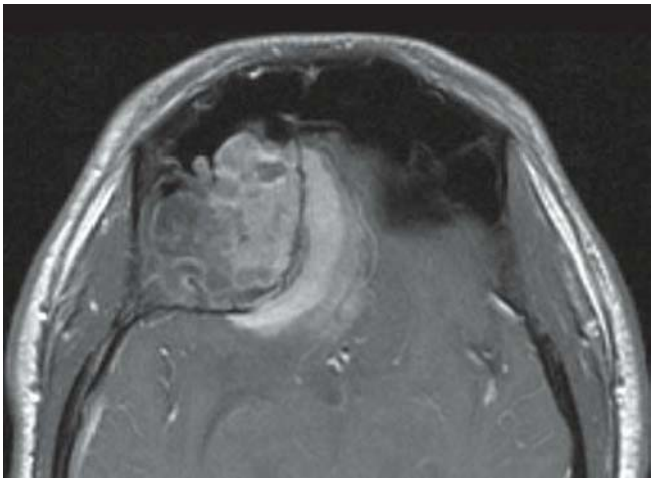


Figure 37.5 GIFR Axial postcontrast T1-weighted MRI of the same patient shown in Figure 37.4 demonstrates enhancement within the granulomatous mass and the adjacent involved brain. Image and caption: Jeffrey Bennett, MD. Department of Radiology, University of Florida College of Medicine, Gainesville, FL.

Granulomatous Invasive Fungal Rhinosinusitis

GIFR, historically referred to as primary paranasal aspergillosis granuloma in Sudan, is a rare condition whose former name reflects both its geographic predilection and causative organism. Reports of GIFR are mainly circumscribed to the regions of North Africa, India, Pakistan, and Saudi Arabia and *Aspergillus flavus* is uniformly identified when positive cultures are obtained. The symptoms, clinical presentation, exam findings, and imaging studies of GIFR are similar to those of CIFR. Long durations of disease can cause significant remodeling of the skull base and maxillofacial skeleton in response to this slow invasive process (Figs. 37.4 and 37.5). CIFR exhibits a predilection for diabetics that GIFR does not (5). Important distinctions in the clinical features include enlarging granulomatous masses in the paranasal sinuses and adjacent regions of the face that can result in proptosis (5).

PATHOLOGY

Histopathologic study of GIFR shows tissue invasion with few hyphae and a variable inflammatory infiltrate. The presence of a granulomatous response with extensive fibrosis and fungal hyphae within multinucleated giant cells

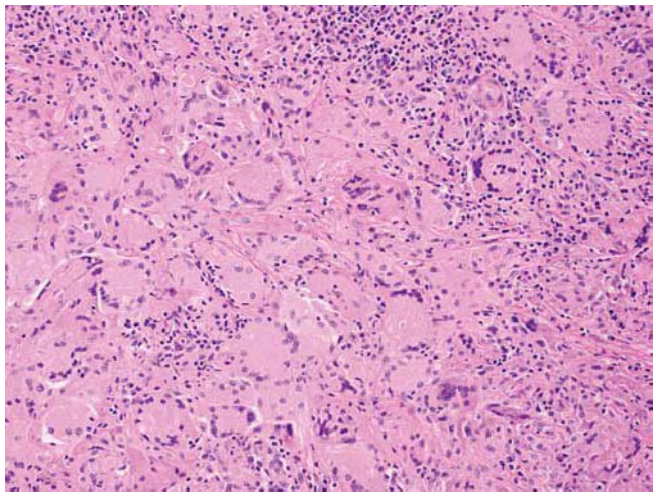


Figure 37.6 GIFR H&E-stained image showing marked granulomatous inflammation with abundant multinucleated giant cells in sinus mucosa. Image and Caption: Anthony T. Yachnis, MD; Department of Pathology, University of Florida College of Medicine, Gainesville, FL.

and noncaseating granulomas distinguishes GIFR from CIFR, which shows more tissue necrosis and purulence (42) (Figs. 37.6 and 37.7).

TREATMENT AND PROGNOSIS

The treatment options for GIFR have closely paralleled those for CIFR. A more sinister clinical course is appreciated for GIFR in comparison to CIFR, with higher rates of relapse and an overall lower survival rate. Aggressive surgery to clear the detectable disease and remove necrotic tissue is recommended in combination with systemic antifungal chemotherapy. Repeat operations for diagnostic surveillance and therapeutic clearance of disease are recommended, as in CIFR. Though specific outcomes data for the antifungal therapy of GIFR are lacking at this time, the reduced toxicity of newer antifungals favors long-term therapy (9).

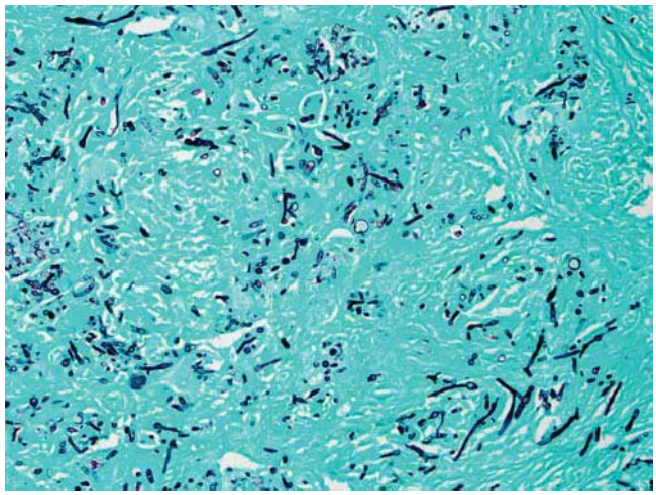


Figure 37.7 GIFR Low magnification samples from patient in Figure 37.6 (original magnification 600×), GMS section showing abundant invasive fungal hyphae. Image and Caption: Anthony T. Yachnis, MD; Department of Pathology, University of Florida College of Medicine, Gainesville, FL.

Noninvasive Fungal Sinus Infections

There are three different forms of noninvasive fungal rhinosinusitis. Localized fungal colonization of nasal or paranasal mucosa, sinus fungus ball, and AFRS are considered below.

Localized Fungal Colonization of Nasal or Paranasal Mucosa

Formerly termed saprophytic fungal infestation, the category of localized fungal colonization of nasal or paranasal mucosa is defined by visible growth of fungus on mucus crusts within the sinonasal cavity and not the presence of fungi demonstrable by culture alone. The condition usually comes to clinical attention during postoperative endoscopic examinations or as a result of a foul odor from the nose. Daily nasal saline irrigation is recommended along with endoscopic examination and debridement until the condition resolves. Imaging studies are not likely to add to the information obtained by a thorough history and physical examination that includes nasal endoscopy. Systemic antifungal medications are not recommended.

Fungal Ball of the Paranasal Sinuses

Fungal ball (FB) of the paranasal sinuses, often erroneously referred to as "mycetoma" is an extramucosal mycosis that fills one or more paranasal sinus with densely tangled, inspissated fungal debris and mucous without invasion of the underlying mucosa.

CLINICAL PRESENTATION

FBs tend to develop in older females who are immunocompetent, nonatopic, and have a prior history of endodontic treatment of the maxillary dentition (44). FB may be asymptomatic or cause the typical symptoms of CRS. Maxillary and ethmoid involvement causes facial pain, nasal airway obstruction, purulent rhinorrhea, and cacosmia while sphenoid disease may cause vertex headache and postnasal drip (45). A prolonged duration of CRS symptoms, unilateral symptoms, and poor response to medical therapy may point to a FB. Nasal endoscopy reveals normal to mild, nonspecific mucosal changes in about half of the patients. Radiographic imaging studies often point to the diagnosis (44).

RADIOLOGY

Fungus balls have characteristic imaging findings. CT scans are the most frequently obtained imaging study of the paranasal sinuses and FB cases will appear as complete or partial

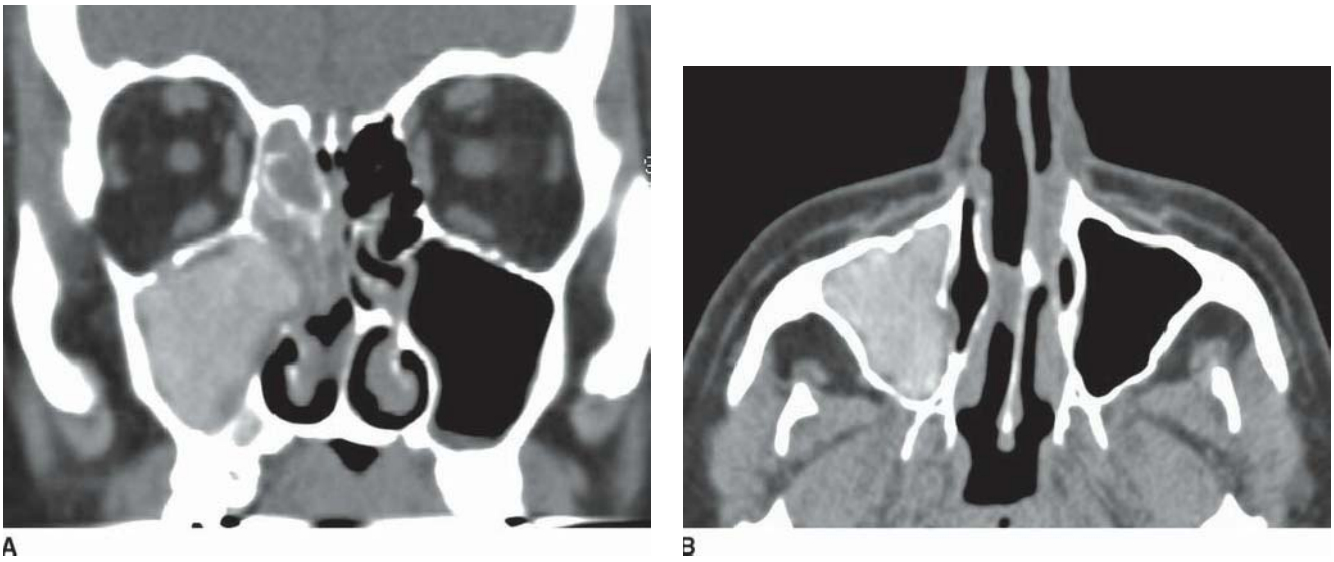


Figure 37.8 **A,B**: Fungus ball of the paranasal sinuses axial and coronal noncontrast CT scans show complete opacification of the right maxillary sinus, higher attenuation densities within the sinus, and thickening of the paranasal sinus mucosa consistent with chronic inflammation. Image and caption: Jeffrey Bennett, MD. Department of Radiology, University of Florida College of Medicine, Gainesville, FL.

sinus opacification (Fig. 37.8). Single sinus involvement is the rule, with less than 10% of cases involving multiple sites (46). Maxillary sinus disease (62% to 84.4%) is reported to be several times more frequent than sphenoid involvement (14.4% to 25%), with the ethmoid site a more rare location (0.6% to 4%) (44,46). Hyperattenuation of the FB on noncontrast CT results from the dense collection of hyphae within the sinus lumen while the inflamed sinus mucosa appears hypoattenuated on CT and hyperintense on T2-weighted MRI (40). The FB itself does not enhance, which can be helpful in differentiating FB from malignant processes or other processes associated with sinus opacification and bone erosion. Maxillary FB is more likely to have microcalcifications seen on CT compared to other paranasal sites (44). Bony erosion or sclerosis occurs in nearly half of cases. The classically described MRI finding of a hypointense signal void in the area of disease on T2-weighted studies as a result of calcifications and chelated paramagnetic metals is present in only 50% of reviewed cases of proven FB of the paranasal sinuses (44).

PATHOLOGY

The pathogenesis of FB is incompletely understood, but epidemiologic features point to possible contributing factors. These include a female predominance (1.87 to 2.97:1), absence of the disease process in children, and a strong association with prior endodontic treatment of maxillary teeth (44,46,47). FB formation requires inhalation of fungal spores and sequestration within the sinonasal passages. A poorly ventilated paranasal sinus favors germination and growth as the fungus evades host immune defenses and avoids clearance from the sinuses by mucociliary transport (4). Bacterial infections may augment fungal growth via purulent secretions that provide valuable nutrient supplies to the fungi (4,46). While culture of sinus contents is often negative, *A. fumigatus* is the most common pathogen isolated (46). Histopathology reveals tightly packed fungal hyphae with a pale center and the thin, septate, acute-angle branching of hyphae that become more apparent at the periphery of the FB (Fig. 37.9). The associated sinus mucosa demonstrates a mild to moderate infiltration of chronic inflammatory cells in the absence of tissue invasion, granulomas, or allergic fungal mucin (42).

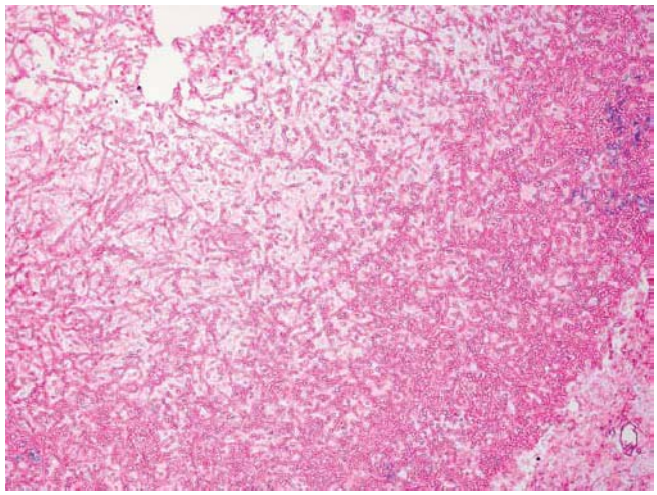


Figure 37.9 Fungus Ball of the Paranasal Sinuses High magnification view of H&E stained material. Enormous abundance of fungal hyphae in a densely matted configuration that is noted to be paler toward the center of the fungal collection. Image and Caption: Anthony T. Yachnis, MD; Department of Pathology, University of Florida, College of Medicine, Gainesville, FL.

FBs preferentially involve the maxillary sinus (61% to 84% of cases), and endodontic treatment of maxillary teeth has been proposed to play a role in pathogenesis (44,46). Zinc oxide-containing materials employed in root-filling during endodontic surgery do promote the growth of *A. fumigatus* and can decrease the protective functions of respiratory epithelium both by paralysis of normal cilia as well as induction of soft tissue hypervascularity and associated edema (47). Park demonstrated endodontic treatment of the ipsilateral maxillary teeth to be a significant risk factor for FB (47). However, FB can involve paranasal sinuses that are removed from the maxillary dentition as well as maxillary sinuses in patients with untreated teeth, so it is clear that other etiologic forces are at play when this disease process occurs in remote paranasal sinus locations.

The average age for patients diagnosed with FB in several studies ranged between 49.4 and 52.7, and given that endodontic procedures increase in frequency with aging, the role of endodontic treatment in maxillary FB is thought to explain the limitation of this disease process to older populations (44,46). The absence of FB in children (less than 19 years old) may reflect the absence of endodontic procedures in this population.

TREATMENT

FBs of the paranasal sinuses are adequately treated by complete surgical removal of the FB and thorough irrigation of the involved sinus. Though traditionally addressed through external approaches, endoscopic techniques are extremely effective in achieving complete extirpation of disease. Trephinations for irrigation, endoscope port placement, or external approaches should be considered in only the most challenging cases. Historical recurrence rates of less than 5% now approach 0% as surgical experience and endoscopic instrumentation have improved (44,45). Postoperative antifungal therapy is never recommended, unless the patient suffers from comorbid conditions with seriously compromised immune function, and then consultation with an Infectious Disease specialist may be warranted.

Allergic Fungal Rhinosinusitis

AFRS is a distinct clinicopathologic entity within the spectrum of CRS that has become increasingly well recognized over the last 30 years. Originally proposed by Millar et al. in 1981 as an upper airway version of allergic bronchopulmonary aspergillosis (ABPA), the newly described allergic Aspergillosis of the sinuses reflected many of the features of the pulmonary disease: a type I hypersensitivity to fungal antigens with production of mucoid impactions (48). By 1983, publication of additional similar cases allowed authors to both describe the histopathologic nature of the mucin that so closely resembles the mucous plugs seen in ABPA and recognize that a significant proportion of CRS patients may have the disease (48). It has been estimated that up to 5% to 10% of all CRS cases undergoing surgery meet modern criteria for diagnosis with AFRS. A complete understanding of this entity is required to optimize the medical and surgical management of this unique subset of CRS patients.

CLINICAL PRESENTATION

Patients with AFRS present with symptoms typical of CRS with nasal polyps: progressive nasal congestion, nasal airway obstruction, hyposmia/anosmia, postnasal drip, periods of exacerbated symptoms with facial pain or pressure, and thick rhinorrhea. Findings that should spur additional inquiry into a diagnosis of AFRS include reports of thick, dark, viscid mucus, recurrence of disease despite appropriate treatment, facial dysmorphia (malar flattening, proptosis, or telecanthus) and asymmetric nasal polyp disease. The clinical presentation may be subtle or dramatic with gross facial disfigurement or complications that have included cavernous sinus thrombosis and visual loss resulting from optic nerve compression (49,50). AFRS cases are more common in the Southern and Southeastern United States (51).

AFRS patients present at a younger age than do those with other forms of polypoid CRS. African Americans and individuals of low socioeconomic status may be disproportionally affected (52). African American patients present at significantly younger ages and with greater degrees of bone erosion than do Caucasian patients (53). Both males and African American patients, across multiple studies, are found to have statistically greater incidences of skull base and orbital erosion in AFRS. Whether this represents a delay in diagnosis resulting from poor access to medical care, a more aggressive course for AFRS in this racial group, or genetic differences in the bony response to inflammatory sinonasal disease is unclear. However, African Americans have been shown to experience a greater improvement postoperatively than Caucasians (54).

DIAGNOSIS

A constellation of clinical, radiographic, and immunologic features are required to establish a diagnosis of AFRS. Although several closely related sets of histopathologic features have been proposed to define the disease,(3) the five criteria set forth by Bent and Kuhn (55) remain the most widely accepted diagnostic criteria. Patients with AFRS demonstrate: (a) type I hypersensitivity to fungi, (b) nasal polyposis, (c) characteristic findings on CT scan including serpiginous areas of high attenuation, (d) gross production of eosinophilic mucin containing noninvasive fungal hyphae, and (e) positive fungal stain. While the disease may be suspected based on physical examination or radiographic findings, a diagnosis of AFRS cannot be established until sinus tissue and mucus obtained during surgery have been reviewed by a pathologist and allergy testing is performed. The retrospective nature by which AFRS is diagnosed has prompted investigators to search for a method of identifying the condition preoperatively.

Dhiwakar et al. (56) found the triad of hyperattenuation on CT imaging, nasal polyps, and elevated titers of anti-*Aspergillus* IgE antibody to preoperatively diagnose AFRS with a sensitivity of 70% and a specificity of 100%. Another study of preoperative diagnosis of AFRS was limited to CRS and noninvasive categories of fungal rhinosinusitis. The combination of type I hypersensitivity, CT findings of hyperattenuation, and bony erosion were shown to predict the diagnosis of AFRS and differentiate this condition from CRS as well as other forms of noninvasive fungal rhinosinusitis (57).

RADIOLOGY

In AFRS, eosinophilic mucin is sequestered within involved paranasal sinus cavities and its accumulation results in typical radiographic findings (Table 37.3). Heterogeneous areas of hyperattenuation on CT scan are noted within the lumen of paranasal sinuses opacified by eosinophilic mucin (40,41). Current evidence points to accumulations of heavy metals (e.g., iron, magnesium, manganese) and calcium salt precipitation within inspissated eosinophilic mucin as the most likely cause of these heterogeneous areas of hyperattenuation. The high protein and low water concentration of eosinophilic mucin in conjunction with heavy-metal precipitate produces a signal void on T2-weighted MR images while the signal intensity is more varied on T1-weighted images (40,41). The loss of signal on T2 helps differentiate AFRS from neoplasms that also produce sinus opacification, bone erosion, and orbital or skull base invasion on CT scan. Inflamed paranasal sinus mucosa is routinely hypointense on T1-weighted images, hyperintense on T2-weighted images, and enhances with gadolinium contrast (40,41) (Fig. 37.10). The combination of CT and MRI findings described above are strongly suggestive of AFRS and can help narrow a patient's differential diagnosis.

CT imaging of patients with AFRS often reveals a surprising degree of paranasal sinus bone erosion with involvement of the orbit and skull base. This common finding is thought to be the result of pressure atrophy from accumulated eosinophilic mucin and bony remodeling that results from the local inflammatory state within the affected sinuses (40). Bone remodeling occurs in 20% to 90% of AFRS cases, with more recent reviews at tertiary care centers indicating frequencies of orbital or skull base erosion occurring in 44% to 56% of AFRS cases (40,53). Orbital involvement occurs more frequently than does skull base erosion, and the ethmoid sinus is the most common site of AFRS associated with bone remodeling.

TABLE 37.3 RADIOGRAPHIC CHARACTERISTICS OF AFRS

CT Characteristics

1. Disease tends toward unilateral or asymmetric distribution
2. Involved sinuses are expanded
3. Bone bordering involved sinuses may demonstrate attenuation or erosion (best demonstrated on bone-weighted algorithms
4. Adjacent anatomic spaces may be displaced
5. Signal heterogeneity within the involved sinuses (best demonstrated with soft tissue algorithm)

MRI Characteristics

T1

1. Involved paranasal sinuses demonstrate variable signal intensity.
2. Enhancement of periphery of the involved paranasal sinuses (mucosal edema)

T2

1. Hypointensity of signal within involved paranasal sinuses (indication of dehydrated state of mucin)
2. Enhancement of periphery of the involved paranasal sinuses (mucosal edema)

Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. *Otolaryngol Head Neck Surg* 2004;114:S155–S212.

PATHOLOGY

The production of eosinophilic mucin (formerly called "allergic mucin") was formerly considered pathognomonic of AFRS. Grossly, this material is thick, tenacious, highly viscous, and can vary in color from light tan to brown or dark green (3). Examination of sinonasal mucosa and polyps obtained during surgery should confirm the absence of tissue invasion by fungal hyphae amidst a background of mixed inflammatory cellular infiltrates and an abundance of eosinophils (42).

The histologic appearance of the mucin is an important diagnostic criterion for AFRS. Hematoxylin and eosin (H&E) staining accentuates the mucin and cellular components of eosinophilic mucin but fails to stain the fungal hyphae. H&E slides demonstrate accumulations of pyknotic and degranulated eosinophils within a background of lightly staining sheets of mucin (42). More deeply staining Charcot-Leyden crystals are found within the scattered cellular material and, often, the sparse fungal hyphae may avoid detection with H&E staining (42) (Fig. 37.11). It is this difficulty in detecting fungal hyphae in cases of presumed AFRS that provided fuel for some of the controversy surrounding the pathogenesis of AFRS. Silver stains can detect even a single cell and are the most sensitive of the commonly used histologic stains. However, silver stains are not as specific as the periodic acid Schiff stain. The Fontana Masson stain is best to detect dematiaceous fungi. With technologic advancement, more sensitive techniques to demonstrate fungal presence are expected; however, sampling error and inconsistencies in the processing of mucin extracted at surgery may still result in the inability to demonstrate fungal presence within eosinophilic mucin.



Figure 37.10 **A–C**: AFRS Axial noncontrast CT scan shows pan-sinus opacification and expansion, with areas of increased attenuation corresponding to fungal colonization and chelated metals. Axial T1-weighted gadolinium-enhanced MRI shows peripheral mucosal enhancement and internal low signal. Coronal T2-weighted MRI demonstrates areas of signal void within the involved ethmoid sinuses. Image and caption: Jeffrey Bennett, MD. Department of Radiology, University of Florida College of Medicine, Gainesville, FL.

FUNGAL CULTURE

Fungal cultures of eosinophilic mucin may provide supportive evidence for the diagnosis of AFRS but must be interpreted with caution. It is important to realize that the diagnosis of AFRS is neither established nor eliminated based upon the results of these cultures. The variable yield of fungal cultures (64% to 100%) renders AFRS in the presence of a negative fungal culture quite possible (3). Conversely, a positive fungal culture fails to confirm the diagnosis of AFRS, as it may merely represent the presence of saprophytic fungal growth. For this reason, the histologic appearance of eosinophilic mucin in combination with other clinical factors remains an important indicator of AFRS.

THEORIES AND CONTROVERSIES SURROUNDING PATHOGENESIS

The histologic similarities between ABPA and AFRS led to early assumptions about the disease that persist to this day. The dominant theory is that atopic individuals sensitized to fungi produce Gell and Coombs type I and III hypersensitivity reactions to extramucosal fungal antigens within the nose and paranasal sinuses (58). The resultant mucosal edema, polyp formation, and stasis of secretions results in sinus ostial obstruction, intercurrent bacterial infection, retained and concentrated fungal antigens, and collection of the characteristic eosinophilic mucin with eventual sinus expansion and bony erosion (58). The intense eosinophilic response

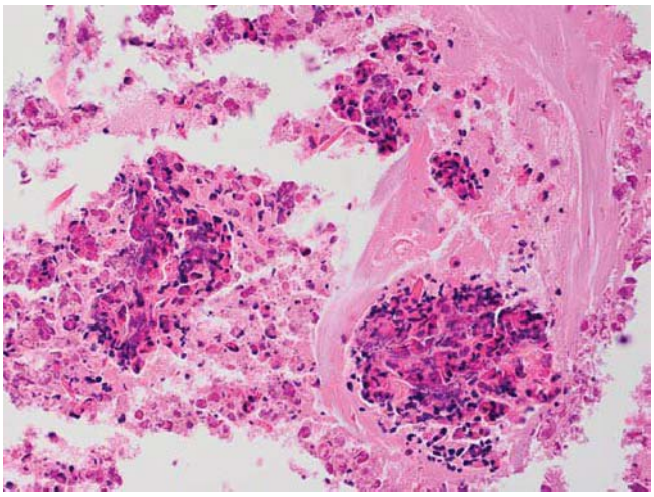


Figure 37.11 AFRS H&E stained section demonstrates clumps of degenerating eosinophils and a background of homogenous, lightly eosinophilic mucoid material, and a few deeply eosinophilic Charcot-Leyden crystals. Image and Caption: Anthony T. Yachnis, MD; Department of Pathology, University of Florida, College of Medicine, Gainesville, FL.

and cycle of inflammation and subsequent sinus obstruction can be attenuated by immunomodulation or surgical therapy to ventilate the sinuses and extirpate the mucin. The most frequently cultured organisms in AFRS include the members of the family dematiaciae (*Bipolaris*, *Alternaria*, *Curvularia*, *Fusarium*, *Exserohilum*, *Helminthosporium*, *Drechslera*) in the United States and *Aspergillus* species in Asia. In AFRS, it is usually possible to detect type I hypersensitivity directed to these fungi (58). The paucity or apparent absence of fungal hyphae in AFRS mucin specimens has led to additional theories regarding the pathogenesis of AFRS.

In 1999, Ponikau et al. (59) suggested that colonizing fungi in sinus mucus play a much broader role in the pathogenesis of CRS. Using an ultrasensitive culture technique, 93% of 101 consecutive patients with CRS demonstrated positive fungal cultures from nasal lavage. Examination of surgical specimens from these patients revealed eosinophils and fungal hyphae within the sinus mucus of nearly all patients. It was also observed that 100% of a group of normal control subjects had positive fungal cultures from nasal lavage (59). Conventional IgE-mediated allergy to fungi was not consistently observed in the CRS patients and many of these patients fulfilled the other criteria required for diagnosis of AFRS. It was proposed that virtually all cases of CRS result from eosinophilic inflammation elicited by certain fungi independent of conventional, allergic, IgE mechanisms, and that the term AFRS be replaced by "eosinophilic fungal rhinosinusitis"(EFRS) (59). The difficulty in demonstrating fungal elements within the eosinophilic mucin of some CRS patients gave rise to the term "eosinophilic mucin rhinosinusitis" (EMRS) to describe those cases in which fungal elements cannot be identified. Ferguson proposed EMRS as a systemic disorder of immune dysregulation with a number of potential pathogenic mechanisms, several of which do not require either fungus or atopy to generate the eosinophilic mucin that characterizes the disease (60). It is not just the absence of fungal elements on histologic examination that encourages categorization of EMRS as a distinct clinicopathologic entity. EMRS patients tend to be older, have bilateral disease, a higher incidence of aspirin sensitivity, greater association with asthma, increased incidence of IgG1 deficiency, and less allergy than those with AFRS (60). In general, nasal polyposis and eosinophilic mucin are prominent in AFRS, EFRS, and EMRS, indicating substantial overlap between the three proposed entities as well as the need for further research to better delineate the conditions. An understanding of the pathogenic roles played by allergy, direct fungal stimulation of the immune system, and the role of humoral immunity will be helpful in generating more specific targets for intervention in the future. At the present time, AFRS is understood to represent a distinct clinicopathologic entity within the spectrum of CRS. While much remains yet to be elucidated regarding AFRS, the understanding of its pathogenesis, clinical properties, and allergic nature are sufficient to guide its medical and surgical management.

TREATMENT

The treatment approach for AFRS is essentially identical to the treatment approach for other forms of CRS with nasal polyposis. There are few treatment studies that have examined AFRS specifically, and treatment recommendations derive from the treatment approach for the analogous disorder, ABPA (58).

Endoscopic sinus surgery (ESS) is the cornerstone of AFRS treatment, but recidivism remains unacceptably high with surgery alone. Modern understanding of the pathogenesis of AFRS as an immunologically mediated hypersensitivity to fungal antigens has prompted a two-pronged attack: (a) utilizing surgery to provide sinus ventilation and thorough mucin removal and (b) medical modulation of the immune response with corticosteroids and immunotherapy to diminish inflammation.

The most important immunomodulatory agents for AFRS are topical and systemic corticosteroids. Preoperative corticosteroids reduce bleeding and facilitate complete surgery. In the early postop period, steroids prevent early polyp recurrence and improve symptoms (61). Patients treated with prolonged course of systemic corticosteroids demonstrate a significant increase in time before revision ESS (62). Brief courses of systemic steroids are used to treat exacerbations or polyp regrowth. The mainstay of medical management for AFRS is topical therapy that consists of saline irrigations and corticosteroids. Saline irrigations help to facilitate mucociliary clearance defense mechanisms, loosen and dislodge inspissated secretions, and reduce mucosal exposure to allergens and other proinflammatory irritants. Daily use of topical intranasal steroids is considered to be safer than long-term oral corticosteroids. There is a dose response effect for nasal steroids in the treatment

of nasal polyp disease, and therefore topical intranasal steroids are often used in an unconventional fashion with high doses delivered via nebulization, irrigation, or drops.

Immunomodulation can also be achieved by means other than corticosteroids. Initial studies addressing the safety of adjunctive immunotherapy for the treatment of AFRS revealed not only that this practice appeared safe, but also lead to a decrease in disease recurrence. In several studies, patients treated with fungal immunotherapy for a period of 1 to 3 years following surgery showed a significant decrease in their rate of recurrence, lower reoperation rates, and a decreased number of office visits. In addition, patients receiving immunotherapy statistically had less mucosal edema as noted on endoscopy and reported better quality of life (62). The efficacy of immunotherapy for the treatment of AFRS has not been substantiated with randomized controlled trials; nevertheless, immunotherapy is a rational treatment approach that may be particularly valuable in patients who have significant allergic symptomatology.

A wide variety of other agents may be employed for their putative anti-inflammatory properties or to eliminate fungal colonization in the sinuses. However, at present there is insufficient data for antifungal therapy, leukotriene inhibitors, or macrolide antibiotics in the medical management of AFRS. Each of these classes of agents has a theoretic rationale and may eventually prove worthwhile in diminishing the overall inflammatory state within the nose and sinuses (63). Topical antifungal agents are clearly ineffective for the treatment of CRS with nasal polyps, but have not yet been studied specifically in AFRS.

HIGHLIGHTS

- ESS is a vital part of the management for all types of fungal rhinosinusitis.
- AIFR is best controlled by the combination of ESS, reversal of the underlying medical morbidities, restoration of normal neutrophil numbers, and systemic antifungal therapy with lipid amphotericin B and azole antifungal medications.
- CIFR has an excellent prognosis and can be treated with surgery alone; however, the reduced side effects of newer antifungal medications favor their use in this infection.
- FBs of the paranasal sinuses are treated with endoscopic surgery and do not require antifungal treatment. Surgical sinusotomies should be large enough to facilitate postoperative surveillance and treatment in the office setting.
- Management of AFRS requires surgical removal of eosinophilic mucin and nasal polyps, creation of wide drainage pathways in addition to long-term medical management with anti-inflammatory medications.

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Complications of Rhinosinusitis

38

Carla M. Giannoni

Acute bacterial sinusitis occurs commonly, usually as a sequela of an upper respiratory infection. Symptoms include cough, purulent nasal discharge, headache, facial pain and pressure, nasal congestion, fetid breath, fever, malaise, and lethargy. Spread of infection outside the sinuses results in complicated sinusitis. The incidence of complications from both acute and chronic sinusitis has decreased fourfold since the 1950s but appear to have stabilized in the past several decades (1–3). This has been attributed to the widespread use of antibiotics for rhinosinusitis but clinical data are lacking in this area (see "Prevention of Complications for Sinusitis" later in this chapter for further discussion). Complications of sinusitis can be divided into three categories: orbital, intracranial, and bony. This chapter reviews each of these complications in detail, describing the pathophysiology, evaluation, microbiology, and medical and surgical treatments.

ORBITAL COMPLICATIONS

Anatomic Considerations

The close proximity of the orbit to the paranasal sinuses, especially the ethmoid sinuses, make it the most commonly involved structure in complications of sinusitis. Orbital complications have a seasonal variation indicating a viral role in the initiation of sinusitis. Children appear to be more prone to orbital complications of sinusitis, probably because of their relatively higher rates of upper respiratory tract infections and sinusitis. Gender has not been identified as a risk factor in preseptal disease. Male gender has been identified as a risk factor in postseptal infections in some series (4) but not in others (5–7) and it appears that the gender predilection becomes more dominant in older children.

Orbital involvement primarily results from a thrombophlebitis and interference with the venous drainage of the orbital contents. The superior and inferior ophthalmic veins are valveless, allowing direct communication between the nose, ethmoid sinuses, face, orbit, and cavernous sinus. In addition, congenital or other dehiscences in the lamina papyracea, which separate the ethmoid sinuses from the orbit, expose the orbital contents to direct extension of sinusitis. The combination of phlebitis and direct entry of bacteria into perivascular structures results in what is generally a continuum of inflammatory and infectious changes. The orbital periosteum, the periorbita, is an important structure because it is the only soft tissue barrier between the sinuses and the orbital contents. It comprises loose fibrous tissue that can be easily elevated off the underlying bone. The orbital septum is a reflection of the periorbita at the margins of the orbit and it passes centrally to fuse with the tarsal plates. The orbital septum lacks lymphatic channels and thus forms a barrier limiting infections from passing directly through the eyelids into the orbit. Orbital infections are divided into two groups based on this element of orbital anatomy: preseptal and postseptal infections.

Classification

Chandler et al. (8) classified the orbital complications of sinusitis into five groups: preseptal cellulitis, orbital cellulitis, subperiosteal abscess, orbital abscess, and cavernous sinus thrombosis (Fig. 38.1). The first complication, preseptal cellulitis is a preseptal infection and the latter four are postseptal. Although often thought of as a continuum, each of these complications should be considered separately and treatment individualized (Table 38.1). These infections are not exclusive and multiple complications can occur in the same patient. A number of other classifications schemes have been proposed but the Chandler classification remains the most widely utilized in clinical practice.

PRESEPTAL CELLULITIS

Preseptal infections are far more common than postseptal infections. Preseptal cellulitis can be a complication of ethmoid sinusitis but it can also occur as a result of infection of the eyelids and orbital adnexa, trauma (including insect

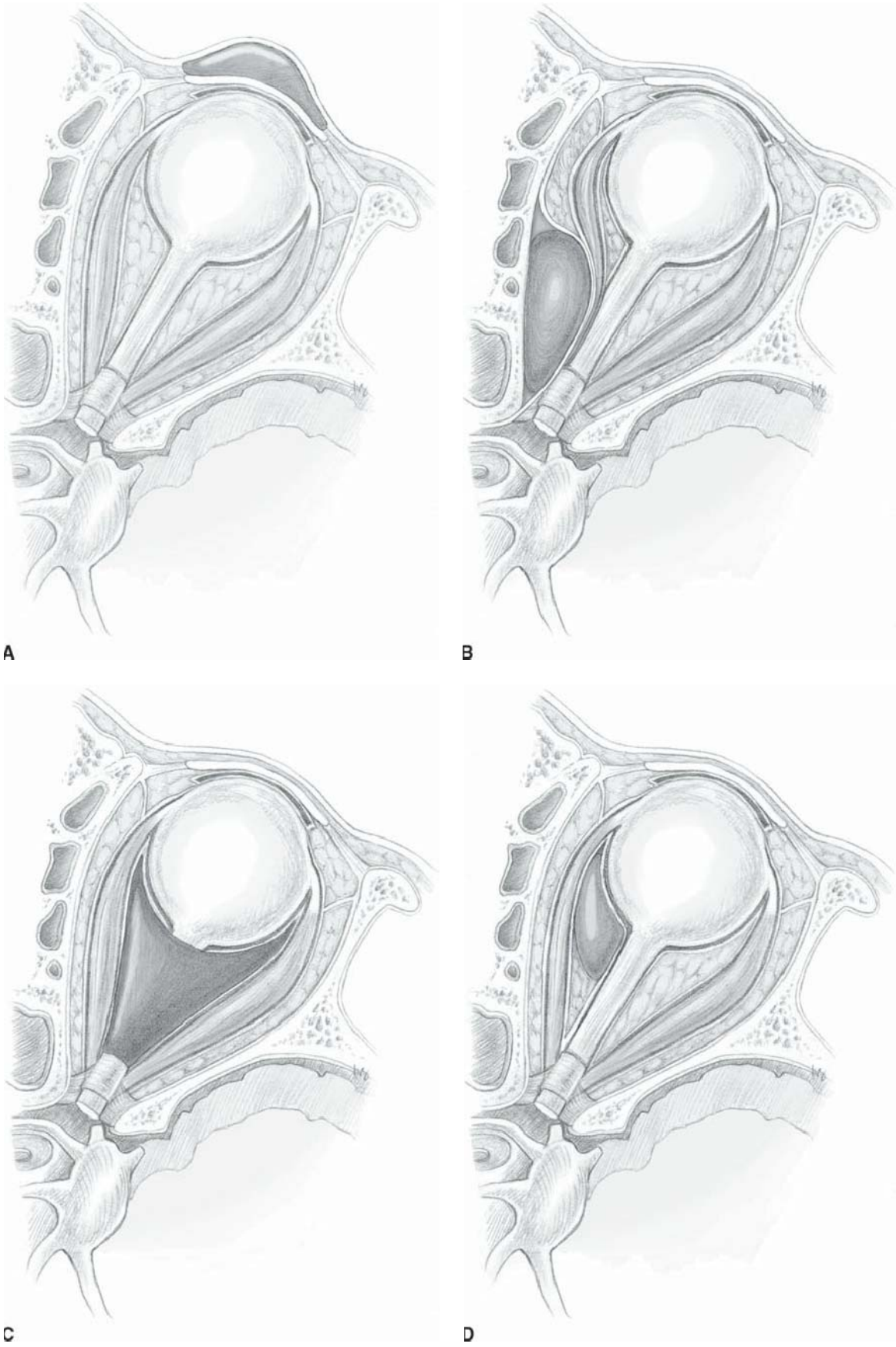


Figure 38.1 Chandler classification of orbital complications of sinusitis. **A**: Preseptal cellulitis (eyelid edema), **(B)** Subperiosteal abscess, **(C)** Orbital cellulitis, **(D)** Orbital abscess,

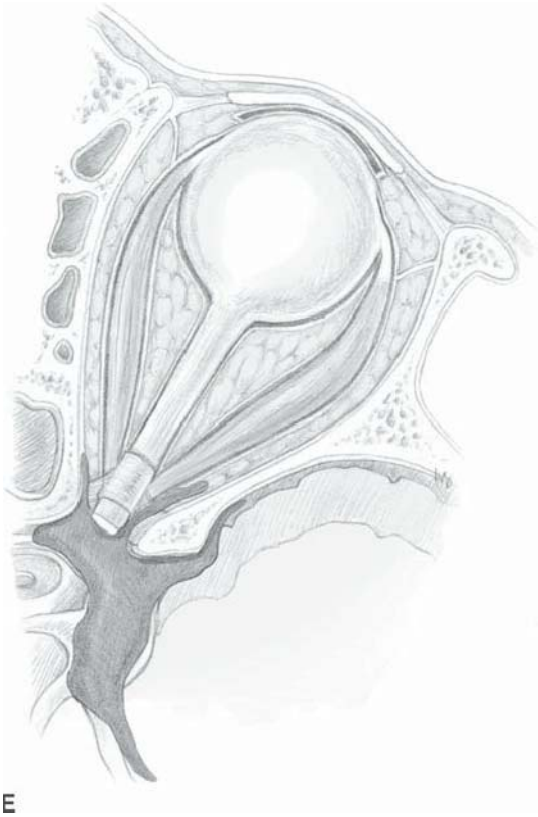


Figure 38.1 *(Continued)* **(E)** Cavernous sinus thrombosis.

bites), or a foreign body (6,7). In contrast to other orbital complications, medical comorbidities such as cystic fibrosis, HIV, leukemia, diabetes, and other immune deficiencies are risk factors for preseptal cellulitis (7). Preseptal cellulitis manifests as eyelid swelling, erythema, and tenderness. Occasionally these may progress to an eyelid abscess (Fig. 38.2) and can also be associated with edema of the orbital (postseptal) contents. There are no limitations of extraocular movements and no impairment of visual acuity. Sinonasal infections cause periorbital swelling due to impaired venous drainage of the ethmoidal vessels that are obstructed by inflammation and pressure.

SUBPERIOSTEAL ABSCESS

With subperiosteal abscess, a collection of pus forms at the medial aspect of the orbit between the periorbita and the lamina papyracea (Fig. 38.3). This is the second most common orbital complication of sinusitis. In response to inflammation in the ethmoid sinus, an inflammatory tissue collection beneath the orbital periosteum can develop and become a subperiosteal phlegmon (9). This subperiosteal phlegmon can then progress into a discrete abscess. A subperiosteal phlegmon or abscess can displace the orbital contents and globe downward and laterally with normal mobility in the early stages. An abscess may occasionally rupture through the orbital septum and present in the eyelids.

Typically, younger children develop isolated orbital complications, especially medial subperiosteal abscesses associated with acute ethmoiditis. Interestingly, a second, notable subset of patients has been identified: teenage males, who develop simultaneous orbital and intracranial complications (10–14). This phenomenon is likely related to the age-dependent development of the frontal and sphenoid sinuses.

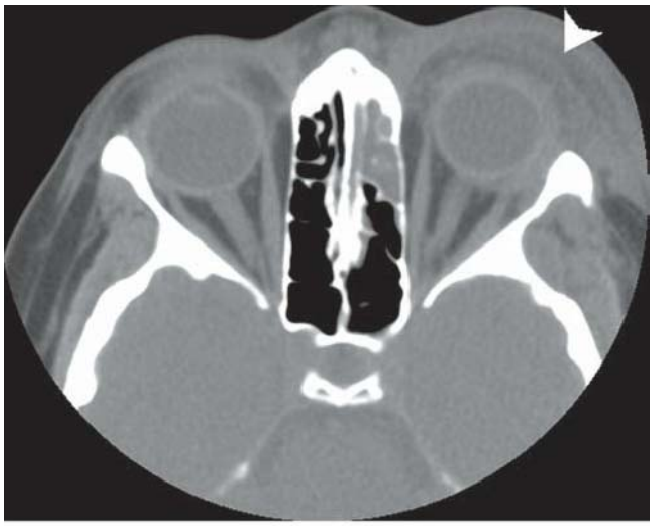
ORBITAL CELLULITIS

Orbital cellulitis is a postseptal infection that manifests as diffuse edema of the orbital contents without a discrete abscess (Fig. 38.4). There is eyelid edema and erythema, proptosis, and chemosis with limited or no impairment of extraocular movements and normal visual acuity early in the disease process. Visual changes and ophthalmoplegia

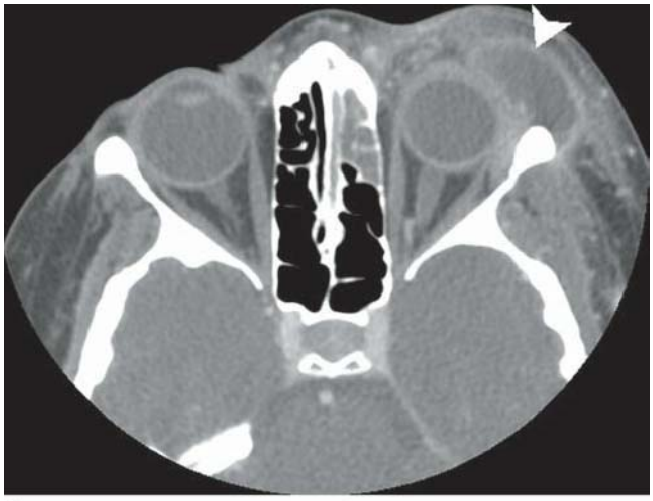
TABLE 38.1 ORBITAL COMPLICATIONS OF SINUSITIS

	Typical Findings	Treatment
Preseptal cellulitis	Edematous, erythematous eyelids Extraocular muscles (EOM) intact Normal vision	Medical therapy (Rarely, drainage of secondary abscess)
Orbital cellulitis	More diffuse orbital edema ± Impaired EOM Usually normal vision until later in disease course	Medical therapy ± Sinus drainage[a]
Subperiosteal abscess	Edematous, erythematous eyelids; Proptosis Impaired EOM Usually normal vision, esp in the case of small abscesses Visual changes more likely with larger abscesses	Medical therapy ± Sinus drainage ± Abscess drainage
Orbital abscess	Severe exophthalmos, chemosis, Ophthalmoplegia, common Visual impairment, common	Medical therapy Sinus drainage, often Abscess drainage, usually
Cavernous sinus thrombophlebitis	Bilateral orbital pain, chemosis, proptosis Ophthalmoplegia CN III, IV, V1, V2, V3, VI can be affected	Medical therapy Sinus drainage, often ± Anticoagulation (controversial)

[a]Surgical sinus drainage may be limited to maxillary sinus aspiration or may include endoscopic or open sinus surgery; its necessity depends on severity of symptoms, physical examination, duration of medial treatment and need for cultures to direct antibiotic therapy.



A



B

Figure 38.2 Preseptal abscess secondary to preseptal cellulitis. **A**: Axial CT scan taken on admission showing the patient with left ethmoid sinusitis and left preseptal cellulitis (*arrow*); patient also had frontal sinusitis (*not pictured*). **B**: Axial CT scan after 4 days of IV antibiotic treatment showing progression of infection to left preseptal abscess (*arrow*). The patient also developed an orbital subperiosteal abscess, scalp abscess, and small epidural abscess.

indicating optic neuritis and/or ischemia can occur as the disease progresses; these are prognostically worrisome findings. Not all cases of orbital cellulitis are due to sinusitis, however. Patients presenting with pain and diplopia and a history of recent orbital trauma or dental surgery should be assessed for orbital cellulitis. In diabetic patients with ketoacidosis and immunocompromised patients, more severe infections such as invasive fungal sinusitis should be considered. Orbital cellulitis is more concerning than preseptal cellulitis because it can evolve into an orbital abscess.

ORBITAL ABSCESS

An orbital abscess occurs when orbital cellulitis coalesces into a discrete collection of pus within the orbital tissues. This is a serious complication that can be associated with

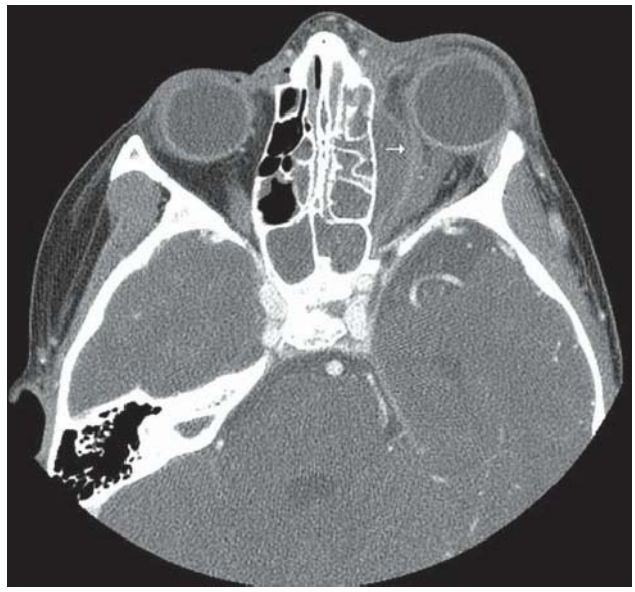


Figure 38.3 Axial CT scan demonstrating a left subperiosteal orbital abscess. The abscess is immediately adjacent to the lamina papyracea (the *arrow* is inside the abscess and identifies the lateral edge of the abscess); note the proptosis and the displacement of the orbital periosteum and medial rectus muscle.

severe exophthalmos and chemosis, complete ophthalmoplegia and visual impairment with a risk for progression to irreversible blindness. On rare occasions there is spontaneous drainage of purulent material through the eyelid.

CAVERNOUS SINUS THROMBOSIS

Cavernous sinus thrombophlebitis or thrombosis is a complication that can be considered an orbital as well as an intracranial complication of sinusitis. Venous congestion

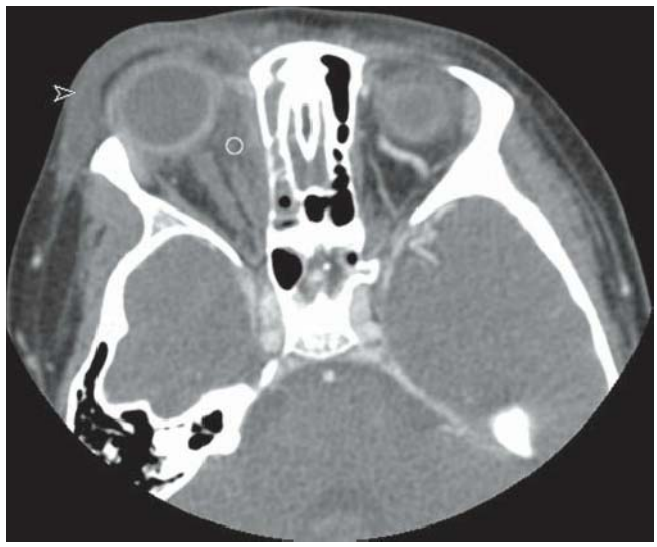


Figure 38.4 Axial CT scan showing right orbital cellulitis with diffuse orbital inflammatory changes that are intra- and extraconal (*open circle*); there is concurrent preseptal edema and inflammatory changes (*arrow*).

in the orbit results in orbital pain, chemosis, proptosis, and ophthalmoplegia. Cranial nerves III, IV, V1, V2, V3, and VI traverse the sinus and can all be affected. Extension of the phlebitis posteriorly into the cavernous sinus results in progression of symptoms in the opposite eye. This contralateral involvement is a distinguishing feature of cavernous sinus thrombosis. It can be associated with sepsis and meningismus or frank meningitis may be present.

DIAGNOSIS AND TREATMENT EVALUATION

A history including recent upper respiratory infection, duration and progression of symptoms, recent trauma (including insect bites and conditions involving the skin such as chicken pox), swimming, ear infection, dental surgery or dental infection, and other systemic illnesses should be obtained when evaluating a patient with orbital findings. Decongestion and examination with anterior rhinoscopy and nasal endoscopy may demonstrate polyps or purulent material under the middle turbinate. The eye must be opened to assess visual acuity, extraocular movements, and proptosis. When orbital infection is suspected, ophthalmologic consultation should be obtained immediately to assess visual status as this may impact the aggressiveness of surgical treatment (5–7). Close follow-up of patients with orbital infections is needed as the infection may evolve or progress during the course of treatment with development of new complications.

Radiography

Imaging is often necessary to appropriately classify orbital complications. Conventional plain film radiography is of limited value in the evaluation of sinusitis because of poor anatomic detail and poor correlation with clinical symptoms. Computed tomography (CT) is considered the gold standard for sinus imaging because it can better depict the anatomy of the globe, retro-orbital tissues, sinuses, and cranium, and provides information for surgical planning. It has been shown to demonstrate good accuracy in diagnosing pediatric chronic rhinosinusitis (9,15). CT of the sinuses and orbits with contrast is indicated when postseptal infection is suspected clinically based on findings of proptosis, gaze restriction or changes in visual acuity, when intracranial complications are suspected, or when symptoms of preseptal inflammation progress in 24 to 48 hours despite treatment (6). The study consists of contrast-enhanced axial and coronal thin cuts of the sinuses and orbits. CT of the brain with contrast and/or magnetic resonance imaging (MRI) may also be indicated if there are symptoms of a concurrent intracranial complication.

In preseptal cellulitis, CT reveals a diffuse increase in density and thickening of the lid and conjunctiva. Postseptal inflammation is characterized by a soft tissue density or low-attenuation area adjacent to the lamina papyracea (9,16). It should be noted that the medial rectus muscle may be displaced, enhanced, or thickened by inflammatory edema in many orbital infectious processes. Abscesses appear as hypodense areas with rim enhancement and mass effect. Subperiosteal abscesses arise adjacent to the lamina papyracea but can also occur in a superior location, adjacent to the orbital roof secondary to frontal sinusitis (17). Extension of the inflammatory process into the intraconal space appears on CT as an ill-defined infiltration of the orbital fat with obliteration of the optic nerve and extraocular muscles. Cavernous sinus thrombosis is better demonstrated on MRI but may be suggested by poor venous enhancement on contrast CT. Contrast-enhanced MRI is performed when intracranial complications are suspected and includes axial and coronal T1 and T2 images (9,16).

Microbiology of Orbital Complications

There is usually little correlation between cultures taken randomly from the nose or nasopharynx and those obtained from sinus aspiration. Culture material can be obtained directly from the sinus by sinus puncture and lavage or during surgical exploration. An exception to this rule is endoscopically directed middle meatal nasal cultures where there may be a more accurate correlation between these nasal cultures and those obtained from the maxillary sinus (18). The organisms responsible for acute suppurative sinusitis are similar for both adults and children and do not always reflect the common causative pathogens of acute and chronic sinusitis (19,20) (Table 38.2). The most commonly identified organisms in acute rhinosinusitis are *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella*, other streptococcal species, and less commonly anaerobes. *Staphylococcus aureus* can be seen in adults and in children with serious sinus infections. Chronic sinusitis in both adults and children is more commonly due to anaerobes as well as alpha-hemolytic streptococci, *S. aureus, H. influenzae*, and *S. pneumoniae*.

Streptococcal organisms play a major role in complicated sinusitis. A thorough understanding of the taxonomy of these organisms is necessary. The majority of streptococci fall into two broad categories: beta-hemolytic and non–beta-hemolytic, which includes alpha-hemolytic and non-hemolytic organisms. The beta-hemolytic group includes Group A and Group B Streptococci. The non–beta-hemolytic group is further subdivided into optochin-susceptible, which includes *S. pneumoniae*, and optochin-resistant, which includes *Streptococcus viridans*. The viridans group includes *Streptococcus bovis* group, *Streptococcus milleri* group and more than 20 other species of viridans streptococci. *S. milleri, Streptococcus constellatus*, and *Streptococcus anginosus* constitute the *S. milleri* group (21).

Excluding preseptal cellulitis, orbital complications are often polymicrobial. *S. viridans*, especially the *S. milleri* group organisms, and *S. aureus* have been implicated as the most common causes of both orbital and intracranial complications of sinusitis in most contemporary

TABLE 38.2 MICROBIOLOGY OF SINUSITIS AND RELATED COMPLICATIONS

Acute sinusitis (children)	More common	*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and other *Streptococcus* species
	Less common	Anaerobic organisms and *Staphylococcus aureus*
Acute sinusitis (adults)	More common	*S. pneumoniae*, *H. influenzae*, other *Streptococcus* sp., and anaerobic organisms
	Less common	*M. catarrhalis* and *S. aureus*
Orbital complications of sinusitis	More common	*Streptococcus viridans* (including *Streptococcus milleri* group), *S. aureus*, and *S. pneumoniae*; these infections are commonly polymicrobial
	Less common	Anaerobic organisms (especially *Bacteroides* sp., *Peptostreptococcus*, and *Eikenella*), other *Streptococcus* sp., *H. influenza*, and other gram negative bacilli
Intracranial abscesses (intracerebral, epidural, subdural abscesses)	More common	*S. viridans* (including *S. milleri* group), *S. aureus*, other *Streptococcus* sp., other anaerobic organisms (*Peptostreptococcus*, *Bacteroides* sp., others), and *S. pneumoniae*; commonly polymicrobial infections
	Less common	Coagulase-negative *Staphylococcus* and gram negative bacilli (*H. influenza*, others)
Meningitis	More common	*S. pneumoniae*, *S. aureus*, and other *Streptococcus* sp.
	Less common	Anaerobic organisms (*Fusobacterium* sp., others), gram negative bacilli, and *H. influenzae*
Pott's puffy tumor (acute osteomyelitis)	More common	*S. viridans* (including *S. milleri* group) and *S. aureus*; commonly polymicrobial infections
	Less common	Anaerobic organisms (*Bacteroides* sp., etc.) and, much less commonly, gram negative bacilli (*Proteus* sp., etc.)

Note: This compilation represents the observed commonalities and average incidence of groups of organisms identified in series published over the last 10 y; the exact predominance of each organism in the listed disease processes varies among different published series.

series (5–7,22) (Table 38.2). Less common but consistent causes of complicated sinusitis are *S. pneumoniae*, other Streptococci, and anaerobic microorganisms. *H. influenza*, *Eikenella*, and other gram-negative bacilli are also implicated in some cases of complicated sinusitis.

Viridans streptococci are usually facultatively anaerobic organisms but some strains may be microaerophilic. It is important to note that the reporting of these sometimes nonpathologic organisms can vary greatly from one laboratory to another and may be missed if awareness for their pathologic nature in the situation of complicated sinusitis is not understood or if anaerobic cultures are not collected.

Immunocompromised patients may develop sinusitis caused by similar organisms as immunocompetent patients; however, they are also susceptible to atypical pathogens and fungus with development of invasive infections. (Fungal rhinosinusitis is discussed more fully in Chapter 37 of this text).

Treatment

Most orbital infections respond to medical treatment. The mainstay of medical treatment is intravenous (IV) administration of a broad-spectrum antibiotic followed by oral therapy. A nasal decongestant, either topical or oral, mucolytics or saline irrigations may help promote sinus drainage.

Preseptal and orbital cellulitis generally respond to medical management. Preseptal cellulitis is treated with antibiotics, head elevation, warm packs, and management of the underlying cause. Some patients with orbital cellulitis who are not responding to medical therapy, especially those with visual changes may also benefit from surgical drainage of their sinuses despite the absence of a discrete abscess. Incision and drainage of a lid abscess is occasionally necessary.

In general, surgical intervention has been recommended in cases when there is CT evidence of abscess formation, 20/60 or worse visual acuity is observed on initial evaluation, progression of orbital signs and symptoms occurs despite medical treatment, or lack of improvement is seen within 48 hours despite aggressive medical treatment. For subperiosteal abscesses that are large and/or lateral, and for orbital abscesses this remains the appropriate course of treatment. A more conservative approach to the management of small, medial subperiosteal abscesses has been advocated in several contemporary series (5–7). Favorable outcomes have been demonstrated in children with small, medial subperiosteal abscesses when no ocular signs are present.

In these cases, surgical intervention is advocated as in the cases of other abscesses: if ocular signs develop such as worsening visual acuity or ocular motility or if there is failure to improve in 48 hours of medical management. A useful framework for assessing patients was outlined by Oxford and McClay (5): a patient with medial subperiosteal abscess with normal vision (better than 20/40), no ophthalmoplegia, intraocular pressure less than 20 mm Hg, proptosis less than 5 mm, and width of abscess less than 4 mm on CT can be considered for possible medical management. These objective criteria were shown retrospectively to predict successful medical management with good outcomes, even in older children.

Treatment of cavernous sinus thrombosis is primarily medical with high-dose IV antibiotics that cross the blood-brain barrier and consideration of the use of anticoagulants. Surgical intervention consisting of drainage of the affected sinuses may be appropriate to facilitate sinus drainage and obtain cultures.

The mainstay of surgical treatment for sinusitis with complications has traditionally been conventional open surgeries such as external ethmoidectomy and Caldwell-Luc procedures for sinus and abscess drainage. (These external drainage procedures and their indications are described more fully in Chapter 41 of this text.) Functional endoscopic sinus surgery is now more commonly used for sinus drainage in patients with infectious complications. (Endoscopic sinus surgery is described more fully in Chapter 40 of this text.) Endoscopic sinus surgery allows for culture of sinus content and may reduce microbial load and aid in sinus aeration. It should be noted that this technique is not without its limitations; the nasal cavity and sinuses are usually quite inflamed and normal anatomy can be obscured or difficult to navigate due to bleeding and edema. In addition to endoscopic sinus drainage, subperiosteal abscesses can, in many cases, be drained intranasally by endoscopic techniques (see Chapter 43 for additional information). In these cases, surgical intervention should include widely opening the ethmoid sinuses and removal of the lamina papyracea. In cases of orbital abscess, this same endoscopic drainage approach can include incision of the periorbita and drainage of the intraconal abscess if the location and anatomy is amenable to the technique. Newer oculoplastic techniques such as a transcaruncular approach, which utilizes a transconjunctival incision extended medially around the lacrimal caruncle, are finding some favor for draining subperiosteal abscesses (Fig. 38.5) (23). Some patients with orbital cellulitis, particularly in cases where there is disease progression or significant ophthalmologic findings, may also benefit from surgical drainage of their sinuses despite the absence of a discrete abscess.

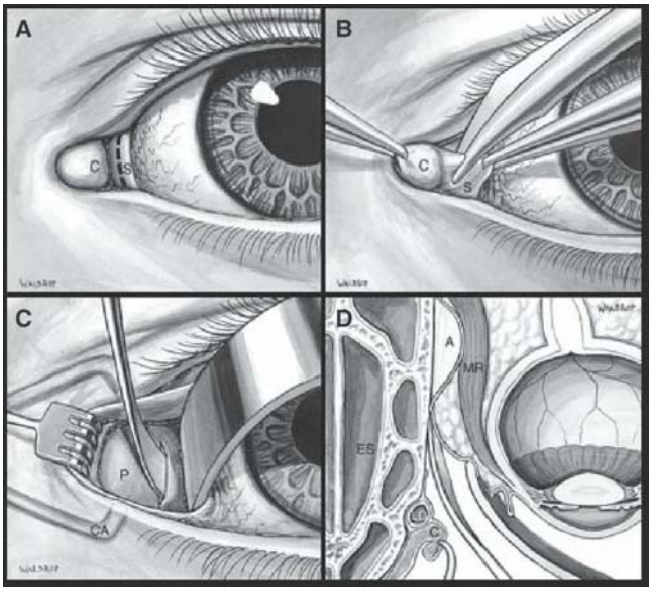


Figure 38.5 Transcaruncular approach to drainage of subperiosteal abscess. **A**: The incision falls between the caruncle (C) and semilunar fold (S). **B**: The tissue between caruncle (C) and the semilunar fold (S) is incised with tenotomy scissors. **C**: While protecting the globe and canalicular (CA) system, the periosteum (P) is incised and elevated with a Freer elevator. **D**: The periosteum is elevated until the abscess (A) is found and drained. ES, indicates ethmoid sinus; MR, medial rectus; LD, lacrimal duct; and C, caruncle. (Adapted from Pelton RW, Smith ME, Patel BC, et al. Cosmetic considerations in surgery for orbital subperiosteal abscess in children: experience with a combined transcaruncular and transnasal endoscopic approach. *Arch Otolaryngol Head Neck Surg* 2003;129:652–655.)

INTRACRANIAL COMPLICATIONS

The paranasal sinuses are an integral part of the anterior and middle skull base. This intimate relationship and the complex venous network that traverses this area result in the occurrence of infectious intracranial complications of sinonasal disease. The incidence, morbidity, and mortality of suppurative intracranial complications secondary to sinusitis have dramatically decreased due to the widespread use of oral antibiotics, improved imaging technology, recognition that involved paranasal sinuses are the primary focus of infection, expeditious treatment of underlying sinusitis, and improved intensive care medicine (4,5).

The risk for developing an intracranial complication in patients requiring hospital admission for sinusitis has been estimated to be 3% (1). Intracranial complications are extremely rare under 7 years of age and appear more commonly in African American and male patients (4,10,13,14). This is presumably related to the fact that adolescents, unlike younger children, have developed their frontal and sphenoid sinuses and also because adolescents are more prone to upper respiratory infections than adults (12). The elderly may form a second, smaller "at risk" group (24).

Intracranial complications do not commonly present with symptoms of acute sinusitis but rather with headache lasting greater than 1 week, often coupled with fever (4,11). Altered mental status, orbital edema, and/or nausea and vomiting are also seen in many patients (11,13,14,25). Focal neurologic deficits can be seen as later findings (4,11,13,14,25). While intracranial complications are often associated with acute or subacute

sinusitis, underlying chronic sinusitis may be a factor in some patients. The presence of a long-standing process characterized by acute exacerbations requiring prolonged courses of antibiotics can result in changes in the mucosa and underlying bone including scarring and polypoid changes. This is theorized to result in hidden foci of infection with poor drainage that have reduced antibiotic penetration (2).

Anatomic Considerations

Routes of spread of infection from the sinuses may be hematogenous or through direct extension. Retrograde septic thrombophlebitis through the valveless diploic veins of the skull and ethmoid bone or communicating veins is the most common route of spread. The intracranial venous system is also valveless, allowing further spread of thrombophlebitis and septic emboli (3,10). Direct extension may occur via preformed routes such as congenital or traumatic dehiscences, through sinus wall erosion or traumatic fracture lines, and by existing neurovascular foramina such as those for the optic and olfactory nerves.

Diagnosis and Classification

The intracranial complications of sinusitis include meningitis, epidural abscess, subdural abscess, intracerebral abscess, and cavernous sinus and venous sinus thrombosis (Fig. 38.6). These infections are all associated with significant morbidity and mortality and warrant immediate attention. Also, multiple complications can occur in the same patient either concurrently or sequentially (10,12,17,24).

A history focusing on recent upper respiratory infection, duration and progression of symptoms, recent trauma, swimming, ear or dental infection or surgery, and other systemic illnesses should be obtained when evaluating a patient with intracranial findings. The patient should be assessed for symptoms of acute or chronic sinonasal complaints such as purulent rhinorrhea and nasal obstruction and symptoms of increased intracranial pressure such as frontal or retro-orbital headache, nausea and vomiting, altered mental status, nuchal rigidity, or papilledema. Intracranial complications may be asymptomatic until late in their course, especially when "silent" areas of the brain are involved such as the frontal lobe. Late findings include seizures, hemiparesis, and other focal neurologic findings; these are associated with a poorer prognosis (11–14,25). While the rate varies widely, review of published series over the last 10 years show that as many as 9% to 38% of patients that do survive have permanent neurologic sequelae and that the mortality averages 4% (10,12,24,25).

Radiographic evaluation is an important component of the diagnosis of intracranial complications. MRI with contrast is considered the study of choice to assess intracranial complications (9,16). CT scan of the sinuses is also generally obtained to assist in treatment planning, especially for possible sinus surgery. Management is multidisciplinary often including an otolaryngologist, neurosurgeon, pediatrician, internist, and critical care and infectious disease specialists.

EPIDURAL ABSCESS

Epidural and subdural abscesses are the most common intracranial sinusitis complications. These abscesses are generally a complication of frontal sinusitis due to venous communications and loosely adherent dura in the frontal region (Fig. 38.7). Initial symptoms include headache, fever, and occasionally orbital edema, local

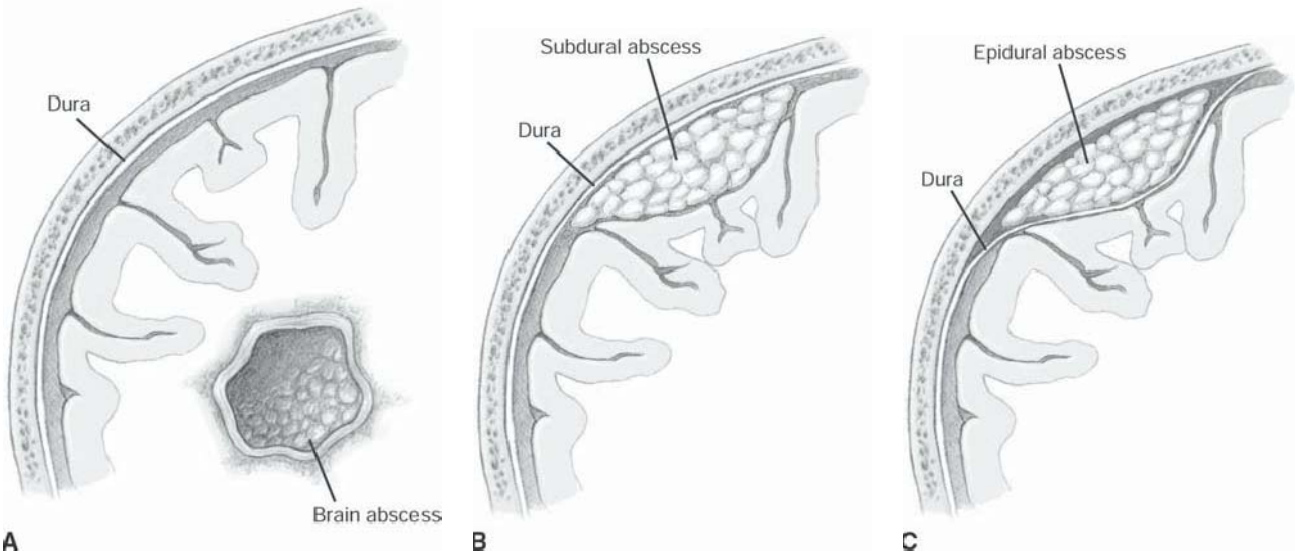


Figure 38.6 Intracranial complications of sinusitis. **A**: Intracerebral (brain) abscess, **(B)** Subdural abscess, **(C)** Epidural abscess.

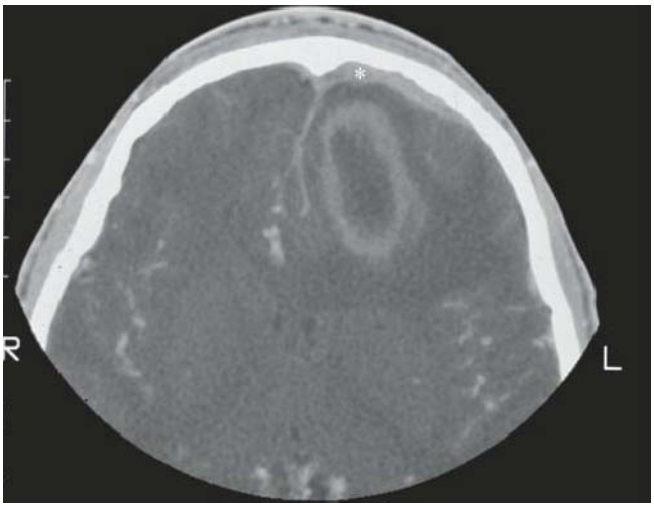


Figure 38.7 Axial CT scan of the brain demonstrating a left intracerebral abscess and epidural abscess (*asterisk*) secondary to frontal sinusitis.

pain, and/or tenderness. The diagnosis can be made using CT or MRI but MRI has greater sensitivity and is the preferred radiologic exam. Unenhanced CT reveals a hypodense or isodense crescent-shaped area adjacent to the inner table of the skull. A curvilinear ring of enhancement may be seen. MRI demonstrates a low-attenuation extraaxial mass (9,16). Outcomes for epidural abscess tend to be more favorable than other intracranial infections (11).

SUBDURAL ABSCESS

As with epidural abscess, subdural abscess is most commonly a complication of frontal sinusitis. Subdural abscesses are usually unilateral. Due to the lack of anatomic barriers, infection can spread over the cortex into the interhemispheric region (Fig. 38.8). Subdural abscesses are notable for having a higher morbidity and mortality than other intracranial complications (4,13,14). A subdural abscess can be a life-threatening emergency because patients can deteriorate quickly. The typical course is headaches, fever, and lethargy followed by coma. Meningismus is often present and the degree of focal neurologic deficits depends on the site of the abscess. MRI reveals a low signal on T1-weighted images and a high signal on T2-weighted images with peripheral enhancement after administration of gadolinium.

INTRACEREBRAL ABSCESS

Intracerebral abscess is a less common complication of sinusitis. These usually involve the frontal and frontoparietal lobes. The most common site of precipitating infection

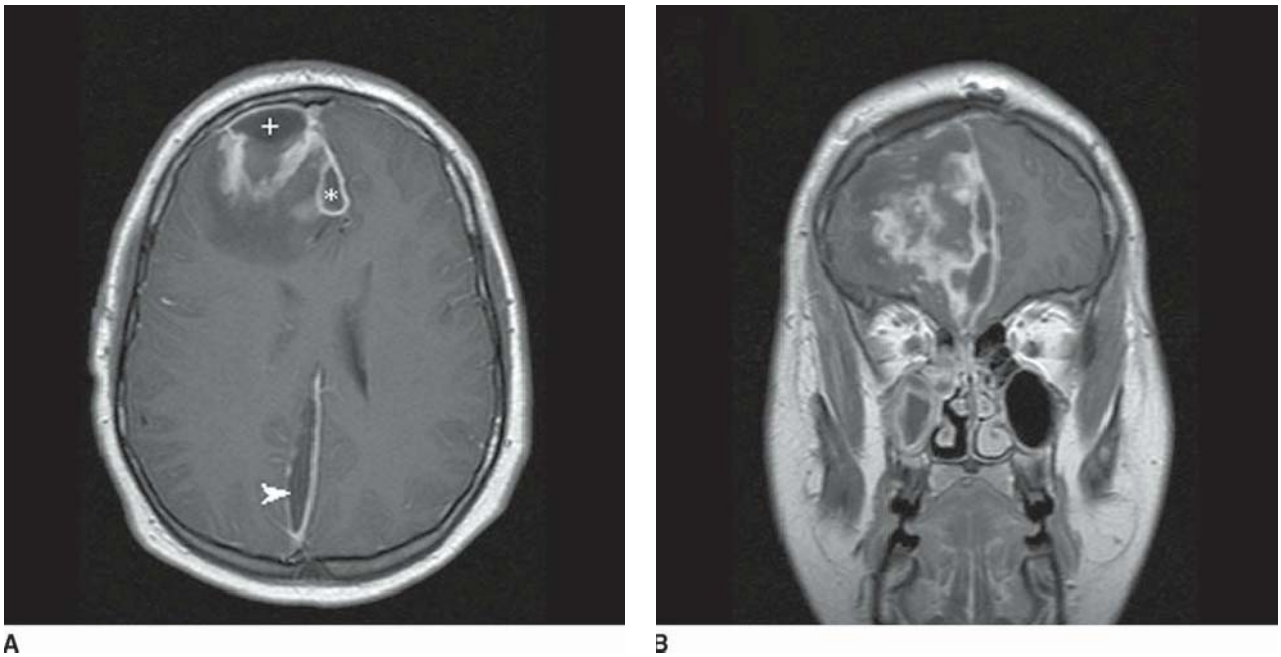


Figure 38.8 MRI images from a 16-year-old male who presented with left leg paresis and was found to have right frontal sinusitis and subdural abscess. Despite aggressive IV antibiotics and immediate treatment with craniotomy and drainage of the subdural abscess, endoscopic sinus surgery, and frontal sinus trephination he had progression of his infectious process. **A**: Axial MRI, taken 12 days after initial drainage procedures, showing a right paramedian falx subdural empyema with a budding abscess (*plus*) that extends into adjacent brain parenchyma with active cerebritis and a right parafalcine subdural collection (*asterisk*) that is located superiorly and centrally near the vertex; this interhemispheric collection extends posteriorly along the right medial parieto–occipital lobe (*arrow*). Local mass effect and shift of the falx due to vasogenic edema is also demonstrated. **B**: Coronal MRI of the same patient showing unilateral right pansinusitis and the interhemispheric subdural collection with frontal lobe involvement.

is the frontal sinus with the sphenoid and ethmoid sinuses less commonly implicated. As with other intracranial abscesses, symptoms include fever, headache, vomiting, and lethargy. Seizures and focal neurologic deficits can also occur, usually as later findings. Frontal lobe abscesses are associated with more subtle symptoms such as mood swings and behavioral changes. Lumbar puncture can be life threatening and should not be performed until radiographic imaging is done and brain anatomy is assessed. MRI demonstrates a cystic lesion with a distinct hypointense strongly enhancing capsule on T2-weighted images (Fig. 38.7).

VENOUS SINUS THROMBOSIS

Sagittal sinus thrombosis develops from retrograde thrombophlebitis from frontal sinusitis. It is usually found in association with other complications such as subdural abscess, epidural abscess, or intracerebral abscess (3). Patients are extremely ill, presenting with meningeal signs or other serious neurologic complications. MRI may reveal focal defects of enhancement after gadolinium administration with decreased cavernous carotid artery flow void. MR angiogram and venogram studies can further delineate the process (2).

MENINGITIS

The frequency of meningitis in series of intracranial complications of sinusitis varies greatly among studies (10–13,17). Isolated meningitis is a relatively uncommon complication of sinusitis. Focal dural enhancement (focal meningitis) associated with other complications of sinusitis is somewhat more common and when these types of meningitis cases are combined, meningitis is seen about as often as intracerebral abscess (11). Meningitis typically results from sphenoiditis or ethmoiditis. As in meningitis due to other causes, initial symptoms include headache, neck stiffness, and high fever. Patients may or may not have complaints of sinusitis but it is demonstrated on CT in affected cases. In severe cases, patients may be septic and demonstrate cranial nerve palsies.

TREATMENT MICROBIOLOGY

Sinogenic meningitis is most commonly due to *S. pneumoniae* and this organism is associated with a higher incidence of neurologic complications such as hearing loss. Cultures from intracranial abscesses are often polymicrobial. *S. viridans* species (including *S. milleri*) and *S. aureus*, other *Streptococcus species* and anaerobes are the most commonly isolated organisms in intracranial infections secondary to sinusitis in both children and adults (Table 38.2) (3,20,22). Even in cases where intracranial abscesses are due to acute sinusitis, this pattern of microbiology is seen. This may in part be due to the fact that although anaerobes and *S. aureus* are not commonly found in acute sinusitis in children they are associated with a higher incidence of complications of sinusitis (19).

Treatment

Upon identification of an intracranial complication of sinusitis, neurosurgical consultation is obtained and multidisciplinary treatment planning is initiated.

Treatment of intracranial abscesses (epidural, subdural, and intracerebral) abscesses includes high-dose, broad-spectrum IV antibiotics with good intracerebral penetration. Neurosurgical drainage of the intracranial abscess is usually performed, although occasionally, patients with small abscesses and mild symptoms are observed for response to medical therapy and drainage performed only if the patient fails to improve or symptoms worsen. Surgical drainage is often eventually required even in these cases due to progression of disease (24). Steroid and anticonvulsant medications may be adjunctively administered to treat any secondary cerebral edema and to reduce the risk of seizures.

In the majority of cases, surgical drainage of the affected sinuses is performed (Table 38.3). Sinus cultures obtained early in the course of the illness can help direct treatment. Endoscopic or external approaches may be used as discussed above in the treatment of orbital complications. Frontal sinus trephination can be used to drain frontal sinusitis. Occasionally, an epidural abscess can be drained via the frontal sinus by opening the posterior table of the frontal sinus. Neurosurgical and otolaryngologic procedures are sometimes performed during the same anesthesia but sinus surgery should only be considered when the patient has been stabilized. It should be noted that while most authors advocate sinus surgery as a component of multidisciplinary treatment for patients with intracranial abscesses, early sinus drainage may not improve outcome or need for neurosurgical drainage procedures (24).

Patients may present with or develop multiple intracranial complications of sinusitis. Repeat imaging of the brain and sinuses can be performed during treatment and prior to hospital discharge to assess response to treatment and identify new complications (13,24). Multiple intracranial drainage procedures are often required to treat new or progressive disease. Antibiotic treatment should be continued for 4 to 8 weeks because as healing takes place, the barriers to drug transport into the central nervous system are repaired (3).

The initial treatment of meningitis is medical with administration of broad-spectrum antibiotics that cross the blood-brain barrier. If the patient has been stabilized, drainage of the affected sinuses may be performed within 48 hours if there is no clinical improvement. Steroid and anticonvulsant medications may be adjunctively administered to treat any secondary cerebral edema. Neurologic

TABLE 38.3 INTRACRANIAL COMPLICATIONS OF SINUSITIS, TREATMENT HIGHLIGHTS

	Sinus Source[a]	Highlights of Disease Process and Treatment
Meningitis	Ethmoid sinus; Sphenoid sinus	High incidence neurologic sequelae (e.g., hearing loss) Medical treatment only, usually
Epidural abscess	Frontal sinus	Aggressive medical treatment; surgical drainage of the abscess, usually Sinus drainage, usually, when medically stable
Subdural abscess	Frontal sinus	Highest rate of neurologic morbidity and mortality Aggressive medical treatment (often includes steroids and anticonvulsants) Surgical drainage of the abscess, usually; sinus drainage, usually, when medically stable
Intracerebral abscess	Frontal sinus (less commonly: ethmoid sinus, sphenoid sinus)	High neurologic morbidity and mortality; usually frontal lobe so symptoms may be subtle Aggressive medical treatment (often includes steroids and anticonvulsants) Surgical drainage of the abscess, usually; sinus drainage, usually, when medically stable
Venous thrombophlebitis	Frontal sinus	Aggressive medical treatment (often includes steroids and anticonvulsants) Anticoagulation is controversial Surgical drainage of the sinuses, sometimes

[a]Most patients with intracranial complications have unilateral or bilateral pansinusitis; the sinus most commonly implicated as the source of intracranial spread of infection is reported.

sequelae are common in patients with meningitis, primarily seizure disorders, and sensorineural deficits such as hearing loss.

Treatment of venous sinus thrombosis includes high-dose IV antibiotics and drainage of the involved sinuses (3). The use of anticoagulants is controversial. When used, the treatment is continued until there is radiologic evidence of resolution of the thrombus (2).

BONY COMPLICATIONS

Frontal sinusitis complicated by osteomyelitis of the frontal bone is known as Pott puffy tumor (Fig. 38.9). It can culminate in an anterior subperiosteal pericranial abscess, a periorbital abscess, or an epidural abscess. The subperiosteal collection of pus in the forehead produces "puffy" fluctuant swelling. It may occur alone but often occurs in combination with other intracranial complications, especially epidural abscess (17). The primary presenting symptoms are severe headache and fever and are not symptoms of sinusitis (17).

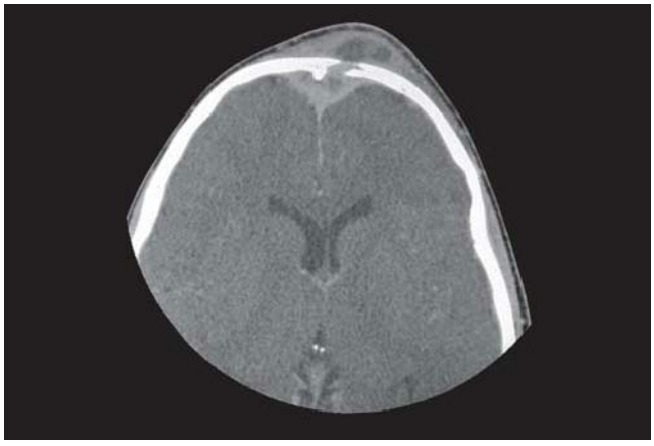


Figure 38.9 Axial CT scan demonstrating a Pott Puffy Tumor secondary to frontal sinusitis. There is bone erosion (due to acute osteomyelitis), a scalp abscess, and a concurrent epidural abscess.

Imaging begins with contrast enhanced CT scan of the sinuses. MRI imaging is the best modality for excluding intracranial pathology and for determining the extent of intracranial involvement and is usually performed when the CT scan identifies or suggests the presence of intracranial infection.

Microbiology

Causative organisms include *S. species, especially S. viridans group and S. aureus* (12,17). These infections are commonly polymicrobial and can include anaerobes and gram-negative rods.

Treatment

Treatment consists of IV antibiotics and drainage of the abscess with removal of infected bone. Surgery should be followed by 6 weeks or more of IV antibiotic treatment (12,17). Definitive endoscopic treatment of the frontal sinuses, frontal sinus obliteration, and reconstructive procedures may then be performed as indicated.

PREVENTION OF COMPLICATIONS OF SINUSITIS

The seriousness of sinogenic complications and the occasionally devastating outcome might cause patients and practitioners alike to question whether or not these

infections could be prevented by early and appropriate use of antibiotics for acute rhinosinusitis. In contrast, high rates of antibiotic use, particularly for upper airway infections that are often viral in nature, are contributing to the dramatic increases in antibiotic resistance seen nationally. In contemporary series, similar complication rates have been seen in patients with acute rhinosinusitis treated with and without prior antibiotics (26). Though the data is limited, early treatment of upper respiratory infections solely in an effort to decrease sinogenic complications is not supported by available clinical data.

Sinogenic intracranial abscesses occur, on average, in only three or four children per million children population (27). The rarity of this condition makes prospective clinical research impractical. An additional challenge to research on early or preventative treatment of acute rhinosinusitis is the fact that the majority of patients with intracranial complications do not have symptoms of sinsusitis at time of presentation.

The conclusions of the audit by the British Rhinological Society of complications of acute rhinosinusitis succinctly summarize the current state of clinical data at this time: "despite prior antibiotic treatment, complications of acute rhinosinusitis seem to occur sporadically… suggesting limited benefit of oral antibiotics in the Primary Care setting" (28). Treatment of complicated sinusitis thus relies on maintaining an index of suspicion for both complications in the setting of sinusitis and sinusitis in the setting of orbital and intracranial infections.

HIGHLIGHTS

- Diagnosing complications of sinusitis requires a high index of suspicion. Presenting symptoms are often not those of sinusitis but rather headache, fever, and/or eye swelling.
- Multiple complications of sinusitis are common, especially in cases of severe orbital or intracranial complications.
- CT scan with contrast of the sinuses and orbits is the study of choice to evaluate orbital complications, whereas MRI with contrast of the brain and orbits is the study of choice for intracranial complications.
- The causative organisms in complicated sinusitis do not always reflect the microbiology of uncomplicated sinusitis.
- Orbital complications are most often caused by *S. viridans* group (including *S. milleri* group). These organisms are facultatively anaerobic or microaerophillic. *S. aureus* and other *S. species* are also common causes of these infections.
- Intracranial complications are often polymicrobial; as in orbital complications, the most common causative organisms in intracranial complications of sinusitis are *S. viridans* group organisms. Other *S. species*, *S. aureus*, and anaerobes are also common causes of these infections.
- All patients with complications of sinusitis require medical management of the underlying sinusitis including appropriate broad-spectrum IV antibiotics.
- Treatment of preseptal cellulitis and orbital cellulitis is primarily medical and rarely require surgical treatment.
- In addition to medical treatment, surgical drainage of subperiosteal and orbital abscesses is usually required although patients with small, medial subperiosteal abscesses without ophthalmologic findings may often be exclusively medically managed.
- An orbital abscess is associated with severe exophthalmos, chemosis, complete ophthalmoplegia, and visual impairment.
- Cavernous sinus thrombosis can progress to bilateral orbital pain, chemosis, proptosis, and ophthalmoplegia. Aggressive medical treatment is needed. Sinus drainage for aeration and cultures may be beneficial.
- Intracranial abscesses can be epidural, subdural, and intracerebral. Multiple abscesses in a patient with complicated sinusitis are common.
- Epidural and subdural spaces are the most common abscess sites. Epidural abscess is associated with a more favorable outcome. Subdural abscesses are especially associated with high mortality and neurologic and developmental sequelae.
- Management of intracranial abscess is usually a combination of medical and surgical treatments.

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39 Medical Management of Chronic Sinusitis

Jeffrey D. Suh *Alexander G. Chiu*

Chronic rhinosinusitis (CRS) is one of the more prevalent chronic illnesses in the United States, affecting at least 14% of the adult U.S. population (1). According to recent 2007 data from the National Health Interview Survey, rhinosinusitis continues to be one of the top 10 leading diagnoses of office visits in the United States. It has been estimated that over $5.8 billion dollars is spent each year treating patients with sinus complaints, and that one in every five antibiotics prescribed are for patients with sinusitis (2). The socioeconomic impact of rhinosinusitis is even greater when indirect costs from decreased work productivity and missed work days are considered. CRS not only causes symptoms directly related to the nasal cavity and sinuses, but also has a substantial negative health impact on quality of life with respect to mood, bodily pain, energy level, physical functioning, and social functioning (3,4). Medically recalcitrant CRS can be even more debilitating than other serious medical conditions such as angina, congestive heart failure, chronic obstructive pulmonary disease, and chronic back pain, or sciatica (3).

Despite its prevalence and importance, the etiology and pathophysiology of CRS is poorly understood. CRS was believed at one time to arise, somewhat simply, from sinus ostium obstruction leading to mucus stasis and subsequent bacterial infection. CRS is now thought to arise from persistent inflammation of the sinonasal mucosa, and perhaps the underlying bone, due to a number of factors. Perhaps the most appropriate broad classification of predisposing factors for CRS is grouping into environmental factors (e.g., pollution, allergens, viruses, bacteria, and molds), general host factors (genetic, granulomatous disorders, immune deficiency, cystic fibrosis, and ciliary defects), and local host factors (chronic localized inflammation, anatomic obstruction, polyps, and tumors) (5). It is clear that CRS is not one disease, but rather is a spectrum of symptoms and signs that can arise from multiple different etiologies.

Although multifactorial in origin, CRS is characterized by a consistent set of symptoms and clinical signs. Persistent mucosal inflammation and thickened mucus often leads to symptoms of postnasal drainage, nasal congestion, decreased sense of smell, and/or facial pressure. Given the consistency of these symptoms, initial medical management of CRS is focused on treating mucosal inflammation and purulent mucus. Those that fail this medical therapy are often recommended to consider sinus surgery. But with a 5% to 10% failure rate from surgery (4), there is an additional subset of patients who are recalcitrant to conventional medical and surgical therapies, leading to alternative therapies centered on anti-infective and anti-inflammatory nasal irrigations.

DEFINITION AND DIAGNOSIS

Clinicians treating CRS must be familiar with the criteria used to make the diagnosis. CRS is defined as persistent symptomatic inflammation of the nasal and sinus mucosa lasting for more than 12 weeks. The diagnosis of CRS is based primarily on medical history and is supported secondarily by confirmatory physical findings. In 2007, an updated clinical practice guideline by the American Academy of Otolaryngology—Head and Neck Surgery was developed by a multidisciplinary expert panel based on evidence from the literature (6) (Table 39.1). Briefly, the diagnosis of CRS requires that inflammation be documented on physical examination, in addition to persistent symptoms that usually include at least two of the following: nasal obstruction, facial congestion/pressure/fullness, discolored nasal discharge, and hyposmia.

STAGING SYSTEMS

A variety of staging systems have been used to stratify patients with CRS according to objective radiologic and endoscopic findings. Familiarity with these staging systems can allow the otolaryngologist to better document changes

TABLE 39.1 CLINICAL PRACTICE GUIDELINES, ADULT SINUSITIS (2007)

Diagnosis of CRS: ≥12 wk duration with
Two or more of the following symptoms
- Mucopurulent drainage
- Nasal Obstruction
- Facial pain/pressure/fullness
- Decreased sense of smell

And

Inflammation documented by ≥1 of the following objective criteria
- Purulent mucus or edema in the middle meatus or ethmoid region
- NP in the nasal cavity or middle meatus
- Radiographic imaging showing inflammation of the paranasal sinuses

in physical examination. Two commonly used staging systems found in the literature are described briefly in this section. These staging systems can be helpful to document exam changes following initiation of medical or surgical therapies.

Lund-Mackay Staging

The Lund-Mackay staging system is widely used in the radiologic assessment of CRS (7). The scoring system is based on computed tomography (CT) scan findings that are often obtained after an adequate trial of medical treatment. Each sinus is evaluated on cross-sectional imaging and noted to be completely clear, partly opaque, or completely opaque and assigned a simple numeric score (Table 39.2). The sinus groups include the maxillary, frontal, sphenoid, anterior ethmoid, and posterior ethmoid sinuses. The ostiomeatal complex is also scored. A total score of 0 to 24 is possible, and each side can be considered separately (0 to 12).

TABLE 39.2 LUND-MACKAY STAGING SYSTEM

Sinus System	Left	Right
Maxillary		
Anterior ethmoid		
Posterior ethmoid		
Sphenoid		
Frontal		
Ostiomeatal complex		
Total points for each side		

Scoring: For all sinus systems, except the ostiomeatal complex: 0, no abnormalities; 1, partial opacification; 2, total opacification. For the ostiomeatal complex: 0, not occluded; 2, occluded.
Adapted from Lund VJ, Mackay IS. Staging in rhinosinusitis. *Rhinology* 1993;31(4):183–184.

Lund-Kennedy Endoscopic Scores

In this staging system, the endoscopic appearance of the nose is examined for the presence of polyps (0, none; 1, confined to middle meatus; 2, beyond middle meatus), discharge (0, none; 1, clear and thin; 2, thick and purulent), and edema, scarring or adhesions, and crusting (for each: 0, absent; 1, mild; 2, severe) (8,9,9a).

MEDICAL MANAGEMENT OF CHRONIC RHINOSINUSITIS

The treatment of CRS is based on a number of factors including the type of rhinosinusitis (acute, chronic, or fungal), concurrent medical comorbidities, symptom severity, and response to previous medical treatments (10). In general, the treatment of CRS is intended to reduce symptoms, improve quality of life, and prevent disease progression or recurrence. More specifically, treatments are aimed at reducing mucosal inflammation, controlling infection, and restoring mucociliary clearance. Medical treatment should be considered the cornerstone of disease treatment for CRS, with sinus surgery reserved for medical failures or for patients with complications.

GENERAL TREATMENT STRATEGIES

CRS has recently been simplified to two subgroups; CRS *with* nasal polyps (NP) and CRS *without* NP (9). In the past, these two entities were considered to be a spectrum of a single disease, with NP being considered the end point of the evolution of CRS. Current data suggest that there are distinct differences between patients in the subgroups, and that the groups can have different responses to medical treatment (9,11). This chapter discusses the most common treatment modalities used to treat CRS, and focus on specific recommendations based on the CRS subgroup (CRS with or without polyps) when possible.

STEROIDS

Corticosteroids constitute first-line therapy in the medical management of CRS. Glucocorticoids have wide-ranging effects on the nasal mucosa. Studies of glucocorticoids show that they can suppress many phases of the inflammatory process by inhibiting the release of vasoactive mediators, reducing vasodilation, fluid extravasation, edema, and local deposition of mediators (12). Glucocorticoid-treated NP have demonstrated a down-regulation of proinflammatory cytokines and adhesion molecules that attract and activate eosinophils (13,13a). Studies of asthma and allergic rhinitis (AR) show that glucocorticoids decrease a wide variety of proinflammatory cytokines, chemokines, adhesion molecules, and mediator-synthesizing enzymes such as inducible nitric oxide synthase, cyclooxygenase-2,

and phospholipase-A2 (13,13a,14). Both topical and oral corticosteroids are used frequently for CRS and are discussed in the following two sections.

Topical Steroids

A number of studies have demonstrated the efficacy of intranasal steroids in the management of CRS with NP. These sprays are used most commonly in the management of symptoms associated with seasonal and perennial AR (15). Nasal corticosteroids have been shown to inhibit both immediate- and late-phase reactions to antigenic stimulation in patients with AR (16). In general, nasal steroids with low systemic bioavailability (such as mometasone furoate, fluticasone propionate, or furoate) have not been associated with bone growth or adrenal suppression, which was first noted with more systemically bioavailable agents such as beclomethasone dipropionate (17). There is also no clear evidence that the use of nasal corticosteroids correlates with systemic changes in bone mineral biology, cataracts, or glaucoma. Adverse effects such as nasal irritation, epistaxis, and crusting with nasal steroids are rare, occurring in less than 10% of patients (18). *Rarely, septal perforations have been reported with nasal steroid spray usage. Therefore, to minimize epistaxis and possible perforation, patients are frequently instructed to direct the nasal spray toward the internal lateral aspect of the nasal cavity and not toward the nasal septum.*

Topical steroids are routinely used to treat CRS with eosinophilic inflammation or NP. Guidelines from the 2007 European Position Paper on Rhinosinusitis and Nasal Polyps (19) recommends topical steroids as the first-line medication based on the results of several randomized controlled trials with fluticasone propionate, beclomethasone dipropionate, budesonide or mometasone furoate. Studies have demonstrated that topical corticosteroids are beneficial in the treatment of small to medium-sized polyps, nasal symptoms, and that this effect can be maintained with continued use (20–24). Corticosteroid nasal sprays have also been shown to delay the recurrence of polyps after surgery (24,25). There has also been some recent literature describing the use of budesonide respules (Pulmicort; AstraZeneca, Wilmington, DE) as an adjuvant method of treating eosinophilic or polypoid CRS when the respules are directly applied as a nasal drop or as an additive to nasal irrigation (26,27). In theory, a much higher concentration of corticosteroids can be applied to the sinus mucosa with budesonide respules compared to conventional nasal steroid sprays.

Despite proven efficacy of intranasal steroids for CRS with NP, benefit for nonpolypoid CRS has been harder to demonstrate (28–31). A randomized, double-blind, placebo-controlled study on patients with CRS without NP found no significant improvement on endoscopy and symptoms scores with fluticasone propionate for 16 weeks (32). More research is required to support the use of intranasal steroids for CRS without NP.

Systemic Steroids

Oral corticosteroids are commonly used in the treatment of CRS with and without NP for recalcitrant cases or when a rapid, short-term improvement is needed (33,34). However, despite widespread use among both general otolaryngologists and rhinologists, there is a lack of strong evidence with respect to indication, dose and duration (35,36). In 2007, a Cochrane review found only one randomized, controlled trial (37) on oral steroid therapy for CRS with NP (33). The results of this study and others have shown that oral steroids can dramatically reduce polyp size in patients with CRS, reduce nasal obstruction, improve quality of life scores, and decrease inflammatory chemokines and cytokines (37–40). But without other adjuvant treatments, these benefits are usually short-lived (40). Recent evidence suggests that combination therapy with oral and intranasal corticosteroids can provide long-term reduction in polyp size and improvements in quality of life without significant adverse effects (41).

The most common side effects of oral steroid use include glucose intolerance, hypertension, gastrointestinal bleeding, and altered mood. Adverse effects associated with long-term use of oral steroids include weight gain, glaucoma, cataracts, gastrointestinal complications, adrenal suppression, growth suppression, diabetes mellitus, osteoporosis, and avascular necrosis (most commonly of the hip) (33). These risks must be carefully considered, and patients must be counseled about these side effects prior to initiating long-term therapy.

ANTIBIOTICS

Antibiotics are commonly used in the management of CRS to decrease bacterial load and to treat acute bacterial exacerbations of CRS. There are significant differences in the bacteria present in CRS as compared to acute rhinosinusitis. Antibiotic therapy for CRS has traditionally been aimed at a mixed population of aerobic and anaerobic bacteria. However, despite level 1A evidence of the efficacy of topical steroids in treating rhinosinusitis, no such evidence of antibiotic efficacy in CRS exists and no antibiotic is U.S. Food and Drug Administration (FDA)-approved for the indication of treating CRS. Commonly used agents include amoxicillin-clavulanate, clindamycin, trimethoprim-sulfamethoxazole, or a fluoroquinolone. The optimal duration of therapy has not been studied prospectively, but is typically 3 to 4 weeks long, with longer courses for recalcitrant cases. When treating CRS with antibiotics, it is important that other modalities, such as nasal irrigation and topical or oral corticosteroids, also be included.

The species of bacteria and the incidence of antibiotic resistance vary widely depending on a variety of factors including the chronicity of the disease and the extent of prior antibiotic

therapy. The microbiology of CRS differs from that of acute rhinosinusitis, with a greater incidence of anaerobic bacteria, *Staphylococcus aureus, and Pseudomonas aeruginosa*, all which must be considered before recommending antibiotics. In a study by Finegold et al. (42) the most common anaerobic bacteria in chronic maxillary sinusitis were *Prevotella* species, anaerobic streptococci, and *Fusobacterium* species. The most common aerobic bacteria were *Streptococcus* species, *Haemophilus* species, *P. aeruginosa*, *S. aureus*, and *Moraxella catarrhalis*. The microbiology of chronic frontal sinusitis is slightly different, with 21% *S. aureus*, 21% coagulase-negative staphylococci, 9% *Haemophilus influenzae*, and 26% multiple organisms in one study (43). Anaerobes were present in 3% and fungi in 4%, and there was no growth in 38%. The bacteriology of odontogenic infections tends to mirror that of oral flora. The microbiology of acute exacerbations of CRS is more similar to the microbiology of acute bacterial sinusitis than CRS (44).

When possible, antibiotics for recalcitrant infections should be started after cultures have been obtained and be based on sensitivities. The results of antimicrobial susceptibilities and bacterial presence changed the therapy of almost 50% of patients in a retrospective, consecutive series of patients with CRS or acute exacerbations of CRS (44). If this is not possible, several factors must be considered prior to selecting empiric antimicrobial therapy. The 2004 Guidelines from the Sinus and Allergy Partnership (45) recommend a fluoroquinolone or high-dose amoxicillin-clavulanate for patients who have received antibiotics within the past 4 to 6 weeks, as recent use of prior antibiotics is a risk factor the presence of antibiotic-resistant bacteria. In cases of penicillin allergy, one alternative would be clindamycin and Bactrim (trimethoprim-sulfamethoxazole) as the combination provides strong anaerobic and aerobic coverage. Antimicrobial susceptibility rates vary geographically and by anatomic location. Local hospital antibiograms may be helpful in guiding empiric antimicrobial choices.

Recent investigations have confirmed the presence of biofilms on the mucosa of patients with CRS (46). Bacterial biofilms are highly organized structures composed of communities of bacteria encased within a protective extracellular matrix. Biofilms are notoriously difficult to eradicate, and might explain the high incidence of symptom relapse in some patient with CRS. *P. aeruginosa*, *H. influenzae*, and *S. aureus* are the most common biofilm-forming bacteria seen in sinus infections. Interestingly, persistent symptoms after functional endoscopic sinus surgery and surgical failures have been recently been attributed to the presence of biofilms (47,48). The most common treatments for biofilm-associated sinusitis include topical antibiotics, surgery, mechanical debridement, and surfactants (46,49).

Antifungal therapy for CRS is still controversial at this time. Recent double-blind, placebo-controlled trials have not shown substantial improvement of CRS based on objective and subjective criteria after treatment with amphotericin B (50,51). Another placebo-controlled trial by Kennedy et al. (52) found no improvement with the antifungal terbinafine on symptoms or radiographing findings in patients with CRS. The preceding topical antifungal and oral antifungal studies were not restricted to patients with fungus present on culture or histopathologically. Seiberling and Wormald (53) showed in a retrospective case series, restricted to patients with refractory allergic or nonallergic sinusitis associated with fungus histopathologically that oral itraconazole improved symptoms and endoscopic examination. Better designed studies targeting patients with evidence of fungus histopathologically are required to fully answer the question of the role of antifungals in a subset of patients with CRS associated with fungus.

TREATMENT OF SINONASAL MRSA

The prevalence of methicillin-resistant staphylococcus aureus (MRSA) positive cultures in CRS is increasing (54–56). Prior ESS may be associated with an increased risk of MRSA presence (57,58). However, because there is a high incidence of nasal colonization, the presence of a positive culture does not necessarily require treatment in the absence of symptoms or purulence on endoscopy or anterior rhinoscopy. A sudden worsening of symptoms from baseline and purulence on physical examination implies an acute exacerbation of CRS, which should be treated. These patients are managed by microbiologic culture, determination of antibiotic sensitivities, and appropriate therapy.

Treatment options for MRSA sinonasal infections include oral antibiotics, intravenous antibiotics, and more recently, topical antibiotics (58–60). Outpatient treatment of MRSA sinusitis should be based on sensitivities and until there is a clinical resolution of symptoms and endoscopic findings. Oral antibiotics available to treat MRSA infections include clindamycin, trimethoprim-sulfamethoxazole, tetracyclines (tetracycline, doxycycline, and minocycline), rifampin, and linezolid (60). Rifampin should not be used in monotherapy due to rapid development of resistance (60). In some cases, intravenous antibiotics are required for MRSA sinusitis. One report of a 6 to 8 week course of intravenous (IV) antibiotics for six patients with MRSA sinusitis showed resolution of MRSA on follow-up cultures in 83% of patients, as well as similar improvements in sinus-related quality of life measures (61). However, side effects with IV antibiotics are not insignificant, and require close monitoring to avoid potentially serious morbidity.

Topical antibiotics have also been used to treat MRSA sinus infections. Antibiotic irrigation and nebulized antibiotics have the theoretical advantage of high local levels of drug with minimal systemic absorption, lower costs, and decreased morbidity compared to long-term parenteral therapy (62). Mupirocin nasal irrigation has been used successfully for exacerbations of CRS due to MRSA (63). Vaughan and Carvalho (64) evaluated the use of nebulized antibiotics for acute exacerbations of CRS in patients

who otherwise would have required IV antibiotics. They found that nebulized antibiotics were safe, with few side effects, and a high level (76%) of bacterial eradication, but found changes in the bacterial flora in some of the study patients after treatment. In general, patients who have had sinus surgery are better candidates for topical therapy for sinusitis, since prior sinus surgery enlarges openings into the sinuses permitting improved distribution to the sinus mucosa. However, data suggest that topical therapies are effective for both surgical and nonsurgical patients with rhinosinusitis. For the antibacterial studies, the highest level of evidence currently exists for studies with post-surgical patients and culture-directed therapy. However, despite the increasing use of topical antibiotics for CRS, there is currently only low-level evidence (level III) supporting its use (62).

Saline Irrigation

Saline nasal irrigation has been recommended in the most recent clinical guidelines published in 2007 for CRS and a Cochrane review (6,65). Saline irrigation mechanically removes mucus, crusts, debris, and allergens from the sinonasal cavity, and potentially has the additional benefit of improving mucociliary clearance, ciliary beat frequency, and protecting the sinonasal mucosa (65). Large volume, low-pressure nasal irrigation is more effective than saline sprays or nebulizers in penetrating the sinus ostia (66,67). In eight randomized trials, nasal saline irrigation for CRS improved symptoms, quality of life, endoscopic findings, and was well tolerated and without significant harmful side effects (65).

Saline irrigation may prevent rhinosinusitis. In a randomized trial, daily hypertonic saline nasal irrigation improved disease-specific quality of life after 6 months (68). With 87% adherence to therapy, side effects in this study were minimal and included: nasal irritation, epistaxis, nasal burning, tearing, and headaches. In a follow-up study, a subset of patients reported reduced sinus symptoms and sinusitis-related medication use for an additional 12 months (69). Other recent data suggest that Dead Sea Salt hypertonic saline irrigation may be more beneficial than standard hypertonic saline irrigation for CRS symptoms (70). Studies on the effects of hypertonic saline irrigation on cilia and mucociliary clearance are conflicting. *In vivo* data suggest that hypertonic solutions may improve mucociliary clearance more than isotonic saline (71), however, there are some *in vitro* data suggesting that hypertonic may cause a temporary decrease in ciliary beat frequency (72,73).

Clinicians should work with patients to develop strategies that facilitate incorporating saline nasal irrigations as part of routine sinus care. It is also important to emphasize that rinse bottles be cleaned at least once a week, as there is evidence that irrigation may increase the frequency of gram-negative organisms on culture (74).

OTHER THERAPIES

Irrigation, antibiotics, and anti-inflammatories make up the majority of CRS treatment. This section discusses other classes of drugs or therapies that can either provide additional symptom relief in select patients, or represent promising novel therapies under investigation.

Antihistamines

Antihistamines are commonly prescribed medications for patients with AR. There is a lack of evidence that antihistamines are effective in the treatment of CRS, but these drugs have been used for patients with concurrent allergies. First generation antihistamines, including diphenhydramine, can cause sedation, dry mouth, urinary retention, and potentially drying of nasal and sinus secretions. These side effects are far less common or absent in newer second generation antihistamines.

Some common antihistamines are listed in Table 39.3. Unlike oral antihistamines, nasal antihistamines are not only effective for rhinorrhea, sneezing, and itchy nose, but are also effective for nasal congestion. Combination of an antihistamine nasal spray with a nasal steroid spray may significantly increase symptom control in AR, compared to either spray used alone (75).

Decongestants

Oral and nasal decongestants are used for rhinorrhea and nasal congestion, but side effects prohibit prolonged use (76). Pseudoephedrine is available behind the counter. Phenylephrine is only a weak decongestant, while phenylpropanolamine was removed from the market because of an association with stroke in young women. Common side effects can include anxiety, insomnia, irritability, headache, palpitations, hypertension, and decreased urinary flow. Contraindications include patients with cardiac disease such as coronary artery disease, and concurrent use of monoamine oxidase inhibitors (MAO)-inhibitors. Prolonged and repeated use of nasal decongestant sprays often results in rhinitis medicamentosa, or severe rebound congestion, after drug withdrawal.

TABLE 39.3 COMMON ANTIHISTAMINES

First Generation	Second Generation
Brompheniramine (Dimetane)	Cetirizine (Zyrtec)
Chlorpheniramine (Chlor-Trimeton)	Desloratadine (Clarinex)
Clemastine (Tavist)	Fexofenadine (Allegra)
Diphenhydramine (Benadryl)	Loratadine (Claritin)
Hydroxyzine (Atarax)	
Promethazine (Phenergan)	

Anticholinergics

Ipratropium bromide (Atrovent) nasal spray is generally used two to four times per day to treat rhinorrhea due to allergic and vasomotor rhinitis (77,78). It is an anticholinergic (parasympatholytic) agent that acts by inhibiting vagally mediated reflexes by antagonizing the action of acetylcholine, thus decreasing secretions from the serous and seromucous glands lining the nasal mucosa. To increase the effectiveness in treating rhinorrhea, anticholinergic sprays can be combined with an intranasal steroid spray (77).

Leukotriene Inhibitors

Inhibitors or antagonists of leukotrienes are approved by the U. S. Food and Drug Administration for the treatment of allergy and asthma. Leukotrienes are inflammatory mediators that are produced by a number of cell types including mast cells, eosinophils, basophils, macrophages, and monocytes (79). Activation of specific receptors leads to a variety of biologic effects including contraction of human airway smooth muscle, chemotaxis, and increased vascular permeability. Leukotrienes as well as other arachidonic acid metabolites have been found in high levels in patients with asthma as well as from patients with NP. Studies have demonstrated that leukotriene inhibitors can reduce sinonasal symptoms and NP, especially in patients with Aspirin-exacerbated respiratory disease (79,80). There is also some evidence that leukotriene-receptor antagonists might be useful after ESS in patients with NP to limit polyp regrowth and improve nasal and pulmonary symptoms (81). At this time, more research is required to determine which subset of patients with CRS with NPs will benefit most from leukotriene inhibitors.

Immunotherapy

The association of AR and CRS is unclear, but because many of the symptoms of AR mimic symptoms of CRS, AR should be thoroughly evaluated and treated in patients with CRS.

Rhinitis is common, affecting up to 40% of children and between 10% and 30% of adults (77). Allergen avoidance is the mainstay of management for patients with AR, with antihistamines and topical nasal steroids for symptomatic relief (82). AR causes symptoms similar to those seen in CRS, such as nasal congestion and nasal drainage. Allergy may cause sinusitis by inducing mucus hypersecretion and obstruction of the ostiomeatal complex by mucosal edema.

Subcutaneous immunotherapy (SCIT) is effective for perennial and seasonal AR. SCIT improves symptoms, reduces medication required, and prevents development of new allergies and asthma in children. These effects can persist for at least 3 years after discontinuation of treatment. The mechanism of SCIT is not completely understood but is associated with the generation of allergen-specific T regulatory cells, which are known to be capable of suppressing allergen-induced proliferation and cytokine response. In addition, antibody class switching of B cells from allergen-specific IgE to allergen-specific IgG4 occurs and these allergen-specific IgG4 antibodies may inhibit binding between allergen and IgE on mast cells and basophils (83). A Cochrane review concluded that SCIT is a safe and valid treatment for AR (84).

Sublingual immunotherapy (SLIT) has emerged as a promising alternative to injection immunotherapy (85,86). Although highly effective, SCIT commonly causes pain and swelling at the injection site with a rare risk of severe systemic and life-threatening reactions. A recent review found support for SLIT in children and for use in AR due to seasonal allergens and dust mites (85). However, more study is necessary to optimize allergen dosages, treatment duration, and improve criteria for patient selection.

Macrolide Antibiotics

The only antibiotic to show efficacy in a blinded placebo-controlled trial in CRS was long-term macrolide therapy (86). In Japan, a reduced mortality rate from diffuse panbronchiolitis with long-term, low-dose macrolide therapy, prompted investigation of macrolides for a variety of chronic inflammatory diseases, including cystic fibrosis and CRS, with promising results (87,88). The effectiveness of this therapy is attributed to the drug's anti-inflammatory and immunomodulatory effects, rather than direct antibacterial effects, although macrolides do decrease biofilm formation in certain bacterial species, such as pseudomonas (89,90).

Macrolides inhibit inflammatory mediators such as interleukin (IL)-1B, IL-8, and intercellular adhesion molecule-1 (90). Other effects include protecting bioactive phospholipids, accelerating apoptosis of neutrophils, and increasing mucociliary transport (91). Macrolides decrease airway mucus secretion, and even have a reparative effect on inflamed airway mucosa (92). Wallwork et al. (93) noted statistically significant improvements in the Sinonasal Outcome Test (SNOT)-20 scores, nasal endoscopy exams, saccharine transit times, and IL-8 levels in lavage fluid in patients on long-term macrolide therapy compared to placebo. After 3 months of erythromycin or clarithromycin in patients with CRS with NPNP, IL8 levels in nasal lavage decreased significantly, corresponding with a decrease in the nasal polyp size (94). Low-dose macrolide therapy is worthy of further study in patients with CRS and low or normal IgE levels refractory to other therapies (92).

Mucolytics

Guaifenesin is a mucolytic used to loosen respiratory secretions. Despite widespread use, there is a paucity of evidence for mucolytic use in the treatment of CRS (34). Rosen and Calhoun (95) found no change in mucociliary transport time in human immunodeficiency virus (HIV)+ patients treated with guaifenesin, but did show improvements

in rhinosinusitis symptoms. In a double-blind study involving HIV+ patients, Wawrose et al. (96) reported less nasal congestion and thinner postnasal drainage at doses of 2,400 mg/day at 3 weeks. Nausea was the major reported side effect in doses greater than 1,200 mg/day.

Surfactants

A small prospective uncontrolled, unblinded study of 18 patients treated with twice daily sinus irrigations with 1% baby shampoo in saline for 4 weeks, resulted in subjective improvement in SNOT 22 scores in slightly less than half of these heavily pretreated symptomatic and refractory CRS patients (97). Baby shampoo is thought to act as a surfactant with the ability to thin mucus, disrupt microbial cell membranes, and potentially break up biofilms. The same group recently demonstrated that irrigation with the surfactant solution in buffered saline resulted in a transient increase in ciliary beat frequency *in vitro*, with no evidence of toxicity to the cilia (98). Prospective, blinded, and controlled studies are required to fully evaluate the role of baby shampoo or other surfactants in the treatment of CRS.

SUMMARY

Best evidence suggests that the treatment of CRS comprises a combination of anti-inflammatory, mechanical, and anti-infective therapy. For CRS *with* NP, long-term use of intranasal steroids and saline irrigation is recommended. Short-term, systemic corticosteroids can be used for relief of severe sinonasal symptoms, or for temporary relief of symptoms due to NP. Saline nasal irrigation is safe and effective for managing symptoms associated for CRS with and without NP, and may reduce exacerbations when used regularly. Antibiotics should be utilized in CRS in situations of acute worsening of symptoms associated with purulence. If possible, cultures should be obtained prior to antibiotic initiation, in order to guide subsequent therapy. Low-dose macrolides, leukotriene antagonists, topical antibiotics, and immunotherapy can be considered in select patients.

CONCLUSION

CRS is a common disease that can have a substantial impact on quality of life. Advances in medical therapy have reduced the morbidity associated with CRS, and can provide long-term benefit when effectively combined. The principles involved in treating of CRS include identifying and treating the underlying cause of inflammation. Treatment goals include the reduction of mucosal edema, restoration of paranasal sinus ventilation, and eradication of infectious pathogens. A better understanding of the pathogenesis of CRS will undoubtedly lead to new and novel therapies in the future.

HIGHLIGHTS

- CRS is a common disease that has a substantial negative impact on quality of life.
- CRS treatments are aimed at reducing sinonasal inflammation, symptoms, and re-establishing mucociliary clearance.
- Topical nasal steroids are first-line therapy in the treatment of CRS with NP and AR. Effectiveness of and type of medical management can differ between CRS *with* NP and CRS *without* NP.
- In general, antibiotics should be not be used alone to treat CRS. Rather, antibiotics should be used when there are signs of infection, and as part of a comprehensive treatment regimen in combination with anti-inflammatory medication and sinus irrigation.
- When possible, endoscopically guided cultures should be performed to direct antibiotic therapy in CRS with purulence.
- Sinus surgery should be reserved for patients that fail appropriate medical therapy.

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Endoscopic Sinus Surgery for Chronic Rhinosinusitis

40

Barry M. Schaitkin *Kenneth D. Rodriguez*

It is imperative that the chapter on medical treatment of sinusitis be read prior to reading this one, as patients deemed surgical candidates for endoscopic sinus surgery (ESS), must be symptomatic with evidence of chronic rhinosinusitis (CRS) despite a trial of medical therapy. Diagnosis of sinus disorders and proper medical therapy are not reiterated in this chapter. Frontal sinus surgery is covered in chapter 46 and a general review of complications of ESS is covered in chapter 44, and these topics are not covered in this chapter. This chapter highlights the surgical philosophy of the authors, surgical technique, surgical landmarks, pearls, and the avoidance of complications. Instrumentation for endoscopic sinus includes a wide variety of nonpowered and powered tools that are rapidly evolving. Residency training allows for use of a multitude of different instruments and techniques and after residency training, continued attendance at sinus conferences allows for further acquisition of skills and familiarity with the latest technologic trends. As a general rule in ESS, mucociliary transport pathways must be maintained and mucosal preservation of normal tissue is crucial.

PREPARATION FOR SURGERY

1. A history and physical exam including a detailed nasal endoscopy after maximal nasal decongestion is essential. Significant septal deviations that may require septoplasty to allow for complete visualization of the paranasal sinuses are noted on exam and the patient should be informed of the possible need for surgical correction of the septum at the time of sinus surgery.
2. Imaging—Noncontrast thin cut sinus computed tomography (CT) with both coronal and sagittal reconstructions is the first line and gold standard for preoperative evaluation for inflammatory sinus disease surgery. The CT should be obtained if the patient is symptomatic, despite a 4 to 6 week trial of maximal or directed medical therapy, in order to determine irreversible bony and mucosal anatomic obstructions and disease, which may be amenable to surgical correction. Review of the sinus CT should be performed at least three times, once with the patient during preoperative planning, once, the night before surgery, and finally, immediately prior to surgical intervention.
3. The senior author of this chapter advocates a two-handed (person) technique for performing ESS (1). This technique allows for the surgeon to use two instruments with the benefit of endoscopic visualization. The assistant, holding the camera, can use a 60-mL syringe with a blunt 18-gauge needle to clear debris from the camera to reduce the time needed for cleaning outside of the nasal cavity. Alternatives include the use of scope scrubbers and self-irrigating powered instruments.

The patient should be treated with a vasoconstrictive intranasal spray, such as 0.5% oxymetazoline in the preoperative holding area at least 30 minutes prior to the start of the procedure. Upon induction of general anesthesia, pledgets, soaked with the same agent used preoperatively, are placed into the nasal cavity on each side of the intended surgery. One pledget is placed on the floor of the nose and another as superiorly as possible, lateral to the middle turbinate. The patient is then sterilely draped with the eyes visualized within the field and treated with lubricant, but untaped so that they are easily examined and palpated. The pledgets are removed from one side and the nasal cavity is inspected. Local anesthesia with 1% lidocaine with 1:100,000 epinephrine is standardly injected in three locations on each side: above and lateral to the superior attachment of the middle turbinate, the inferior aspect of the uncinate, and the tail of the middle turbinate (Fig. 40.1).

To allow for maximum vasoconstrictive effects of the injected local with epinephrine one must allow 5 to 10 minutes prior to operative intervention. Thus after injecting one side, the pledgets are removed from the contralateral side and repeat injections are performed. Once injections are complete, one side of the nasal cavity can be repacked while operating on the contralateral side.

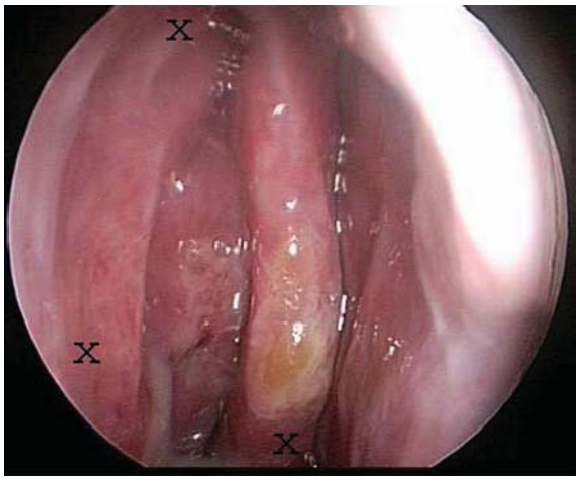


Figure 40.1 Standard three right nasal cavity injection sites.

MAXILLARY SINUS

Key anatomical landmarks:

- Middle turbinate
- Uncinate process
- Lacrimal duct
- Orbit

The first key structure to be identified is the middle turbinate. The middle turbinate should be gently medialized mindful that there is transmission of force to the lateral lamella of the cribriform plate. If a concha bullosa is present, it can be opened in a lateral to medial manner as outlined in the ethmoid sinus section. The middle turbinate can also be reduced in size if it is abnormally bulky or paradoxical in nature again proceeding from lateral to medial sparing as much mucosa as possible. This lateral shaving of the turbinate allows for the preservation of most middle turbinates without risking synechia formation. At all times care should be taken to minimize trauma to the nasal mucosa. The most common minor complication in several series is middle turbinate adhesions along with entry into the orbit (2,3).

Next, the posterior free margin of the uncinate process is identified and medialized with a ball probe, followed by retrograde dissection with the use of a pediatric back-biting forceps beginning approximately one-third of the way above the attachment of the uncinate to the inferior turbinate (Fig. 40.2). This can be efficiently performed by taking multiple bites moving forward as long as the movable tip of the instrument is able to wiggle the mobile uncinate anterior to its path. Moving the uncinate with the tip of the pediatric side biter prior to engaging and biting the bone, can prevent inadvertent nasal lacrimal duct injury, which was more prevalent with the historical technique of anterior to posterior uncinate dissection. The lacrimal duct can be as close as 4 mm anterior to the natural ostium of the maxillary sinus (4).

The uncinate is removed from the superior aspect of the surgically created window up to the level of the agger nasi with a microdebrider. The remaining portion of the inferior uncinate is composed of the medial nasal mucosa, residual uncinate bone, and the lateral mucosa adjacent to the maxillary sinus. The mucosa on the nasal side of the uncinate bone can be removed with the microdebrider and the residual uncinate bone can be dissected and elevated from the sinus side mucosa with a double ball probe. This bone can then be removed with the microdebrider or ethmoid forceps leaving the lateral mucosa in place, thus protecting the natural ostium and preventing the risk of ostium stenosis (Figs. 40.3 and 40.4).

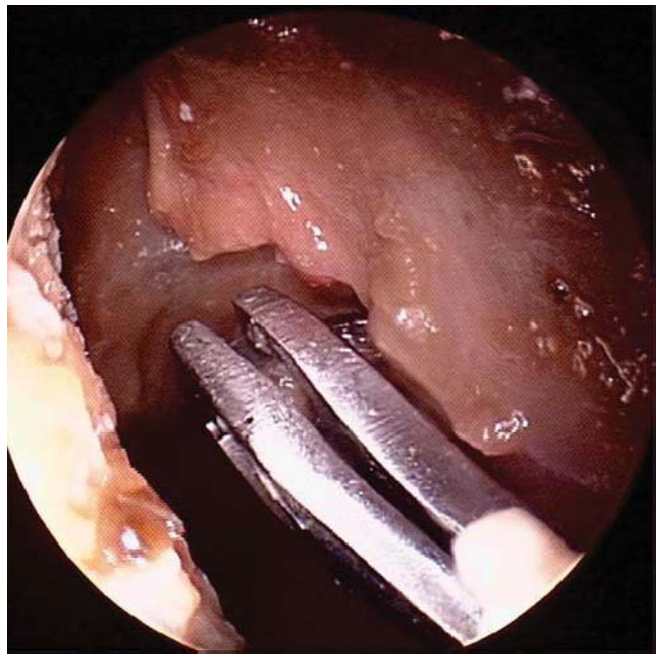


Figure 40.2 Left nasal cavity. Pediatric backbiter removing uncinate process creating the uncinate window.



Figure 40.3 Left nasal cavity. Natural os of maxillary sinus healed following ESS using the technique of the uncinate window. Notice that the natural ostium lies in a parasaggital plane.

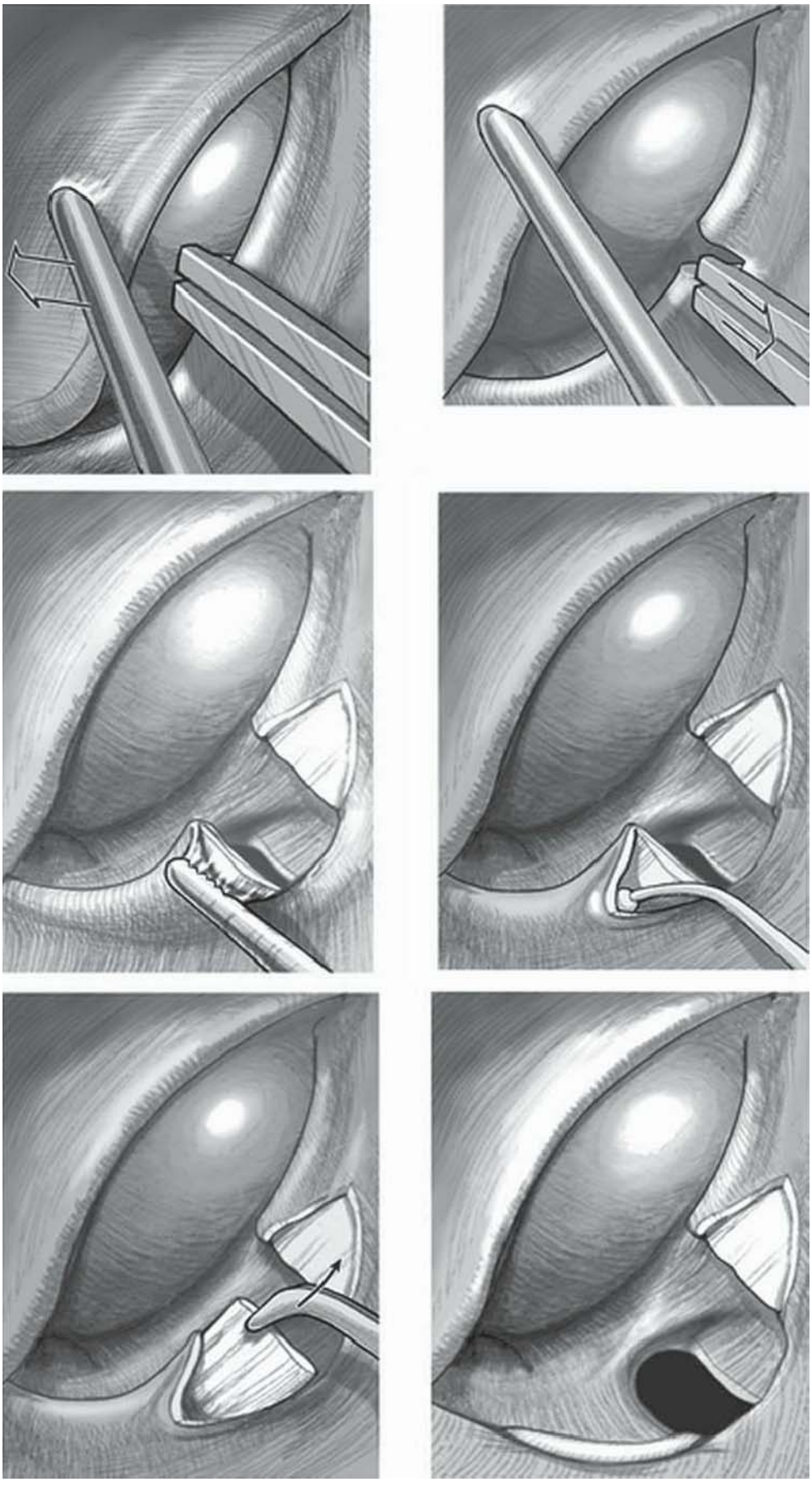


Figure 40.4 Minimally invasive maxillary technique.

Most primary cases do not require a formal antrostomy unless the patient has a mucosal disease process in addition to their chronic or recurrent acute sinus history (i.e., Kartageners, allergic fungal sinusitis, massive polyposis, Samter syndrome, cystic fibrosis, etc.).

Accessory ostia are not universally incorporated into the antrostomy unless they are in the drainage pathway of the sinus putting the patient at risk for recirculation. Haller cells can usually be left in place with just marsupialization into the ethmoid. The opening of the maxillary sinus as described will usually remove any impingement of the Haller cell on the outflow tract.

This procedure is based on the premise that preservation of the mucociliary clearance mechanism is to be maintained whenever possible. Maxillary pathology, such as an antrochoanal polyp will sometimes be accessed via a combination of a middle meatal antrostomy (combining the accessory ostia where the polyp exited to the natural ostia) with inferior meatal instrumentation to improve access and avoid a large antrostomy. This can be done with straight and curved microdebrider tips. It is the senior author's experience that excessive enlargement of the maxillary antrostomy is associated with the development of some of the most refractory cases of maxillary sinusitis, including those with biofilms, and in the senior author's experience, symptomatic biofilms are rare to nonexistent in those with a functioning ostia, normal gas tensions, and normal mucociliary action devoid of surgically introduced scar tissue.

ETHMOID SINUS

Key anatomical landmarks:

- Skull base
- Lamina papyracea
- Ethmoid bulla
- Middle and superior turbinates

Two key anatomic boundaries of the ethmoid air cells are the orbits laterally and the skull base superiorly. The most serious complications of sinus surgery are damage to the globe and cerebrospinal fluid (CSF) leak, and avoiding these complications requires complete understanding of these key anatomic boundaries. Pneumatization patterns of the ethmoid air cells are widely varied and number anywhere from 1 to 2 cells to more than 15 cells. Preoperative review of the patient's CT scan may reveal the presence of an Onodi, Haller, or suprabullar cells. The ethmoid air cells are divided into anterior and posterior at the basal lamella of the middle turbinate. The anterior ethmoid air cells drain into the middle meatus while the posterior air cells drain into the superior meatus. As one proceeds in an anterior to posterior direction, the skull base slopes inferiorly several millimeters, which can lead to entry into the skull base within the posterior ethmoid air cells (Fig. 40.5). As a technical point, while using the microdebrider during an ethmoidectomy, the device should at all times point superiorly, inferiorly, or medially and never laterally when working near the lamina to avoid inadvertent entry and injury to the orbital contents.

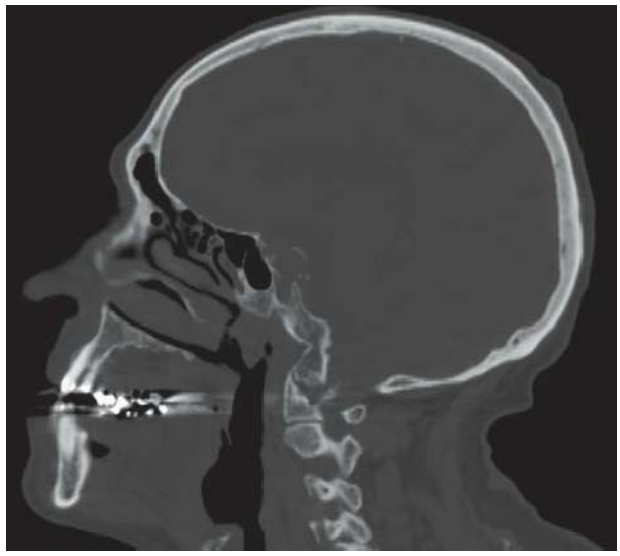


Figure 40.5 Sagittal cut of CT demonstrating the superior to inferior slope of the skull base.

ANTERIOR ETHMOIDECTOMY

A topical decongestant is administered approximately 30 minutes prior to general anesthesia and surgical intervention. The middle turbinate is injected with local anesthesia as described in the maxillary antrostomy section and then gently medialized to identify the ethmoid bulla, which varies from one to several connected cells located just posterior to the free edge of the uncinate. The bulla can be entered in a multitude of ways but the senior author prefers the microdebrider. The bullae are entered medially with the microdebrider inserted between the bulla and the middle turbinate directed laterally which decreases risk to the orbit. If care is taken, one can identify the drainage pathway of the bulla posteromedially into the semilunar hiatus superior, and this natural os should be incorporated into the opening of the bulla (Fig. 40.6).

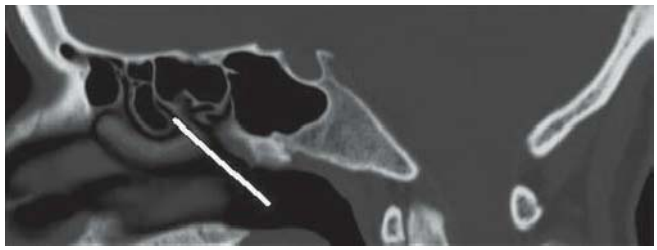


Figure 40.6 Sagittal cut of CT demonstrating drainage of ethmoid bulla between the bulla and the basal lamella in the semilunar hiatus superior (marked by *white line*).

Dissection is concluded at the lamina papyracea although the bulla does not have to be taken flush to this bony plate, it just needs to be opened and adequately drained. Posteriorly, the basal lamella remains intact after anterior ethmoid surgery.

CONCHA BULLOSA

The mere presence of a concha bullosa, or aerated middle turbinate, is not an indication for surgery. However, if an enlarged middle turbinate is causing airway obstruction and/or limited visualization of the surrounding sinuses for planned surgical intervention, it should be reduced at the time of surgery. Lidocaine with 1:100,000 epinephrine is injected into the middle turbinate as described in the maxillary antrostomy section. Multiple options exist for its reduction. The space anterior–lateral to the concha can be entered with the microdebrider and the lateral aspect of the turbinate reduced in a lateral to medial direction with sparing of the medial aspect of the turbinate to prevent scarring to the septum. Damage to the superior medial aspect of the turbinate in some cases can lead to olfactory impairment and this should be discussed with the patient during routine preoperative risk assessment if any middle turbinate surgery is planned. Alternatively, a sickle knife can be used to enter the airspace anteriorly in a vertical fashion. The incision can be extended posteriorly and the lateral aspect of the concha can be removed with a microdebrider or sharp cutting instruments. The concha is a sinus and as such is opened always to include the outflow tract of this intra nasal sinus to enable mucociliary clearance as is done with every sinus procedure.

POSTERIOR ETHMOIDECTOMY

Inspection of the CT scan preoperatively in all three orientations will provide crucial information about the number and orientation of the posterior ethmoid air cells, continuity of the lamina, and height of the skull base. The posterior ethmoid air cells are encountered by entering the basal lamella of the middle turbinate just superior to the point at which the middle turbinate transitions from horizontal to vertical. This can be identified by taking a 0-degree endoscope and passing it under the middle turbinate posteriorly and then withdrawing it anteriorly (Fig. 40.7). The basal lamella is then perforated at the medial and inferior aspect and the posterior ethmoid sinuses are entered. To maintain stability of the middle turbinate the inferior basal lamella should be preserved. Dissection of the basal lamella puts the surgeon into the superior meatus but not the posterior ethmoid air cells that require further dissection to enter. At this point, the resident surgeon is often unclear about their location in the dissection. It can at times be difficult to determine if one is looking at another layer of cells or the skull base. When one is unsure if they are facing another layer of cells or the skull base, one should never enter the next space by pushing through without certainty.

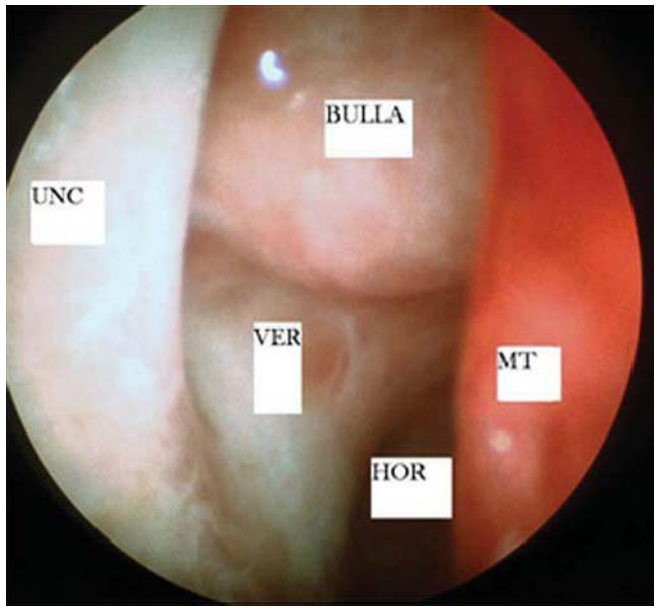


Figure 40.7 Left-sided endoscopic overview. UNC, uncinate; MT, middle turbinate; VERT, vertical basal lamella; HOR, horizontal basal lamella; BULLA, ethmoid bulla.

Possible ways to be certain one is in a posterior ethmoid cell and not at the skull base, include: finding a ledge and opening the posterior cell by pulling rather than pushing on the lamella with a ball probe or kerrison, entering the sphenoid and finding the roof there and coming back anteriorly, using computer navigation, or dropping inferiorly in the dissection and looking for a safe entry point away from the skull base. Dissection can be continued until the superior turbinate and superior meatus are clearly identified.

Identification of the face of the sphenoid and skull base can be facilitated by image guidance and aided by further air cell removal. At the conclusion of this procedure, one should be able to see the lamina papyracea laterally, the skull base superiorly, and the superior turbinate medially. As with all surgery, wide visualization will facilitate safe surgery. While leaving small bony septations anteriorly and at the skull base is acceptable, large overhangs force the surgeon to work in a narrow field and results in an inadequate and less safe ethmoidectomy predisposing the patient to complications.

SPHENOID SINUS

Key anatomical landmarks:

- Nasal septum
- Arch of the choana
- Superior turbinate
- Carotid artery
- Optic nerve

The approach to the sphenoid has been described as transseptal or transnasal. We focus on the latter approach in this text. In addition, pituitary surgery is increasingly being

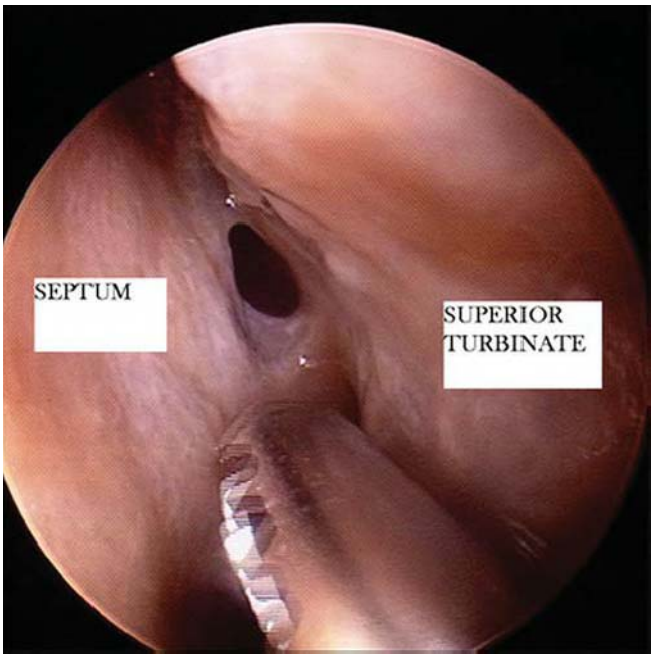


Figure 40.8 Natural os of the sphenoid sinus medial to the superior turbinate.

carried out via endoscopes through an endoscopic transsphenoidal approach. This technique is described in the skull base section of this text. Careful review of imaging should be performed prior to surgical intervention in this region with careful attention to the intimate relationship with the carotid artery and optic nerve in the lateral aspect of the sinus. The carotid artery is partially dehiscent in up to 25% of individuals and the optic nerve in 6% (5). The key anatomic landmark to identify the natural ostia of the sphenoid is the superior turbinate. The natural ostia of the sphenoid sinus can be reached either medial to the middle turbinate through the nasal cavity or lateral to the middle turbinate in a transethmoidal fashion. The middle turbinate is injected in the same fashion as outlined in the maxillary sinus section. Proceeding medial to the middle turbinate, the turbinate is lateralized and the superior turbinate is identified using a 0-degree scope. The natural ostia is identified consistently medial to the superior turbinate (Fig. 40.8) (6).

If needed, the inferior one-third of the superior turbinate can be removed to facilitate identification of the ostia. As advocated for the maxillary sinus, minimal mucosal trauma to the natural ostia should be the goal. A 1 or 3 mm Kerrison (either up or down biting) can be used to enlarge the ostia in an inferior/medial direction. We strongly advocate no use of powered instruments in the sphenoid sinus and complete removal of inflammatory disease is discouraged and is unnecessary when compared with the catastrophic complication of damage to the carotid artery or optic nerve. If the natural ostium cannot be identified using the above technique, providing the sphenoid is well aerated, a point 1.5 cm above the arch of the choana between the septum and superior turbinate can be used as an entry point. This can then be connected to the natural ostia when identified. Of note, inferior opening below the fontanelle with Kerrison forceps will frequently traverse the posterior nasal artery if it is not deliberately avoided, and suction cautery should be used on the artery to avoid postoperative bleeding.

If a total ethmoidectomy has been performed, the sphenoid can be approached as a direct extension of this procedure. The basal lamella is traversed using a ballpoint probe to make a vertical incision just anterior to the superior turbinate that is easily palpated through the basal lamella. This is enlarged slightly with the microdebrider and the lower half of the superior turbinate is removed with through-cutting forceps. The sphenoid ostia can then be seen or easily palpated. It can be gently enlarged inferiorly if necessary exploiting the fontanelle of the sphenoid sinus. For primary cases, if a large sphenoid ostia is required (fungus ball, polyposis, allergic mucin, mucocele, etc.), it is performed inferiorly leaving normal mucosa superior to the sphenoid os.

BALLOON SINUPLASTY

The first U.S. Food and Drug Administration (FDA)-approved dilating balloon catheter system for use in the paranasal sinuses was introduced in 2005. Since that time, more than 88,000 patients have been treated using balloon systems (7). The appeal of this technique is to provide a minimally invasive option to open the ostia of the paranasal sinuses with avoidance of significant mucosal trauma. This method can be used on the maxillary, frontal, and sphenoid sinuses. If combined with an ethmoidectomy performed by traditional means the procedure is termed "hybrid." Depending on the type of balloon system, fluoroscopy may be needed for guidance with associated radiation exposure to both the patient and surgical staff. The advent of lighted guide wires with resultant transillumination or image guidance has reduced the need for fluoroscopy (8,9).

Review of the current literature reveals a minimal number of studies when compared with the prevalence of balloon usage. One of the most frequently cited articles is the CLEAR trial (Clinical Evaluation to Confirm Safety and Efficacy of Sinuplasty in the Paranasal Sinuses), a prospective, multicenter evaluation of balloon sinuplasty published in 2007 (10). One- and two-year follow-ups were subsequently published (11,12). Both follow up studies demonstrated the potential for durable ostial patency over the length of the 2-year follow up with no major complications. However, this remains a single-armed, uncontrolled, observational study and fails to answer many questions about the applicability of balloon sinuplasty. Batra et al. reviewed the current body of balloon sinuplasty literature and concluded that the efficacy and utility of balloon sinuplasty is still unclear and prospective randomized trials are needed (13). The senior author of this text agrees with this conclusion. The use of balloon systems must be evaluated on a case-by-case basis in both a clinical and economic

context. Studies indicate a minimum of complications; however, there is a report of CSF leak following a hybrid sinus case involving balloon sinuplasty (14). This suggests that no matter how safe an instrument is perceived to be, serious complications can ensue.

IMAGE GUIDANCE

There is currently no level-1 evidence for the use of image guidance in endoscopic sinus procedures. That being said, given the low incidence of serious complication that might be decreased by using image guidance, it would require an enormous number of patients to determine a difference and it is likely a study will never be conducted to that end. In 2002, the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) released a consensus statement on indications for the use of image guidance that is listed below (15).

- Revision sinus surgery
- Distorted sinus anatomy of development, postoperative, or traumatic origin, which includes surgery in the absence of normal landmarks or in the presence of anatomical pitfalls
- Extensive sinonasal polyposis
- Pathology involving the frontal, posterior ethmoid, or sphenoid sinuses
- Disease abutting the cranial base, orbit, optic nerve, or carotid artery
- CSF rhinorrhea or conditions where there is a skull base defect
- Benign and malignant sinonasal neoplasms

Fried et al. (16) in a 2008 review on image guidance in sinus surgery emphasized that the core principle of image guidance is as a guide and not a substitute for proper training. In addition, as the boundaries of ESS are challenged through advanced skull base procedures, the role of image guidance becomes more critical. Although this technology is readily available at most institutions, it is the role of the physician to be judicious with its use. Merely having the technology available is not an indication for its use.

REVISION SURGERY

Revision sinus surgery requires forethought and extensive experience. The reason for failure must be addressed in an objective manner and should include that the patient was a poor surgical candidate to start with or medical therapy trial was inadequate. Incorrect diagnosis including failures to send adequate tissue or interpret the pathology can also be a cause for failure. Image guidance can be a useful adjunct but the use of anatomic landmarks and spatial relationships is still the most important component of successful revision sinus surgery. Presented here are six landmarks that can be found in sequence at the time of revision sinus surgery and serve as a guide to progress in a safe manner. Each landmark should be present despite prior surgical intervention (17).

1. The anterior arch of the middle turbinate
2. The maxillary sinus antrostomy
3. The lamina papyracea
4. The ridge
5. The posterior choanal arch
6. The sphenoid sinus roof

The anterior arch of the middle turbinate is formed between the posterior superior aspect of the lacrimal bone and the anterior superior attachment of the middle turbinate. The landmark defines the anterior border and entrance into the ethmoid air cells, and is present even with removal of the middle turbinate. Once within the ethmoid air cells, keeping laterally along the lamina will decrease the risk of penetrating the ethmoid roof, as the frontal bone cap of the ethmoid is thickest laterally.

It is key at the time of revision surgery to ensure that the natural ostium of the maxillary sinus is patent. All retained uncinate must be removed and the natural os identified. Once the maxillary sinus antrostomy has been opened widely, one can identify both the lamina papyracea and "the ridge." The easiest way to identify the lamina is to follow the floor of the orbit medially. The lamina is located just superior to the maxillary antrostomy. It is crucial that the preoperative CT scan be reviewed and careful attention paid to the continuity of the medial orbital wall and any dehiscence, either congenital or iatrogenic identified.

"The ridge" is the bony extension of the orbital floor between the maxillary antrostomy inferiorly and the lamina superiorly. The benefit of this landmark is the posterior ethmoid air cells will be superior to this ridge and the sphenoid sinus inferior (Fig. 40.9). This will play a key role in polyp patients who have undergone multiple prior procedures with dramatic changes to their native anatomy.

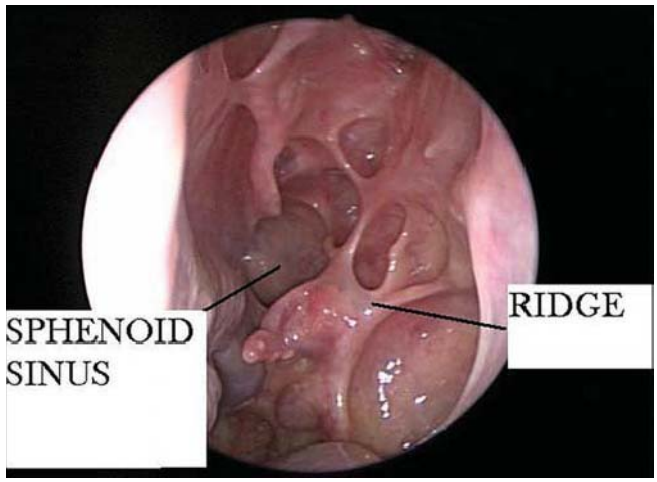


Figure 40.9 Left-sided endoscopic view after maximal endoscopic surgery showing ridge and relation of opened sphenoid sinus extending below the ridge.

The posterior choanal arch allows for identification of the sphenoid sinus and safe entry in the scarred or difficult-to-identify sphenoid ostium. The surgeon, even when using image guidance, can check anatomic coordinates using the posterior choanal arch, the ridge, and the posterior aspect of the nasal septum. The surgeon can grasp the mucosa over the front face of the sphenoid and dissect it inferiorly to displace the posterior nasal branch of the sphenopalatine artery. 1.5 cm above the arch and near the septum, the surgeon can enter the sphenoid safely through the newly exposed bone. The safest point of entry into the sphenoid is medial and inferiorly through the newly exposed bony face of the sphenoid. This opening is then enlarged laterally and superiorly to incorporate the natural ostium. Careful attention should be paid preoperatively to the location and bony covering of the carotid artery and optic nerve within the sphenoid sinus. In the case of stenosis of the sphenoid os, once the sinus is reopened a septal flap can be used to line the floor of the sinus at the conclusion of the revision surgery to prevent stenosis. For revision surgery, a balloon is an excellent option if an opening can be found to dilate or it can be used for initial dilation of a narrow sphenoid os followed by using of a kerrison to continue to widen the os.

On sagittal CT of the paranasal sinuses, one can readily identify that the ethmoid and sphenoid sinuses share a common roof (Fig. 40.5). Once the sphenoid has been entered and opened to the roof, one can proceed in a posterior to anterior direction clearing residual ethmoid air cells to the level of the skull base because the most inferior limit of the skull base has now been defined. This is an effective method for avoiding entrance at the skull base posteriorly.

The method described is one of many revision techniques found in the literature. Regardless of method, if landmarks are identified in order, a safe and effective operation can be achieved. Although all surgeons will face revision work at some time, it is imperative to learn from the mistakes made and think critically about why failure ensued.

OUTCOMES OF FUNCTIONAL ENDOSCOPIC SINUS SURGERY

There are several hundred studies in the past several decades evaluating changes in CRS symptoms following ESS. The assessment of symptoms, outcomes, and techniques vary considerably from study to study making pooling of data a challenge. A comprehensive review is beyond the scope of this chapter but several recent reviews cover the breadth of the literature and demonstrate improvement in symptoms following ESS in appropriate candidates (18,19). ESS failure results from a lack of proper identification of the natural ostium, scarring of the middle turbinate or sinus os, and missed obstructing agar nasi cells. All of the shortcomings listed can cause poor outcomes and therefore should be kept in mind during any sinus operation. The senior author's group reported revision rates following ESS after their first 100 cases. The overall success in relieving sinus symptoms decreased from 98% at early follow-up to 91% at 4-year follow-up (20). Most series report success rates greater than 80%. Failure and recurrence of nasal polyposis is the rule rather than the exception for that pathology. The patient needs to understand the goals of the procedure, and it should always be done as safely as possible.

CONCLUSION

Most patients who undergo routine sinus surgery do not require significant postoperative care or long-term follow up. Clearly underlying allergic disease, malignancies, or patients with cystic fibrosis or primary ciliary dyskinesia require more specialized care over the long-term. Minimizing mucosal trauma and exposed bone along with tailoring the surgery to the needs of the patient will result in minimal morbidity and complications. Careful documentation from initial nasal endoscopy through medical therapy and surgical intervention is also immensely helpful especially if revision surgery by another practitioner is eventually required.

At the resident level, proper patient positioning and placement of the instruments at the nasal valve create an ergonomically favorable beginning. Reading, continued cadaver dissection, and attending course provides an appropriate base of knowledge and continued maturing, which allows more advanced work to be mastered over time. Failure to continue learning in the dynamic field of ESS relegates one quickly to dinosaur status. At the attending level, knowing one's own limits and picking optimal surgical candidates can prevent unwanted surgical failures.

HIGHLIGHTS

- Endoscopic sinus surgery is for those who have failed medical therapy.
- Mucosal preservation is important.
- Anatomical progression of the surgery allows for maximum safety
- Revision surgical landmarks include the "ridge" seen endoscopically as the floor of the orbit, the arch of the choana, the nasal septum, and the anterior superior attachment of the middle turbinate.
- Computer navigation is helpful in complex and revision sinus surgery.
- Balloon sinuplasty is a new technology that will continue to evolve in its role for endoscopic indications.
- Anatomical landmarks for primary sinus surgery case using minimal techniques
- Anatomical landmarks for revision sinus surgery
- Philosophy of current technologies (including balloon and navigation)

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41 External Approaches in Sinus Surgery

Carlos D. Pinheiro-Neto *Carl H. Snyderman*

Open approaches to the nasal cavity and paranasal sinuses are based on facial, scalp, and/or sublabial incisions to expose the facial skeleton and provide adequate space for osteotomies. The development of endoscopic endonasal techniques in sinus surgery has dramatically reduced the indications for external approaches. However, persistent indications for open approaches to the facial skeleton include facial trauma surgery, orthognathic surgery, and external anterior ethmoidal artery ligation. In some circumstances, the open approach is combined with endoscopic endonasal techniques to treat sinonasal pathologies and skull base lesions. Therefore, even with the evolution of endoscopic endonasal surgery, it is imperative for a sinonasal surgeon to be familiar with external approaches. In this chapter, the current indications and techniques of open approaches in sinus surgery are presented according to specific anatomic sites.

MAXILLARY SINUSES

In the late 19th century, two surgeons working independently described the external approach to the maxillary sinus. George Caldwell and Henri Luc were the first to describe the procedure to access the maxillary sinus to remove infection and inflamed mucosa (1). According to the authors, a maxillary antrostomy in the inferior meatus was routinely performed to establish a new drainage pathway for the sinus. The Caldwell-Luc procedure remained the principal surgical intervention to treat inflammatory maxillary sinus disease until the advance of endoscopic endonasal techniques in the mid-1980s and the concept of a middle meatus antrostomy at the natural ostium of the maxillary sinus (2). Notwithstanding the procedure is not performed anymore as originally described, the term Caldwell-Luc still remains and is often used to refer to the anterior transmaxillary approach, which requires an incision in the superior gingivolabial sulcus and anterior maxillary antrostomy to access the maxillary sinus.

Indications

The anterior transmaxillary approach is indicated for sinonasal tumors that are not completely accessible using an endonasal approach. This includes tumor involvement of the anterior, inferior, and posterolateral walls of the maxillary sinus. The approach is also indicated in surgeries to address the infraorbital nerve when there is perineural spread of neurotrophic cancers (adenoid cystic carcinoma, squamous cell carcinoma). The anterior transmaxillary approach guarantees access to the posterior wall of the maxillary sinus and can be used as a corridor to reach the pterygopalatine fossa, lateral recess of the sphenoid sinus, masticator space, and infratemporal fossa. Classically, this approach is associated with endoscopic endonasal techniques for resection of selected cases of juvenile nasopharyngeal angiofibromas and inverted papillomas with maxillary sinus involvement (3).

In the field of oral–maxillofacial surgery, the anterior transmaxillary approach is routinely used for the treatment of a variety of dental tumors and for orthognathic surgery. Edentulous patients with insufficient maxillary alveolar bone height for insertion of dental implants may require augmentation of the maxillary alveolus (4). With facial trauma, open reduction and repair of comminuted orbital floor fractures can be facilitated with the use of this approach (2) (Table 41.1).

Operative Technique

Following infiltration with local anesthetic with vasoconstrictor, a sublabial incision is carried from the canine tooth to the first molar. It is important to leave a 5-mm cuff of mucosa above the gingiva to facilitate closure of the mucosa at the end of the procedure. Dissecting in the subperiosteal plane, the soft tissue of the cheek is elevated to the level of the infraorbital nerve. The ideal place to open

TABLE 41.1 SURGICAL INDICATIONS FOR OPEN APPROACHES TO THE SINUSES

Maxillary sinus	Sinonasal tumors (involvement of the anterior, inferior, and posterolateral walls of the maxillary sinus)
	Infraorbital nerve resection (adenoid cystic carcinoma, squamous cell carcinoma).
	Corridor to reach the pterygopalatine fossa, lateral recess of the sphenoid sinus, masticator space, and infratemporal fossa.
	Juvenile nasopharyngeal angiofibromas
	Inverted papillomas
	Dental tumors
	Orthognathic surgery
	Augmentation of the maxillary alveolus.
	Open reduction and repair of comminuted orbital floor fractures
Frontal sinus	Osteoplastic flap for frontal sinus obliteration.
	Osteomyelitis (frontal bone)
	Subperiosteal abscess
	Epidural abscess
	Sinonasal tumors (lateral extension or involvement of the anterior wall of the frontal sinus)
	Displaced fractures of the anterior table
	Posttraumatic CSF leaks
	Displaced fractures of the posterior table
Ethmoid sinus	Resection of malignant tumors
	Repair of complex midfacial fractures
	External ligation of the anterior ethmoidal artery
	Adjunct to frontal sinus surgery
Sphenoid sinus	Microscopic pituitary surgery

the maxillary sinus is the canine fossa, which is an area of thin bone just superior to the root of the canine tooth. A small hole is made with a drill or osteotome and enlarged with a bone rongeur to the margins of the sinus (pyriform sinus, orbital rim, maxillary alveolus). Care is taken to avoid injury to the infraorbital nerve superiorly and dental roots inferiorly. In pediatric patients, unerupted teeth are at risk for exposure. In case an extended lateral exposure is needed, the entire lateral buttress of the maxilla can be removed.

After the anterior maxillary antrostomy is completed, the surgeon can work in the maxillary sinus under direct or endoscopic visualization. Depending on the case, the posterior maxillary wall can be removed providing access to the pterygopalatine fossa and infratemporal fossa. The medial wall gives access to the nasal cavity, and the roof to the orbit. At the end of the procedure, the anterior wall is not reconstructed and the incision is closed in one layer with absorbable suture (Fig. 41.1)

Complications

Facial edema is expected during the early postoperative period and can be minimized with elevation of the head by 30 degrees and application of an ice pack. Complications that can result from the anterior transmaxillary approach include wound infection, wound dehiscence with oroantral fistula, and bleeding with hematoma formation. Removal of the bone around the infraorbital nerve and retraction of soft tissues can injure the infraorbital nerve and cause transient or permanent numbness of the cheek and upper lip. In the presence of a large bone defect, loss of periosteum can result in scar contracture of the cheek. In pediatric patients, elevation of periosteum may affect subsequent facial growth with asymmetry of the facial skeleton. Disruption of dental roots can result in devitalized teeth or delayed eruption of secondary teeth. (Table 41.2)

FRONTAL SINUSES

Because of the complex anatomy of the frontal sinus drainage pathway, surgery to restore frontal sinus function is one of the most challenging aspects of sinus surgery. The frontal recess is a narrow stricture between the frontal sinus and the ethmoidal infundibulum. The recess is limited anteriorly by the *agger nasi* and posteriorly by the bulla ethmoidal and/or suprabullar cells. In 1914, Lothrop described a procedure to enlarge the frontal recess using an external approach. The aim of the Lothrop procedure was to create a common drainage pathway for both frontal sinuses (5). Because of the removal of portions of the lamina papyracea, orbital fat tissue would commonly prolapse medially, obstructing the frontal drainage and contributing to high failure rates (6).

In the 1950s, Montgomery popularized the operation to permanently obliterate the frontal sinus using an open approach (7). Frontal sinus obliteration has been considered the final surgical attempt in cases of refractory frontal sinusitis (8). The principle of this operation is to obliterate the frontal sinus using a variety of autologous tissues and alloplastic materials and block the frontal recess. Although frontal sinus obliteration has a high success rate of 93% at 8 years, complications are relatively high, occurring in over 20% of patients (9,10)

With the advent of endoscopes in sinus surgery, it was feasible to approach the frontal recess and restore the function of the frontal sinus avoiding obliteration. In the 1990s, Draf (11) modified the surgical concept described by Lothrop using endoscopic endonasal techniques to resect the frontal sinus floor and create a common drainage pathway for both frontal sinuses.

Indications

Endoscopic endonasal techniques are ideal to approach the frontal recess and restore the outflow of the frontal sinus in cases of refractory chronic sinusitis. However, intractable disease may require an external approach and osteoplastic flap for frontal sinus obliteration. The open approach is also needed in cases of infectious complications like osteomyelitis and subperiosteal or epidural abscesses. Although

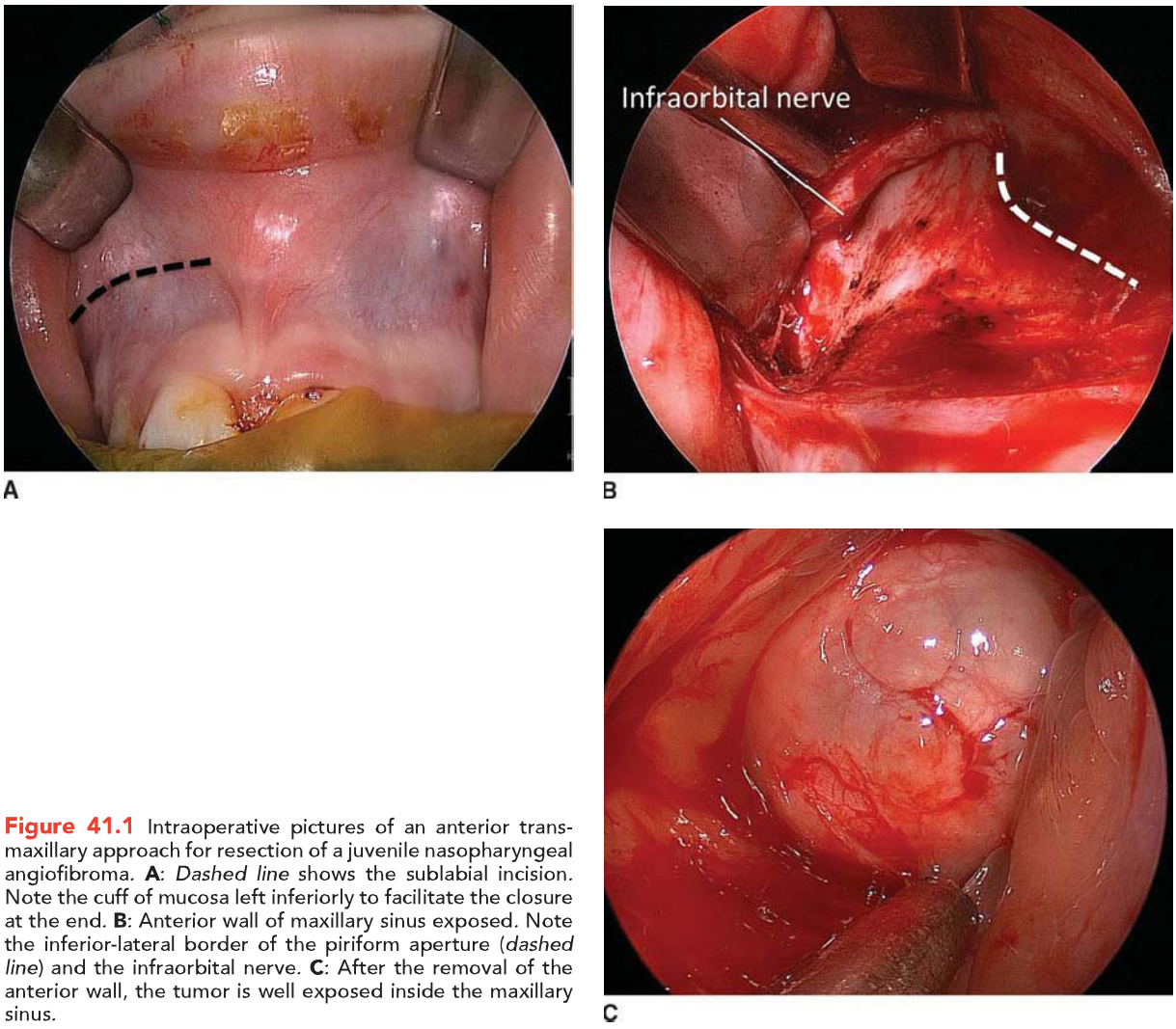


Figure 41.1 Intraoperative pictures of an anterior transmaxillary approach for resection of a juvenile nasopharyngeal angiofibroma. **A**: *Dashed line* shows the sublabial incision. Note the cuff of mucosa left inferiorly to facilitate the closure at the end. **B**: Anterior wall of maxillary sinus exposed. Note the inferior-lateral border of the piriform aperture (*dashed line*) and the infraorbital nerve. **C**: After the removal of the anterior wall, the tumor is well exposed inside the maxillary sinus.

many sinonasal tumors can be removed using endoscopic techniques, lateral extension or involvement of the anterior wall of the frontal sinus will necessitate an open approach.

External approaches to the frontal sinus are indicated in the setting of craniofacial trauma. Displaced fractures of the anterior table of the frontal sinus require open reduction and internal fixation (Fig. 41.2) Posttraumatic cerebrospinal fluid (CSF) leaks and displaced fractures of the posterior table are more easily repaired with an external approach (Table 41.1).

Operative Techniques

Trephination

Frontal sinus trephination is performed through a small incision at the medial aspect of the eyebrow. Because of the elasticity of the skin, the eyebrow incision can be mobilized superiorly and the sinusotomy placed over the frontal sinus. A 4 to 5 mm diameter hole is drilled through the anterior table of the frontal sinus. It is mandatory to assess the pneumatization of the frontal sinus with x-rays or CT scan before the procedure. Direct access to the frontal sinus through a trephination allows collection of material for culture, irrigation of the sinus with saline or antibiotic, and inspection of the sinus with endoscopes. Irrigation of the frontal sinus with saline can be used to localize the frontal recess during endoscopic sinus surgery. However, with the evolution of endoscopic endonasal techniques and intraoperative navigation systems, the applications of the frontal sinus trephination are limited.

Lynch Incision

A Lynch incision extends from the lateral nasal dorsum (level of medial canthus) to the medial brow. It provides access to the medial orbit and ethmoid sinus and the inferomedial aspect of the frontal sinus. Subperiosteal dissection is performed and the orbital tissues are gently retracted. The exposure is bounded inferiorly by the lacrimal fossa and sac. The anterior and posterior ethmoidal arteries traverse the surgical field at the level of the frontoethmoidal suture line. The surgical field is bounded superiorly by the trochlea that anchors the superior oblique muscle and the supratrochlear sensory nerve located superior to the trochlea.

TABLE 41.2 POTENTIAL COMPLICATIONS OF THE EXTERNAL APPROACHES TO THE SINUSES

Maxillary sinus	Facial edema
	Wound infection
	Wound dehiscence with oroantral fistula.
	Bleeding with hematoma formation.
	Infraorbital nerve injury (transient or permanent numbness of the cheek and upper lip).
	Scar contracture of the cheek.
	Asymmetry of the facial skeleton (pediatric patients). Disruption of dental roots
Frontal sinus	Diplopia
	Orbital hematoma
	CSF leak
	Meningitis
	Intracranial hemorrhage
	Cerebral contusion
	Frontalis muscle palsy
	Injury to the supraorbital/supratrochlear nerves (dysesthesia)
	Cosmetic deformity
	Frontal sinus mucocele
Ethmoid sinus	Epiphora
	Diplopia
	Retrobulbar hemorrhage
	Optic nerve injury
	CSF leak
Sphenoid sinus	Septal perforation
	Deviated nasal septum
	Saddle nose deformity
	Optic nerve injury
	Carotid artery injury

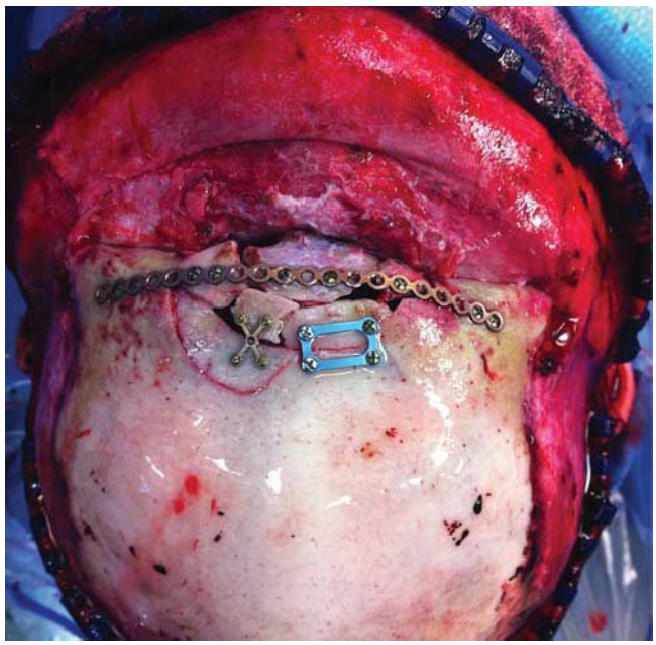


Figure 41.2 Intraoperative picture of anterior wall of frontal sinus repair. Patient had a comminuted fracture of the anterior table of the frontal sinus and bicoronal approach for reduction and fixation of the fragments.

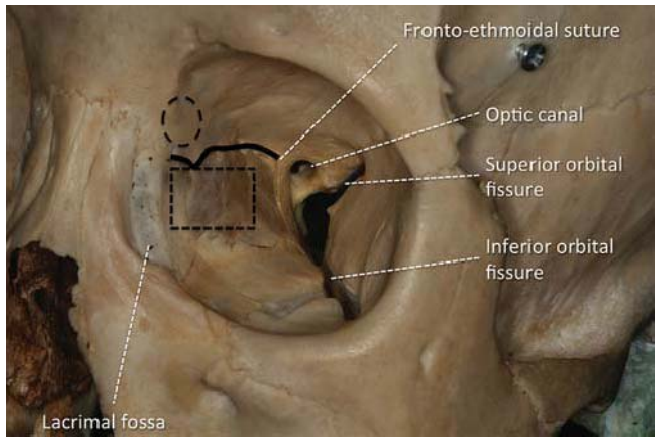


Figure 41.3 Dry skull to show the regions approached through a Lynch incision. The lateral wall of the frontal recess is exposed and the frontal sinus can be accessed (*circle*). External ethmoidectomy is performed after a wide exposure of the medial orbital wall and the ethmoid is entered through the lamina papyracea. The level of the skull base is defined by the frontoethmoidal suture line and bone is removed inferior to this line (*rectangle*).

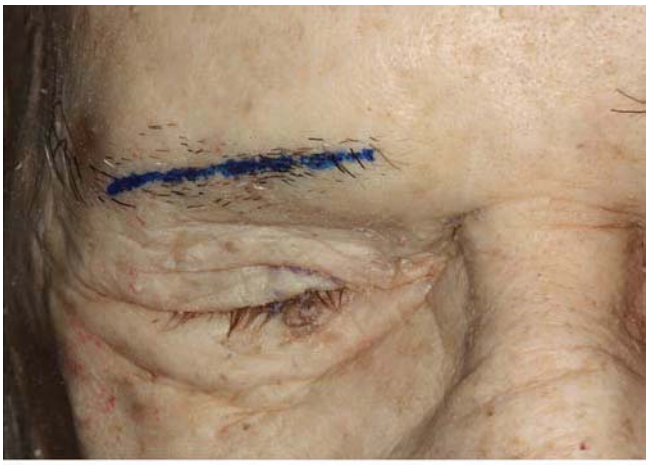
The frontal sinus may be accessed by drilling the bone of the orbital roof medially or by opening the ethmoid sinus below the frontoethmoidal suture line and following the nasofrontal recess to the frontal sinus. The external frontoethmoidectomy provides access to tumors and frontoethmoidal mucoceles. The Lynch incision can also be used to treat infectious complications of sinusitis such as a subperiosteal orbital abscess (Fig. 41.3)

The Lynch incision provides limited access to the frontal sinus and may be complicated by injury to the supratrochlear or supraorbital nerves. Detachment of the trochlea can impair extraocular motion and result in dysconjugate gaze. Injury to the ethmoidal arteries can result in a retrobulbar hematoma, a potential ophthalmologic emergency.

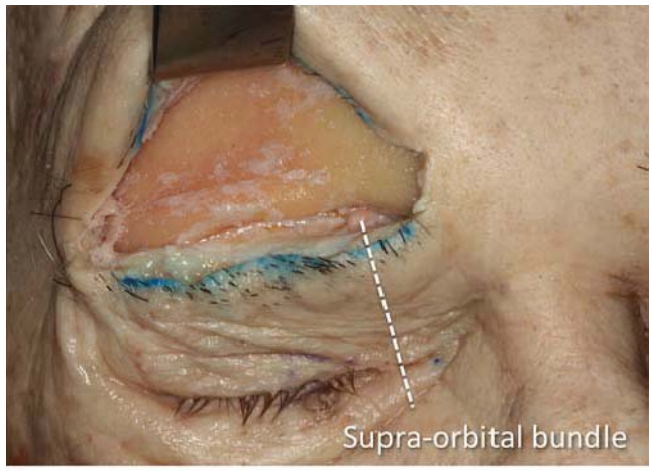
Eyebrow Incision

The eyebrow incision gives direct access to the superior orbital rim and anterior wall of the frontal sinus. The incision can be placed within the brow or immediately adjacent. The incision should be beveled at the angle of the hair follicles to avoid loss of hair and an unsightly scar. Careful dissection in a subperiosteal plane is necessary to identify and avoid injury to the supratrochlear and supraorbital arteries and nerves. In the presence of a complete supraorbital foramen, the inferior bony bridge of the foramen can be removed. This maneuver allows retraction of the supraorbital artery and nerve with the orbital tissues.

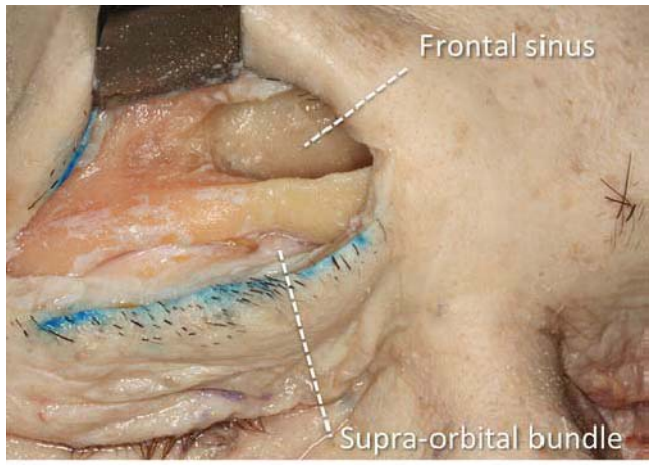
The eyebrow approach is useful for lesions localized laterally in the frontal sinus. The anterior table can be drilled or an osteotomy is performed to gain access to the frontal sinus. If the bone is not replaced, the defect is reconstructed with titanium mesh to avoid retraction of the soft tissues and a depression in the forehead. The use of image guidance system is imperative to establish



A



B



C

Figure 41.4 Dissection pictures to show the eyebrow approach to the frontal sinus. This approach gives good exposure of the lateral aspect of the frontal sinus when well pneumatized. **A**: Incision. **B**: Exposure of the anterior wall of the frontal sinus. **C**: Frontal sinus open.

the limits of the frontal sinus before the osteotomies are performed to prevent inappropriate opening of the intracranial space (Fig. 41.4)

Mid-Forehead Incision

In patients with a deep forehead crease or trauma patients with a scalp laceration, a transverse incision in a natural skin crease provides excellent access to the anterior table of the frontal sinus with a favorable cosmetic result. Disadvantages of the transverse incision include sensory denervation of the frontal scalp superior to the incision and disruption of the pericranium in case an anteriorly based pericranial flap is needed for repair.

Bicoronal Approach

The bicoronal incision avoids a facial incision and provides wide exposure of the frontal cranium. The incision extends from the tragus of one ear to the other and posterior to the hairline. The scalp is elevated in a subperiosteal plane with separation of the periosteum from the deep temporal fascia along the attachment of the temporalis muscle (superior temporal line). If extra pericranium is needed for a pericranial flap, the posterior scalp flap can be elevated deep to the galea to access additional pericranium. The scalp is elevated to the level of both orbital rims. Careful dissection should be performed close to the superior orbital rim to avoid injury to the supraorbital neurovascular bundles. The supraorbital and supratrochlear arteries are the primary blood supply for a pericranial flap.

Surgical navigation has replaced the use of 6-ft Caldwell x-ray templates for delineation of the boundaries of the frontal sinus. Osteotomies of the anterior table of the frontal sinus are performed with a drill or oscillating saw, staying within the confines of the sinus. After the osteotomies are completed, the single piece of bone is out-fractured and separated from the interfrontal sinus septum. Wide exposure of both frontal sinuses is achieved.

The bicoronal approach is the most versatile approach and allows the resection of benign and malignant neoplasms (osteomas, inverted papilloma, squamous cells carcinoma) as well as treatment of advanced inflammatory disease with infectious complications (Potts puffy tumor or osteomyelitis of the frontal bone with subperiosteal abscess, epidural and subdural abscesses). During a bicoronal approach to the frontal sinus, two options are possible regarding the frontal sinus recess: functional restoration or obliteration. The functional restoration follows the same principle described by Lothrop in 1914. The frontal sinus

floor needs to be removed from orbit to orbit. The interfrontal septum and the superior nasal septum are resected to create a common outflow pathway for both frontal sinuses. The mucosa of the sinus should be preserved, if possible. The medial wall of the orbit should be preserved, because the medial protrusion of orbital fat can cause obstruction and failure of the procedure. In the 1990s, Draf (11) modified this technique applying the same surgical concept through the endoscopic endonasal approach.

Obliteration of the frontal sinus is usually considered when the frontal recess obstruction cannot be relieved by more conservative techniques or when the mucosal disease is diffuse and irreversible. The mucosa of the frontal and supraorbital ethmoid cells must be completely removed. The bone needs to be drilled to eliminate remnants of mucosa, thus minimizing the possibility of mucosal regrowth and mucocele formation. Abdominal fat or pericranium are still the best materials for sinus obliteration. Because the fat is nonvascularized, it may shrink with healing and result in incomplete obliteration. It can be difficult to distinguish fat from scar tissue postoperatively with imaging, and exclusion of ongoing infection is difficult if symptoms persist. The use of pericranium as an osteoplastic flap to obliterate the frontal sinus was popularized by Montgomery in the 1950s (7). The pericranial flap provides vascularized tissue for obliteration and provides an effective barrier for the nasofrontal recesses and coverage of exposed dura. An inferiorly based flap is elevated from the scalp and placed inside the frontal sinus cavity covering the frontal recess. The interfrontal septum should be drilled to allow adequate contact of the pericranial flap to the posterior table of the frontal sinus.

Cranialization is an alternative method of frontal sinus obliteration that consists of the complete removal of the posterior table of the frontal sinus. The frontal recesses are covered with a pericranial flap to separate the nasal cavity from the intracranial space. The anterior table of the frontal sinus is incorporated into the intracranial space and all of the mucosa of the frontal sinus needs to be entirely removed to prevent a mucocele or infection. Cranialization is more commonly indicated for craniofacial trauma, especially with severe comminuted fractures of the posterior table of the frontal sinus.

At the end of the procedure, the anterior table is replaced and fixed with titanium plates and screws. If a pericranial flap was used, a gap in the bone should remain along the inferior aspect of the osteotomy to provide space for the transposition of the pericranial flap into the frontal sinus and avoid compression of the flap pedicle. In cases where the anterior table cannot be used as a bone graft, titanium mesh is a good alternative for reconstruction. In the presence of active infection, reconstruction with synthetic materials should be postponed.

The bicoronal approach can be also used for Riedel's procedure, which consists of the removal of the entire anterior table of the frontal sinus and its floor (12). The procedure allows the frontal scalp to be in direct contact with the posterior table of the frontal sinus or dura and obliterate the frontal sinus, resulting in forehead concavity. This disfiguring procedure is rarely used except as part of a staged reconstructive procedure with infectious complications.

Complications

Because of the proximity, external approaches to the frontal sinus can result in orbital and/or intracranial complications. Loss of periorbita with protrusion of orbital fat can lead to displacement of the globe and diplopia. Orbital hematoma is also a complication, especially if the anterior ethmoidal artery is injured. Placement of osteotomies outside the margins of the frontal sinus can result in a CSF leak and brain injury. Dural lacerations can be repaired directly or with a fascial graft. Other intracranial complications that may occur are meningitis, intracranial hemorrhage, and cerebral contusion. Injury to the frontalis branch of the facial nerve causing frontalis muscle palsy or injury to the supraorbital/supratrochlear nerves resulting in dysesthesia may occur during the approach. Other complications are lack of resolution of symptoms, cosmetic deformity, and frontal sinus mucocele (Table 41.2).

ETHMOID SINUSES

The ethmoid bones are situated between the orbits with close relationship to the anterior cranial base. The natural corridor to approach the ethmoid sinuses is the nasal cavity. Even before the advent of the endoscopes, ethmoid sinus surgeries have been performed transnasally, with or without magnification (microscope). Endoscopic endonasal techniques provide improved access and visualization and are generally preferred. External approaches to the ethmoid sinuses are rarely indicated but can be useful in selected patients for the resection of malignant tumors; repair of complex midfacial fractures; for external ligation of the anterior ethmoidal artery; or as an adjunct to frontal sinus surgery (Table 41.1).

Operative Technique

The external approach to the ethmoid sinuses starts with a Lynch incision. The incision begins at the inferior margin of the medial aspect of the eyebrow and extends inferiorly along the lateral nose midway between the nasal dorsum and the medial canthus to the level of the medial canthus. The angular vessels are controlled with bipolar cautery, and the supratrochlear bundle is preserved superiorly. Subperiosteal dissection is performed and the periosteum is preserved to ensure the integrity of the medial canthal ligament, trochlea, and lacrimal sac as well as to prevent herniation of orbital fat. Herniation of orbital fat interferes with the visualization and dissection of the posterior orbit. As the medial wall of the orbit is widely exposed, the anterior ethmoidal artery is encountered in the frontoethmoidal suture line approximately 24 mm posterior to the anterior lacrimal crest. This vessel is clipped or coagulated with a bipolar

electrocautery and, if necessary, divided. The periorbita is protected with a malleable retractor to prevent herniation of orbital fat into the field. Additional elevation demonstrates the posterior ethmoidal artery approximately 11 mm posterior to the anterior artery and approximately 6 mm anterior to the optic foramen (13). These proportions are not constant, and great care must be exercised in dissecting the area of the posterior ethmoidal artery to avoid retrobulbar hemorrhage and injury to the optic nerve. Periorbital elevation is not routinely performed posterior to the anterior ethmoidal artery. After a wide exposure of the medial orbital wall, the ethmoid is entered through the lamina papyracea. The level of the skull base is defined by the frontoethmoidal suture line and bone is removed inferior to this line. Remember that the cribriform plate is often lower than the roof of the ethmoid sinus; careful dissection is necessary to prevent injury to the lateral lamella of the cribriform and a CSF leak. Further dissection of the ethmoid sinus can be performed with a headlight or endoscopic assistance (Fig. 41.3)

Complications

Complications related to the external approach to the ethmoid sinuses include epiphora, diplopia, retrobulbar hemorrhage, optic nerve injury, CSF leaks, and postoperative neuralgia. Persistent epiphora from injury to the nasolacrimal apparatus is an unusual but significant complication and may necessitate a dacryocystorhinostomy. Temporary diplopia is common and usually self-limited as edema resolves. Horizontal gaze diplopia, however, may result as a consequence of trauma to the medial rectus muscle with subsequent fibrosis. Blindness is a potential consequence of retrobulbar hemorrhage or direct injury to the optic nerve. Leakage of CSF and intracranial hemorrhage can occur if the fovea ethmoidalis or cribriform plate is disrupted. Inappropriate placement of the incision or poor surgical technique can cause hypertrophic scar formation, medial canthal scarring, or rounding of the medial canthus. Anesthesia, hypesthesia, or neuralgia of the median forehead can occur if the supratrochlear nerve is injured (Table 41.2).

SPHENOID SINUS

The sphenoid sinus is located deep in the central part of the head and is surrounded by all three cranial fossae. The roof of the sphenoid sinus is the planum sphenoidale and forms part of the anterior cranial fossa. The posterior wall is part of the clivus and is related to the posterior cranial fossa. The lateral wall borders Meckel's cave in the middle cranial fossa. Important structures that are related to the sphenoid sinus include the optic nerves, internal carotid arteries, cavernous sinus, and pituitary gland.

External approaches to the sphenoid sinus include superior, lateral, and anterior approaches. A superior approach through the planum sphenoidale is usually part of a craniofacial resection for sinonasal malignancy. A bifrontal craniotomy with subfrontal approach provides access to the planum sphenoidale and is limited posterolaterally by the optic nerves. A lateral skull base approach (infratemporal) provides access to the sphenoid sinus between the second and third divisions of the trigeminal nerve. This opening into the lateral recess of the sphenoid sinus is very limited in exposure. The sphenoid sinus can be accessed through a transseptal route or through craniofacial translocation.

Anterior approaches to the sphenoid sinus include transethmoidal and transseptal approaches. The sphenoid sinus can be reached through an external ethmoid incision. Dissection along the medial wall of the orbit and below the roof of the ethmoid sinus leads to the anterior wall of the sphenoid sinus. Transseptal approaches to the sphenoid sinus are less morbid and still used by microscopic pituitary surgeons. However, with the development of endoscopic endonasal techniques, external approaches to the sphenoid sinus are disappearing.

The transseptal approach is based on exposure of the anterior face of the sphenoid through submucosal tunnels in the septum. With a transnasal route, a hemitransfixion incision is extended across the nasal floor and a subperichondrial/subperiosteal dissection of the septum and nasal floor is performed to the rostrum of the sphenoid. With a sublabial route, a mucosal incision in the superior gingivolabial sulcus provides similar access to the nasal septum and nasal floor for a subperichondrial/subperiosteal dissection. The nasal septum is disarticulated from the maxilla inferiorly and from the bony septum posteriorly. Bilateral subperiosteal dissection of the ethmoid and vomer bones is then performed until the rostrum and anterior sphenoid are exposed. A "pituitary" speculum is placed into the tunnel on both sides of the septal bones to displace the tissues and expose the sphenoid rostrum. The bone of the posterior septum, rostrum, and anterior sphenoid wall is removed with a drill or rongeurs and the sphenoidotomy is widened to the margins of the sinus. Once the sphenoid sinus is open, the visualization can be enhanced using the operating microscope or endoscope.

Other anterior approaches to the sphenoid sinus that may be employed in selected patients include midfacial degloving associated with Le Fort I osteotomies; maxillary translocation; and transoral associated with palatal split.

Complications

Complications of transseptal approaches to the sphenoid sinus include injury to nasal structures and the skull base. Dislocation of the nasal septum can result in septal perforation, deviated nasal septum, or loss of vertical height with tip rotation or saddle nose deformity. Placement of the speculum into the sphenoid sinus can result in fracture of the lateral sphenoid with injury to the optic nerves or carotid arteries. The biggest risk of external approaches to the sphenoid sinus, however, is limited access with poor visualization (Table 41.2).

CONCLUSIONS

Although endoscopic endonasal techniques have dramatically decreased the need for external approaches to the paranasal sinuses, there is still a need in selected patients. Factors to be considered in choosing the optimal approach include the site and extent of the pathology, prior treatment and reconstruction considerations, patient comorbidities and preferences, and the experience of the surgeon.

HIGHLIGHTS

- The transmaxillary approach is indicated in surgeries to address the infraorbital nerve when there is perineural spread of neurotrophic cancers (adenoid cystic carcinoma, squamous cell carcinoma).
- The ideal place to open the maxillary sinus is the canine fossa, which is an area of thin bone just superior to the root of the canine tooth.
- The approach provided by the Lynch incision is bounded inferiorly by the lacrimal fossa and sac and superiorly by the trochlea that anchors the superior oblique muscle and the supratrochlear sensory nerve located superior to the trochlea.
- The anterior and posterior ethmoidal arteries traverse the surgical field at the level of the frontoethmoidal suture line.
- In the presence of a complete supraorbital foramen, the inferior bony bridge of the foramen can be removed. This maneuver allows retraction of the supraorbital artery and nerve with the orbital tissues.
- During external ethmoidectomy, the level of the skull base is defined by the frontoethmoidal suture line and bone is removed inferior to this line. The cribriform plate is often lower than the roof of the ethmoid sinus.
- A lateral skull base approach (infratemporal) provides access to the sphenoid sinus between the second and third divisions of the trigeminal nerve. This opening into the lateral recess of the sphenoid sinus is very limited in exposure.
- The transnasal transseptal approach to the sphenoid provides similar exposure as the sublabial approach without the need for a sublabial incision.

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42 Septoplasty, Turbinate Reduction, and Correction of Nasal Obstruction

Neal C. Gehani *Steven M. Houser*

Nasal obstruction is one of the most common complaints in an otolaryngology practice. The differential diagnosis for this symptom is broad and can be multifactorial. There are a variety of both mucosal and structural abnormalities that can alter the sensation of nasal airflow, including septal deviation, turbinate hypertrophy, nasal cartilage deformity, sinus infections, sinonasal neoplasms, and systemic diseases. It is important for the otolaryngologist to be aware of the various etiologies of nasal obstruction while evaluating a patient and recommending appropriate treatment options.

EVALUATION AND ASSESSMENT

History

It is essential to obtain a thorough history when assessing a patient with nasal obstruction. The clinician should pay particular attention to unilateral versus bilateral symptoms, onset, seasonal variation, and associated nasal symptoms. The nasal cycle is a periodic alteration of engorgement of the erectile tissue in the inferior turbinates, typically cycling every 2 to 7 hours, with subsequent changes in nasal airflow. Mucosal inflammation caused by rhinosinusitis or allergic rhinitis may exacerbate the normal nasal cycle. Unilateral nasal obstruction, especially with epistaxis, could be a symptom of a sinonasal neoplasm. Obstruction, either unilateral or bilateral, following nasal trauma may indicate a fracture or structural abnormality of the nasal septum or pyramid. Obstruction that fluctuates seasonally or with environmental exposure indicates a reversible mucosal abnormality rather than a fixed structural obstruction. Associated symptoms, including facial pain or pressure, nasal discharge, and hyposmia may indicate rhinosinusitis. Nasal obstruction, associated with serous otitis media requires evaluation of the nasopharynx for possible neoplasm. Nasal obstruction can also cause nonnasal symptoms such as dry mouth, sore throat, snoring, halitosis, and decreased appreciation of taste sensation, presumably from impaired smell.

In addition to eliciting subjective complaints, one must also review the patient's past medical and surgical history, current medications, and social habits. Numerous systemic diseases may have a nasal manifestation of obstruction, including aspirin-exacerbated respiratory disease, cystic fibrosis, Wegener granulomatosis, sarcoidosis, rhinoscleroma, fungal infections, and lymphoma. Normal fluctuations of estrogen during the menstrual cycle and pregnancy can also lead to temporary nasal obstruction. A prior rhinoplasty may cause nasal valve collapse, while a prior aggressive turbinectomy or reduction may lead to subjective nasal obstruction due to atrophic rhinitis or empty nose syndrome. Medications that may induce nasal obstruction include aspirin and other nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, alpha-adrenoceptor antagonists, methyldopa, beta-blockers, and oral contraceptives. Lastly, alcohol can produce vasodilation with nasal obstruction, while smoking impairs mucociliary clearance, exacerbating rhinitis, and cocaine abuse can cause extensive destruction of nasal support structures, leading to obstruction (1).

Physical Examination

The physical examination of nasal congestion includes evaluation of the external framework of the nose, with attention to any bony or cartilaginous deformity or nasal dorsal deviation. Rarely, pyriform aperture narrowing or stenosis contributes to obstruction. A horizontal nasal crease at the supratip area usually indicates chronic nose wiping, as in the "allergic salute." Tip ptosis contributing to obstruction can be assessed by pushing the nasal tip superiorly. The Cottle maneuver, in which the cheek skin and nostril are retracted laterally to assess changes in subjective nasal airflow, detects contributions to congestion at the nasal valve. In a modification of the Cottle maneuver,

an ear curette is used to selectively retract the upper lateral and then lower lateral cartilages to detect their contribution individually to nasal obstruction. The presence of alar collapse with inspiration indicates dynamic external nasal valve collapse, while supra-alar pinching indicates internal nasal valve collapse. Turbinate contribution to nasal obstruction can be assessed before and after topical decongestants with anterior rhinoscopy. Significant improvement following topical decongestants, indicates primarily a potentially reversible cause of nasal congestion such as allergy. Reddened, ulcerated, or friable nasal mucosa may indicate exposure to toxins, rhinitis medicamentosum, food allergy, or systemic disorders. Septal spurs, deviations, or perforations are the most common septal findings. Nasal polyps, purulence, excessive secretions, tumors, choanal stenosis, eustachian tube or nasopharyngeal pathology can usually be visualized with thorough rigid or flexible nasal endoscopic evaluation.

Investigations

Further investigations to determine the etiology of nasal obstruction will vary depending on the suspected differential diagnosis. Blood tests, such as angiotensin converting enzyme level (for sarcoidosis), cytoplasmic-antineutrophil cytoplasmic antibodies (C-ANCA) level (for Wegener granulomatosis), erythrocyte sedimentation rate, and syphilis serology, may be helpful if systemic inflammatory disorders are suspected. *In vitro* assessment of specific immunoglobulin E (IgE), intradermal testing, or skin prick testing may be useful if allergy is considered. Subjective complaints of anosmia or hyposmia may be quantified using validated testing kits, including the University of Pennsylvania Smell Identification Test (Sensonics, Haddon Heights, NJ), the alcohol smell test, and Sniff'n sticks. Further assessment of smell is discussed in more detail in the chapter on olfaction. A directed nasal swab is considered if purulent drainage is noted during anterior rhinoscopy or nasal endoscopy to direct medical management.

Acoustic rhinometry and rhinomanometry have been used for many years to objectively assess nasal airway resistance and obstruction. Acoustic rhinometry measures the cross-sectional area (CSA) of the nasal cavity by presenting a shock wave to the nasal airway and measuring the reflected sound. The CSA is measured while the patient is apneic and during inspiration. Normally, the inspiratory to apneic CSA ratio should be around 1. A ratio significantly lower than 1 indicates nasal valve collapse during inspiration, while significantly low CSA during both apnea and inspiration may indicate a fixed obstruction. The limitation of acoustic rhinometry is the wide variation of normal CSA and therefore difficulty in interpreting results. Rhinomanometry, which was first described by Coutade in 1902, is a method of simultaneously measuring nasal airflow at a fixed pressure differential during the nasal respiratory cycle. A pressure-flow curve is then generated, yielding another objective assessment of nasal obstruction. Both acoustic rhinometry and rhinomanometry are obtained for experimental purposes; however, they are not considered standard of care when evaluating a patient for nasal obstruction (2).

Imaging is considered in certain patients presenting with nasal obstruction. Plain x-rays of the sinuses may be helpful in evaluating particular clinical entities, such as a nasal fracture; however, it has largely been replaced by computed tomography (CT) scan due to wide availability, rapidity of the study, and superior anatomic detail of structures. A CT scan is considered in patients with concern for rhinosinusitis, trauma, inflammatory disease, sinonasal neoplasm, or congenital abnormality. If malignancy is considered, magnetic resonance imaging may be obtained to provide enhanced soft tissue information.

Differential Diagnosis

Patients with a variety of conditions may present with a chief complaint of nasal obstruction. It is important for the otolaryngologist to keep the differential diagnosis in mind when obtaining further diagnostic studies or recommending therapeutic interventions (Table 42.1).

Treatment Options

The management of patients with nasal obstruction can be divided into medical or surgical interventions. In general, patients with an anatomic abnormality, such as septal deviation, inferior turbinate hypertrophy, nasal valve collapse, choanal atresia, or nasal polyposis will require surgical intervention; however, they may also benefit from medical

TABLE 42.1 DIFFERENTIAL DIAGNOSIS OF NASAL OBSTRUCTION

Diagnosis	Symptoms
Septal deviation	Usually unilateral nasal obstruction, deviated nasal septum on examination
Turbinate hypertrophy	Turbinate enlargement on examination
Nasal valvular collapse	Nasal valve collapse on deep inspiration
Polyps	Unilateral or bilateral nasal obstruction, altered sense of smell
Sinusitis	Infectious mucopus on anterior rhinoscopy
Adenoid hypertrophy	Unilateral or bilateral nasal obstruction, mouth breathing, snoring
Neoplasm	Unilateral nasal obstruction, epistaxis, nasal mass on examination
Choanal atresia	Unilateral or bilateral nasal obstruction, clear or purulent rhinorrhea
Allergy	Bilateral nasal obstruction, history of seasonal obstruction, pale or bluish nasal mucosa
Vasomotor rhinitis	Clear mucous
Nasal foreign body	Unilateral or bilateral purulent drainage

TABLE 42.2 TREATMENT OPTIONS

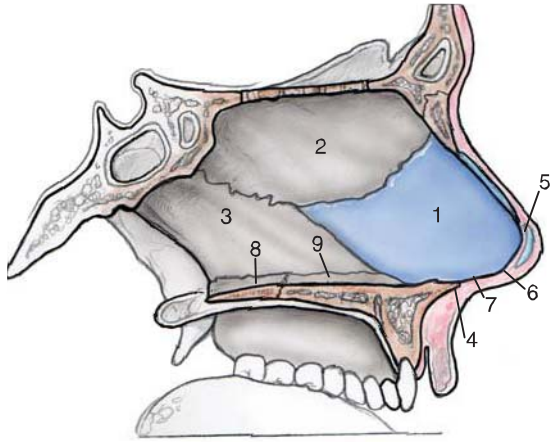
Diagnosis	Treatment
Septal deviation	Septoplasty
Turbinate hypertrophy	Nasal decongestants, inferior turbinate reduction
Nasal valvular collapse	Adhesive supporting strips, nasal valvular reconstruction
Polyps	Endoscopic sinus surgery
Sinusitis	Antibiotics, topical or systemic steroids, endoscopic sinus surgery
Adenoid hypertrophy	Adenoidectomy, topical steroids
Neoplasm	Resection
Choanal atresia	Transpalatal or transnasal repair
Allergy	Avoidance of or desensitization to the allergen, topical steroids and antihistamines, leukotriene modulators

treatment before and after surgery to optimize outcomes. Patients with physiologic etiology, such as allergy, rhinosinusitis, and systemic inflammatory diseases, should be treated with medical therapies including local or systemic corticosteroids or avoidance, prior to considering surgical intervention (i.e., endoscopic sinus surgery) (Table 42.2).

DEVIATED NASAL SEPTUM

Surgery for correction of a deviated nasal septum has evolved over the course of the years. Submucous resection of septal cartilage was initially described by Ingals in 1882, followed by Freer, who described resection of both the bony and cartilaginous portions of the deviated septum in 1902. Killian further modified the procedure in 1904; however, both Freer and Killian advocated not addressing deflections of the dorsal and caudal portions of the septum to prevent postoperative nasal deformities. In 1946, Cottle and Loring described removal of all deviated portions of the septum and replacement of bone and cartilage in the intramucosal space to prevent postoperative saddle nose deformities and a retracted columella (3). More recently, endoscopic septoplasty was introduced as a technique to address the deviated nasal septum for enhanced visualization during endoscopic sinus surgery.

A thorough understanding of the anatomy of the nasal septum is important when performing a septoplasty. The bony portion of the nasal septum is composed of the perpendicular plate of the ethmoid bone superiorly and the vomer inferiorly. Posteriorly, the bony septum defines the medial aspect of the nasal apertures, or choanae. Superiorly, the perpendicular plate of the ethmoid bone is contiguous with the cribriform plate of the skull base and the posteriosuperior aspect fuses with the sphenoid rostrum. Inferiorly, the vomer fuses with the maxillary crest. Anteriorly, the bony septum fuses with the cartilaginous



1. Quardrangular cartilage
2. Perpendicular plate of Ethmoid Bone
3. Vomer
4. Nasal Spine
5. Anterior septal angle
6. Middle septal angle
7. Posterior septal angle
8. Maxillary crest palatine component
9. Maxillary crest maxillary component

Figure 42.1 Septal anatomy in sagittal view

septum. The cartilaginous nasal septum, also known as the quadrangular cartilage due to its shape, has attachments to the upper lateral and lower lateral cartilages anteriorly and maxillary crest inferiorly (Fig. 42.1). The keystone area, the junction of the quadrangular cartilage, perpendicular plate of the ethmoid, and paired nasal bones (4), is critical to the support of the nasal dorsum and should be preserved when performing a septoplasty.

Indications

There are numerous indications for the surgical correction of a deviated nasal septum, which are listed in Table 42.3.

Operative Procedure

Many techniques and variations of septoplasty have been described in the literature. Although the procedure can be performed under local or general anesthesia, the latter is

TABLE 42.3 INDICATIONS FOR SEPTOPLASTY

Deviation of the nasal septum with partial or complete nasal obstruction
Anatomic obstruction that hinders endoscopic sinus procedures
Persistent or recurrent epistaxis
Improve CPAP therapy efficacy in patients with OSA
An approach during transseptal transsphenoidal skull base procedures

CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

preferred, especially in anxious patients or those undergoing additional procedures, such as sinus surgery. The procedure is initiated with the infiltration of a hemostatic agent, such as 1% lidocaine with 1:100,000 epinephrine, in the subperichondrial plane to assist in raising submucosal flaps and maintaining hemostasis throughout the procedure. The nasal cavities are then packed with pledgets soaked with a decongesting agent such as 4% cocaine, oxymetazoline, or neo-synephrine.

An incision is then made through the mucosa of the septum. The side of the incision depends on the patient's anatomy or surgeon preference (e.g., a right-handed surgeon may prefer a left-sided incision). The authors prefer making an incision on the side with the convex aspect of the deviation to assist in raising an intact mucosal flap. If a prominent septal spur is located anteriorly, then dissection may be best achieved from that side even if it is not the convex side. A Freer's hemitransfixion incision (on the caudal aspect of the cartilaginous septum) may be used for caudal deviations (Fig. 42.2) or a Killian incision (1 cm posterior to the columella at the mucocutaneous junction) may be used for more posterior deviations. Once the incision is made, a mucoperichondrial–mucoperiosteal flap is carefully raised on the side of the incision over the cartilaginous septum, posteriorly over the bony septum, and inferiorly onto the maxillary crest (Fig. 42.3). An incision through the quadrangular cartilage is then usually made 1 cm posterior to the dorsal and caudal portions of the cartilaginous septum ("L-strut"), and a mucoperichondrial–mucoperiosteal flap is then raised on the contralateral side of the septum. The cartilaginous septum is then disarticulated from the bony septum and the posterior cartilaginous septum is removed and preserved for reimplantation later. Alternatively, the cartilage can be left essentially intact if the bony septum is the main area of deflection. The keystone area should not be disrupted during this portion of the procedure. The bony septum is then carefully removed.

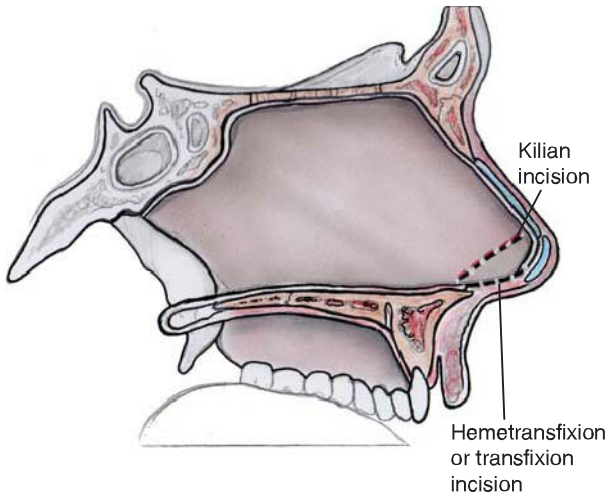


Figure 42.2 Hemitransfixion incision.

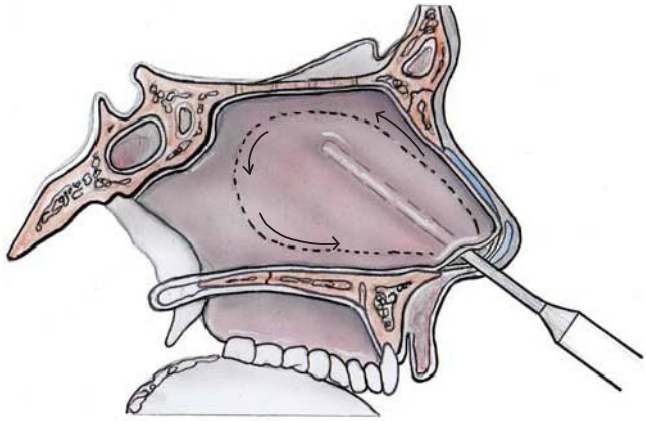


Figure 42.3 Elevation of mucoperichondrial flap.

Care is taken not to rock the perpendicular plate of the ethmoid bone, as rocking may lead to a fracture of the cribriform plate and cerebrospinal fluid (CSF) rhinorrhea. Redundant bony or cartilaginous septum over the maxillary crest can be removed using an osteotome. The mucosal flaps are then inspected. Ideally, the flaps should remain intact, since tears will delay healing and increase the risk of septal perforation postoperatively. Large or bilateral mucosal tears should be repaired. The removed cartilage is either morselized, scored, or crushed to remove memory and reinserted between the mucosal flaps to maintain integrity of the septum and nasal support. The incision is then closed with absorbable suture. A unilateral mucosal incision is then made in the ventral portion of the septum to allow for drainage of blood, preventing postoperative septal hematoma. Silastic nasal splints are then inserted and secured in place to prevent synechiae formation as well as eliminate dead space between mucosal flaps. Quilting sutures may also be used instead of splints.

Endoscopic septoplasty is a technique which was developed as a result of limited nasal access during endoscopic sinus surgery. Commonly, the surgeon's endoscopic view is obscured due to septal spurs or deviations. Endoscopic septoplasty is initiated by injecting the nasal septum with local anesthetic with vasoconstrictive properties under endoscopic guidance. An incision is then made either over the spur or just anterior to the deviation and a mucoperichondrial–mucoperiosteal flap is raised above and below this area with an instrument, such a suction Freer elevator (Fig. 42.4). The deviated cartilage or bone is then resected as described earlier, however, with endoscopic guidance. The mucosal flaps usually do not need to be closed; however, this is considered if the incision is large.

Since the dorsal and caudal septum provide support for the middle and lower third of the nose, correction of deviation of this portion of the septum can be most challenging. Removal of the deflection will result in external collapse. The simplest technique to correct caudal deflection involves vertically scoring, incising, or morselizing the caudal strut to reshape it. Overaggressive manipulation

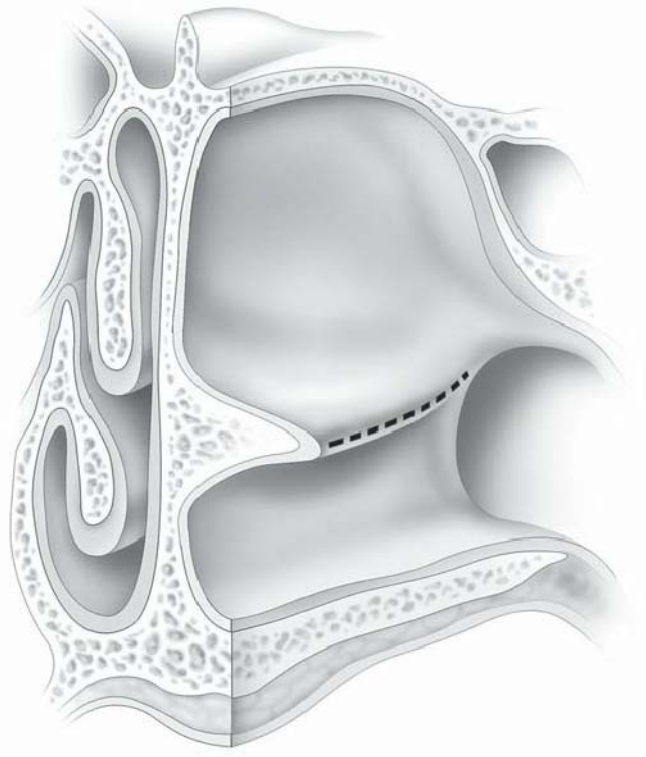


Figure 42.4 Endoscopic septoplasty: Mucoperichondrial flaps are elevated above and below the septal spur.

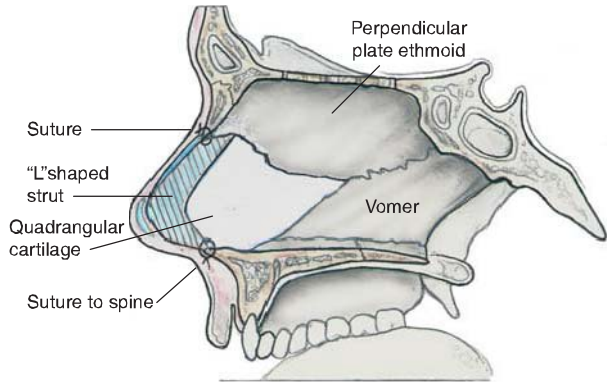


Figure 42.5 Explantation and reimplantation of L-shaped strut during extracorporeal septoplasty.

will result in loss of tip support and tip ptosis. Graft material, such as septal cartilage, ethmoid perpendicular plate, or vomer bone, may be used as a splint to prevent repeat deviation as well as provide support to the caudal septum. The graft material is placed on both sides of the straightened caudal septum and sutured into position. Another technique introduced by Metzenbaum in 1929 and subsequently modified by others involves removing a vertical wedge of cartilage on the convex side of the caudal deformity and suturing the remaining cartilage to the anterior nasal spine. A modification of this technique involves wedge resection followed by translocation and securing the caudal septum to the other side of the anterior nasal spine to prevent the septum from returning to its native position (4). Finally, extracorporeal septoplasty has been employed for severe deviation of both the caudal and dorsal septum. This technique involves separation of the cartilaginous septum from the upper lateral cartilages, perpendicular plate of the ethmoid bone, vomer, and maxillary crest, followed by en bloc removal (5). The appropriate dimensions of the desired dorsal and caudal strut is then measured and carved from the straight segments of the previously removed quadrangular cartilage. The strut is then placed between the mucoperichondrial flaps and sutured into appropriate position (Fig. 42.5). For isolated caudal deviation, a 1 cm dorsal strut of quadrangular cartilage is left *in situ* and the remainder of the cartilaginous septum is removed. The caudal strut is reconstructed with a straight piece of resected cartilage and sutured to the dorsal strut and maxillary crest. The remaining resected cartilage is then morselized or scored and placed between the mucoperichondrial flaps prior to closure.

Outcomes

The American Academy of Otolaryngology-Head and Neck Surgery Foundation supported a multicenter study investigating outcomes after septoplasty. Fifty-nine patients completed a validated survey (the Nasal Obstruction Septoplasty Effectiveness scale) before and 3 and 6 months after septoplasty. Only 6% of patients reported they were not pleased with the procedure. The remaining patients in the study reported improvements in nasal obstruction, which remained stable 6 months postoperatively (6). More recently, another study reviewing 86 patients after septoplasty using the same survey reported 89.5% of patients with subjective improvement in nasal obstruction postoperatively (7).

Complications

Complications from septoplasty are rare, but most significantly include septal hematoma, epistaxis, and very rarely CSF leak and anosmia, and more commonly septal perforation and occasionally dorsal saddling. Septal hematomas are usually prevented by hemostasis prior to closure, a quilting stitch, and placement of small perforations in septal mucosa. A postoperative septal hematoma, should be treated in the standard manner as soon as it is recognized, with evacuation of the hematoma, and usually resplinting for several days. Epistaxis is best avoided by recognition of coagulopathies preoperatively and meticulous operative hemostasis. Topical fibrin and thrombin products may be helpful in achieving hemostasis. CSF leak is best treated by preventing its occurrence using appropriate techniques discussed in the prior operative section on septoplasty. Once recognized, the usual algorithm of endoscopic closure of CSF leaks should be employed, which are discussed in the chapter on skull base techniques. Nasal septal perforation occurs in 1.6% to 6.7% of septoplasties (8). A septal perforation complication

is prevented using careful mucosal handling, limiting electrocautery, preventing opposing mucosal tears, and avoiding quilting sutures that are excessively tight and could cause flap ischemia. A perforation may be managed with surgical closure with mucosal flaps and autologous or artificial grafts or a septal button. Saddle nose deformity may occur due to a weakened dorsal strut or displaced caudal septum postoperatively. Management of this deformity is discussed in Chapter 181. Anosmia may occur in up to 3% of patients and usually improves over time. Patients may also develop palate denervation if the long sphenopalatine or greater palatine nerves are injured while removing the maxillary crest or posterior bony septum, respectively. Dental anesthesia may also occur with injury to the nasopalatine nerve (8).

TURBINATE REDUCTION

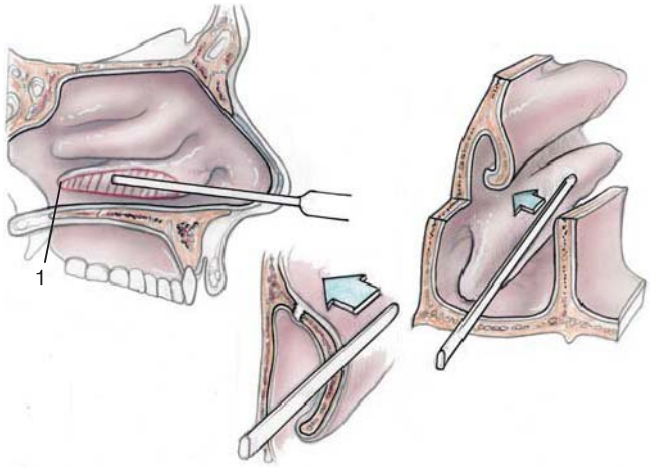
Inferior turbinate hypertrophy is a fairly common etiology of nasal obstruction. Surgery of the inferior turbinates has been reported as the eighth most common procedure performed by otolaryngologists. The inferior turbinates are composed of conchal bone covered by lamina propria (including erectile tissue) and ciliated, pseudostratified, columnar epithelium. The autonomic nervous system controls the level of congestion of the inferior turbinates. The nasal cycle is a cyclic alteration of inferior turbinate vasculature, occurring every 2 to 7 hours. The anterior head of the inferior turbinate forms the posterior aspect of the internal nasal valve, and therefore turbinate congestion can severely impact nasal patency.

Inferior turbinate hypertrophy is typically caused by rhinitis of many etiologies, including allergic, infective, vasomotor, hormonal, or induced by medications. The vast majority of patients with inferior turbinate hypertrophy respond appropriately to medical management, such as topical or systemic corticosteroids, antihistamines, and decongestants. Unfortunately, long-term hypertrophy may become irreversible, thus surgical intervention is warranted (9).

In addition to mechanical obstruction of the nasal passages, the inferior turbinates may also play a role in functional obstruction. The sensation of appropriate nasal airflow is dependent upon the proper nasal airway resistance. Both excessively high and low resistances will lead to a subjective complaint of nasal obstruction. Therefore, patients with injured mucosa or complete absence of inferior turbinates may present with subjective nasal obstruction despite a widely patent nasal airway on examination.

Operative Procedure

Over the course of the years, numerous techniques have been developed to address the hypertrophic inferior turbinate, including partial or total inferior turbinectomy, outfracture, submucous resection, laser, electrocautery, cryosurgery, and radiofrequency ablation (10). Partial or total inferior turbinectomy was widely practiced in the early 1900s; however, concerns of postoperative bleeding, crusting, dryness, atrophic rhinitis, and empty nose syndrome made this technique fall out of favor. Inferior turbinate outfracture is a technique with very minimal morbidity, involving the use of a blunt elevator to fracture the conchal inferior turbinate bone laterally (Fig. 42.6). This procedure tends to be performed in conjunction with other procedures to address the hypertrophic inferior turbinate. Electrocautery of the inferior turbinate can be performed under local anesthesia in the office or under general anesthesia when combined with other procedures in the operating room. This procedure includes surface monopolar electrocautery, bipolar electrocautery, or submucous diathermy. Surface electrocautery has a tendency to injure the mucosa of the inferior turbinate with resultant nasal crusting and dryness. Submucous diathermy involves inserting an insulated needle electrode into the head of the inferior turbinate and extending submucosally to the posterior aspect of the turbinate. The diathermy is then activated for 5 to 10 seconds while the needle is withdrawn from the turbinate. Although immediate benefit is apparent, multiple studies have demonstrated long-term improvement is variable. Radiofrequency turbinate reduction is another popular technique to address inferior turbinate hypertrophy. In this procedure, the electrode probe is inserted submucosally into the inferior turbinate, similar to the diathermy technique. The radiofrequency pulses induce ionic agitation at the cellular level, inducing thermal injury to the deep mucosa, leading to scar contraction and a reduced inferior turbinate. In contrast to submucous diathermy, the radiofrequency technique creates much lower tissue temperatures and therefore thermal injury only extends 2 to 4 mm around the electrode, inducing a more controlled deep mucosal injury and preserving mucosal epithelium and function. Carbon dioxide laser turbinate reduction has the advantages of minimal blood loss and postoperative discomfort. The laser does, however, cause eschar formation on the surface of the turbinate, which may slough and lead to postoperative hemorrhage. Additional



1. Area of out fractured bone

Figure 42.6 Inferior turbinate outfracture.

disadvantages of the laser technique include the expense of the equipment and requirement of additional training and expertise. Cryosurgery involves placing a cryoprobe on the medial and lateral surfaces of the inferior turbinate for 60 seconds. This treatment seems to be most effective in patients with vasomotor rhinitis and multiple treatments may be required to control symptoms.

Submucous resection of the inferior turbinate involves the removal of the underlying erectile tissue and conchal bone. This procedure was first described by Spielberg in 1924. Traditionally, an incision is made in a posterior to anterior fashion along the inferior border of the anterior two-thirds of the inferior turbinate. Mucoperiosteal flaps are then raised to expose the inferior turbinate bone. The bone is then resected using turbinate scissors, Jansen-Middleson rongeur, or Takahashi forceps (Fig. 42.7). The mucoperiosteal flaps are then laid back into anatomic position and excessive mucosa is trimmed. The nasal cavity is then either packed with antibiotic-impregnated gauze or plicating horizontal mattress sutures are used to ensure proper healing. The microdebrider-assisted technique is an alternative method using powered instrumentation to remove the erectile tissue in the inferior turbinate. An incision is made in the anterior head of the inferior turbinate and a submucosal pocket is created. The microdebrider is then inserted into the pocket to remove the submucosal tissue (Fig. 42.8). Alternatively, a specialized microdebrider blade with a sharp tip for elevation and a 3-mm blade for turbinate reduction can be used. The microdebrider blade is then positioned laterally to remove the erectile tissue while preserving an intact overlying mucosal pocket. Suction electrocautery can be used to achieve hemostasis if needed. The reduction in the inferior turbinate is immediately appreciated and the procedure is completed (9,11).

Numerous studies have been performed comparing the various inferior turbinate reduction techniques. Huang et al.

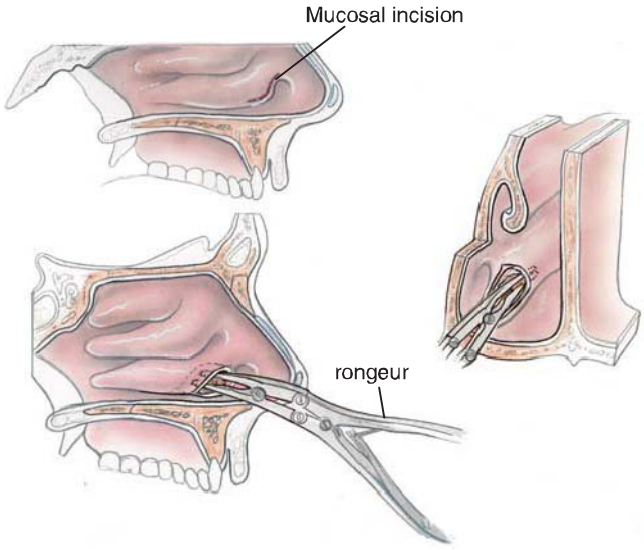


Figure 42.7 Submucosal resection of the inferior turbinate.

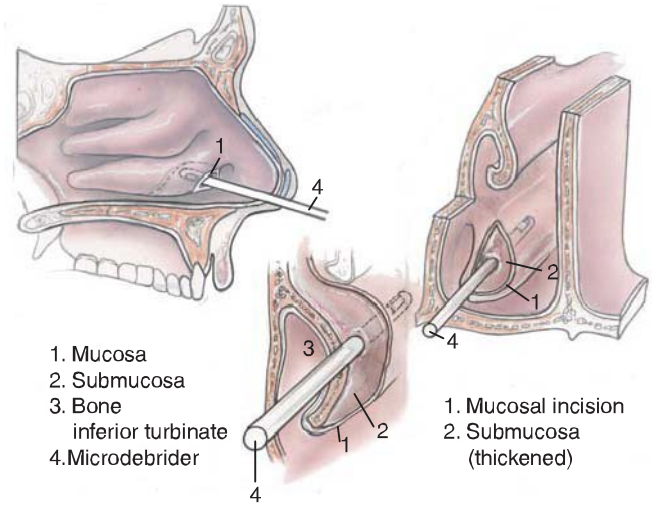


Figure 42.8 Microdebrider-assisted inferior turbinate reduction.

compared the microdebrider-assisted submucous resection technique with radiofrequency turbinate reduction in 120 patients and noted improved outcomes in the microdebrider group 3 years postoperatively (12). Wormald et al. studied 19 patients who underwent cauterization on one inferior turbinate and microdebrider-assisted submucous resection on the other. Symptom scoring, endoscopic scoring, as well as acoustic rhinometry were performed periodically for 5 years postoperatively. The microdebrider-assisted technique was superior to inferior turbinate cauterization in all endpoints studied. Additionally, cauterization was associated with recurrence of inferior turbinate hypertrophy, whereas microdebrider-assisted submucosal resection had stable long-term results (13).

Complications

Complications after inferior turbinate reduction are best avoided by appropriate intraoperative technique. The surgeon should strive to maintain as much intact mucosa as possible during any inferior turbinate procedure in order to preserve mucociliary function and to prevent nasal crusting, synechia formation, and hemorrhage. Manipulations at the posterior-most aspect of the turbinate should be avoided to prevent injury to branches of the sphenopalatine artery, resulting in immediate or delayed bleeding.

Rhinitis sicca and empty nose syndrome may develop after turbinate surgery. Classically, these entities occur with partial or total turbinectomy; however, they may also occur with excessive injury to the turbinate mucosa. The inferior turbinate is much more commonly involved than the middle turbinate. Patients with empty nose syndrome present with paradoxic nasal obstruction despite a widely patent nasal airway on examination. Patients report a feeling of nasal stuffiness in addition to the lack of nasal airflow sensation, which may lead to subjective complaints of difficulty breathing, shortness of breath, or even suffocation. Empty nose syndrome occurs in a small

percentage of patients who undergo turbinate procedures, but the clinician should be aware of this entity and strive to maintain the integrity of turbinate mucosa to avoid this complication. Atrophic rhinitis is a distinctly different condition; atrophic rhinitis is a chronic, degenerative condition characterized by inflammation and atrophy of the nasal mucosa. Patients present with significant crusting, foul odor, and nasal obstruction. *Klebsiella ozaenae* is often the culpable bacteria. Anatomically, empty nose syndrome and atrophic rhinitis patients may look similar, and submucosal implantation may benefit both conditions, although they have different origins (14).

NASAL VALVE OBSTRUCTION

The internal nasal valve is the narrowest portion of the nasal airway and therefore may contribute to obstruction. It is the site of maximal nasal airway resistance and it is hypothesized that its function is to assure nasal airflow does not exceed the ability of the nose to humidify and warm inspired air. The valve has a tendency to collapse at high airflow rates due to Bernoulli forces. This valve consists of the cartilaginous septum medially, the floor of the nose inferiorly, the caudal aspect of the upper lateral cartilage superiorly, the bony pyriform aperture laterally, and the head of the inferior turbinate posteriorly (Fig. 42.9). Deformities of the internal nasal valve include inferiomedially displaced upper lateral cartilage, septal deviation, inferior turbinate hypertrophy, and pyriform aperture stenosis. The external nasal valve is formed by the septum, the medial and lateral crura of the lower lateral cartilage, and the premaxilla (Fig. 42.9). Deformities

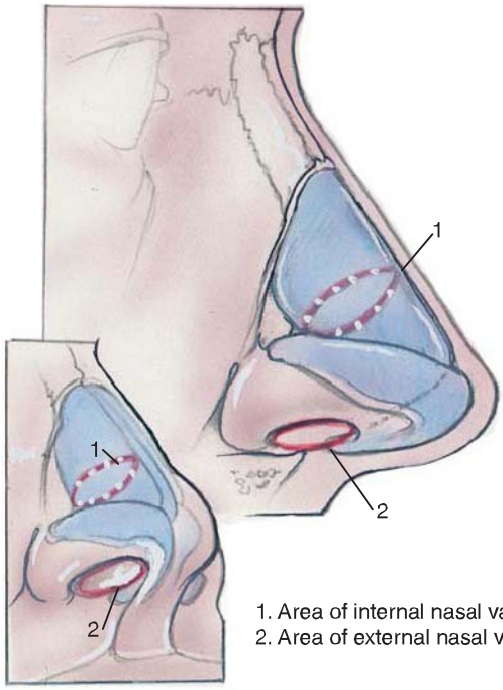


Figure 42.9 External and internal nasal valves.

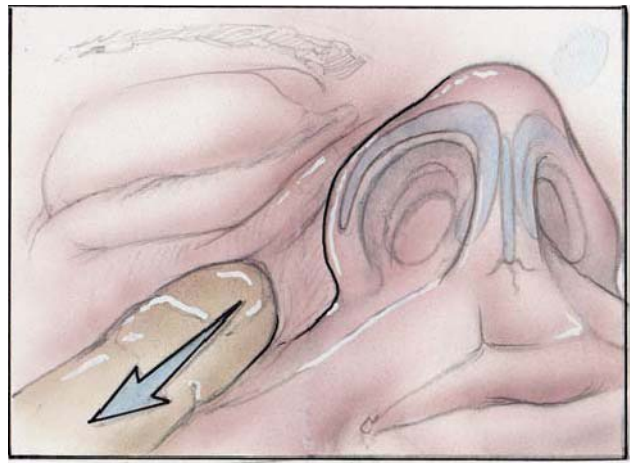


Figure 42.10 The Cottle maneuver.

of the external nasal valve may occur as a result of destabilization of the nasal septum and lower lateral cartilage, leading to upper lateral cartilage collapse. This may occur postoperatively, in particular after reduction rhinoplasty (15). Additionally, improvement of nasal congestion with a Cottle maneuver (Fig. 42.10), directs the otolaryngologist to consider nasal valve surgery to correct the obstruction.

Operative Procedures

There are numerous surgical treatments available to address the internal nasal valve. The otolaryngologist must choose the appropriate combination of procedures to adequately alleviate symptoms of nasal obstruction. Nasal septal deviation and inferior turbinate hypertrophy can contribute to obstruction in the nasal valve region and must be addressed at the time of surgery. Operative techniques specifically targeting the internal nasal valve can be performed with an open or an endonasal approach, depending on the surgeon's preference.

The most common surgical technique is application of spreader grafts, which was first described by Sheen in 1984. The 1 to 2 mm thick rectangular shaped grafts are harvested from the quadrangular cartilage and placed in a submucosal pocket between the septum and the upper lateral cartilage (Fig. 42.11). The grafts span the entire distance of the upper lateral cartilage to the nasal bone and therefore increase the angle between the septum and upper lateral cartilage resulting in an increase in the CSA of the internal nasal valve (15,16).

Numerous other types of cartilaginous grafts have also been described to address the nasal valve. In 1998, Guyuron et al. described splay grafts, in which conchal cartilage is placed concave side down over the dorsal septum and underneath the caudal aspect of the upper lateral cartilages. The graft uses the nasal dorsum to splay the upper lateral cartilages apart and widen the nasal airway. Butterfly grafts are a modification of this technique, in

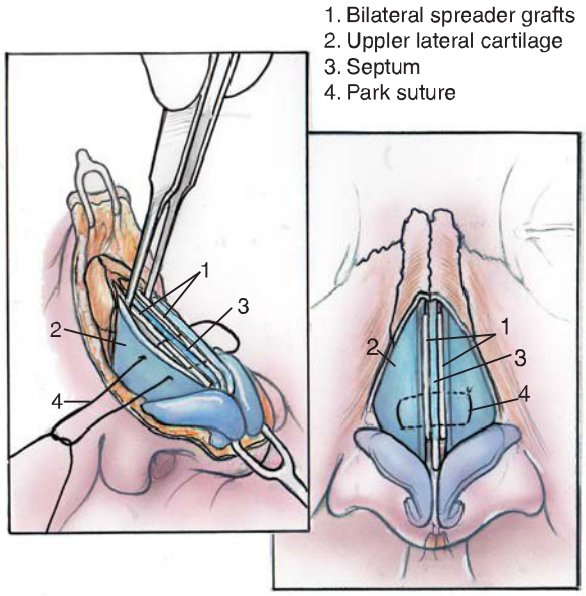


Figure 42.11 Placement of spreader grafts and Park suture.

which a conchal or septal cartilage graft is placed between the upper lateral and lower lateral cartilages, with its caudal border under the cephalic aspect of the lower lateral cartilage. Lastly, alar batten grafts have been described to support a weakened or absent lateral crus of the lower lateral cartilage, strengthening the external nasal valve. These grafts are harvested from the concha or septum and placed in a submucosal pocket caudal to the lower lateral cartilage and extending laterally over the bony pyriform aperture (Fig. 42.12).

Flaring or "Park sutures" have also been described to alleviate internal nasal valve obstruction. This technique involves a horizontal mattress suture placed at the lower border of the upper lateral cartilage, spanning across the nasal dorsum, and secured to the lower border of the contralateral upper lateral cartilage. As the suture is tightened, the upper lateral cartilages begin to flair, widening the internal nasal valve (Fig. 42.11). Paniello in 1996 described the use of a suspension suture to address the internal nasal valve. In this technique, a suture is placed through the periosteum of the inferior orbital rim through a lower eyelid transconjunctival approach and secured to the upper lateral cartilage, suspending the cartilage superiolaterally and widening the nasal valve (2,16). Although this technique is effective in the immediate postoperative period, the long-term efficacy of this procedure has not been reported.

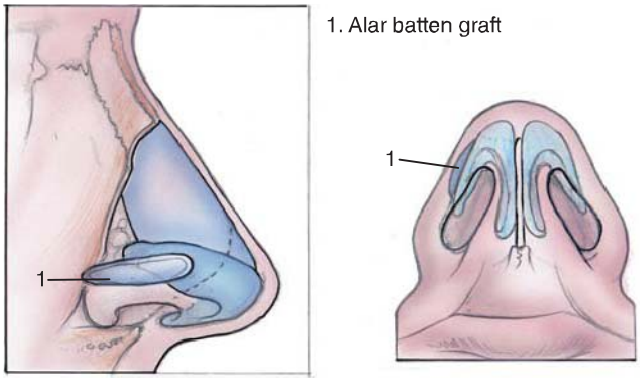


Figure 42.12 Placement of a batten graft.

CONCLUSION

Nasal obstruction is a common presenting complaint and has numerous etiologies. A thorough history and physical examination must be obtained in order to determine the most appropriate treatment regimen. Patients should be optimized with medical therapies prior to considering surgical intervention. A variety of techniques are available to address a deviated nasal septum, hypertrophic inferior turbinates, or nasal valve obstruction. The otolaryngologist should be aware of these various procedures in order to choose the most appropriate combination for each patient.

HIGHLIGHTS

- Nasal obstruction is common and caused by numerous etiologies, some reversible with medical therapy and some requiring surgical correction.
- Patients should be optimized with medical therapies even when a surgical intervention is planned.
- Causes of nasal obstruction amenable to surgical correction include septal deviation, turbinate hypertrophy, nasal valve collapse, nasal polyps, choanal atresia, and sino-nasal tumors.
- Caudal septal deflections can be challenging to correct, and care must be taken to provide a caudal strut to prevent postoperative nasal saddling.
- The most common complication of septoplasty is a septal perforation; however, other complications include nasal saddling, anosmia, septal hematoma, failure to correct deflection, and rarely CSF leak.
- A combination of techniques may be used to address the hypertrophic inferior turbinate with successful outcomes.
- Overly aggressive inferior turbinate reduction or resection may lead to rhinitis sicca or empty nose syndrome postoperatively.
- The internal and external nasal valve is complex and numerous structural abnormalities, including destabilization of the nasal septum and lower lateral cartilage, contribute to obstruction in this region.

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43 Endoscopic Orbital and Lacrimal Surgery

Erik Kent Weitzel *Raymond I. Cho*

With the advent of endoscopic approaches to the sinuses, creative surgeons recognized additional potential for these techniques and quickly developed approaches to the medial and inferior orbit. The benefits were obvious when targeting the orbital apex that is exposed safely and completely with endoscopic techniques. Over time, the techniques have expanded to a wide range of procedures including dacryocystorhinostomy (DCR), optic nerve decompression, and anterior ethmoidal artery (AEA) ligation.

PERTINENT ORBITAL ANATOMY

Bony Anatomy

The orbit is defined as the bony confines circumferentially surrounding the eye and the extraocular musculature. The bony anatomy of the orbit involves a complex contribution of seven different bones of the skull. The medial orbital bone progresses anterior to posterior from the robust frontal process of the maxilla, to a thin lacrimal bone, then to an extremely thin ethmoid bone contribution also known as the lamina papyracea, and finally to the lesser wing of the sphenoid that houses the optic foramen. It is important when performing endoscopic DCR to understand that the lacrimal fossa is formed by fairly equal contributions of two bones joined vertically (see Fig. 43.1): anteriorly, the thicker frontal process of the maxilla and posteriorly, the very thin lacrimal bone. The orbital floor slopes superiorly as it courses from anterior to posterior and includes the orbital surface of the maxillary bone, zygomatic bone (anterolateral), and the orbital process of the palatine bone. The lateral wall consists of the orbital surface of the zygomatic bone anteriorly and the greater wing of the sphenoid posteriorly. The roof consists of the orbital surface of the frontal bone anteriorly and the lesser wing of the sphenoid posteriorly.

Vascular Anatomy

The endoscopic orbital surgeon must be an expert on the vascular anatomy of the orbit, particularly the ethmoidal arteries. Virtually, the entire arterial supply of the orbit arises from the ophthalmic artery, the first branch of the internal carotid artery, which enters the orbit through the optic foramen and gives rise to the central retinal, ethmoidal, lacrimal, zygomatic, supraorbital, and supratrochlear arteries. The AEA enters the anterior ethmoidal foramen through the frontoethmoidal suture at or just under the level of the skull base (fovea ethmoidalis) (Fig. 43.2). Because of its consistent relationship to the skull base, the AEA is safely used as an upper limit of entry into the anterior ethmoidal sinuses when entering the ethmoid sinuses through an orbital approach to prevent cerebrospinal fluid (CSF) leak (also known as external ethmoidectomy). The AEA bridges across the anterior ethmoid sinus between the second and third ethmoidal lamellae (1) along a posterolateral to anteromedial trajectory and back into the intracranial space through the lateral lamellae of the cribriform plate. There is often a natural dehiscence of the orbital bone around the anterior ethmoidal foramen that may be evident after anterior ethmoidal dissection when pushing on the eye. The posterior ethmoidal foramen lies 12 mm posterior to the anterior ethmoidal foramen and houses the posterior ethmoidal artery (PEA). Unlike the AEA, the PEA will not lie in a mesentery and is positioned at the junction of the anterior face of the sphenoid's intersection with the skull base.

The infraorbital artery, a branch of the maxillary artery, does not normally enter the orbital space, but deserves specific mention because of the potential for the endoscopic orbital surgeon to encounter it during medial orbital decompression. Traveling with the infraorbital nerve and vein, it enters the infraorbital groove/canal from the pterygopalatine fossa, sending a perforating branch into the

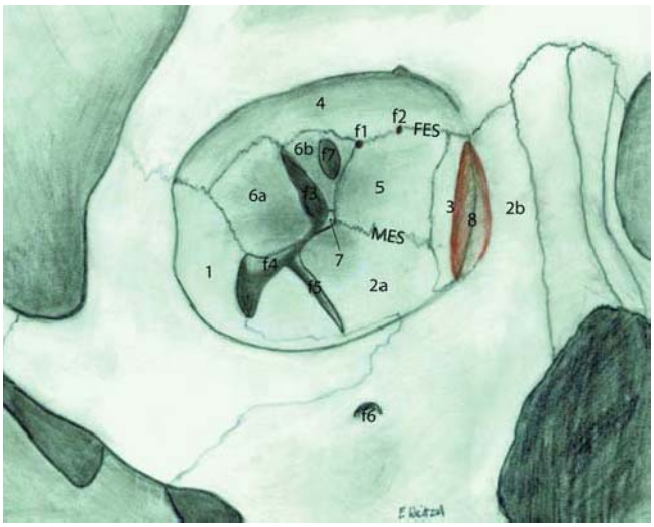


Figure 43.1 Right orbital skeleton highlights: (*1*) Zygomatic bone, orbital surface; (*2a*) Maxilla, orbital surface; (*2b*) Maxilla, frontal process; (*3*) Lacrimal bone; (*4*) Frontal bone, orbital surface; (*5*) Ethmoid bone, orbital plate or lamina papyracea; (*6a*) sphenoid bone, greater wing's orbital surface; (*6b*) Sphenoid bone, Lesser wing's orbital surface; (*7*) Palatine bone, orbital process; (*8*) Lacrimal fossa (from maxillary and lacrimal bones); (*f1*) Posterior ethmoidal foramen; (*f2*) Anterior ethmoidal foramen; (*f3*) Superior orbital fissure; (*f4*) Inferior orbital fissure; (*f5*) Infraorbital groove; (*f6*) Infraorbital foramen; (*f7*) Optic foramen; (*MES*) Maxilloethmoid suture; (*FES*) Frontoethmoid suture.

orbit through the floor before exiting the maxillary bone in the medial midface.

An intimate knowledge of the vascular anatomy of the orbit is essential for the endoscopic orbital surgeon to avoid the potentially devastating consequences of orbital hemorrhage. Maintaining patency of the central retinal artery and ophthalmic veins are critical for vision, and temporary interruptions of the blood supply can lead to permanent visual loss in less than 2 hours. Orbital compartment syndrome frequently develops as a result of retrobulbar hemorrhage or volume-occupying orbital lesions, and the orbit must be decompressed when the orbital pressure nears the occlusion pressure of the central retinal artery. Signs and symptoms of impending visual loss include blurred vision, loss of color vision, afferent pupillary defect, severe proptosis, or ophthalmoplegia. Monitoring intraocular pressures during such events with tenotomy is critical to indicate vascular perfusion to the retina. Intraocular pressures are normally between 10 and 21 mm Hg with a mean of 16 mm Hg. Pressures exceeding 30 to 40 mm Hg necessitate emergency surgical intervention, including lateral canthotomy with inferior and/or superior cantholysis, and orbital decompression if necessary. Studies have shown that lateral canthotomy and inferior cantholysis can effectively reduce intraocular pressures by 30 mm Hg (2). Involvement of an ophthalmologist in the management of orbital compartment syndrome is mandatory.

Neuromuscular Anatomy

Relevant neuromuscular anatomy includes the optic nerve and orbital apex contents. The orbital apex is variably defined, but typically described as the region of the posterior orbit starting at the annulus of Zinn where the rectus muscles originate and extending posteriorly to the optic foramen. Anatomical organization of the posterior orbit is best discussed in relation to the foramina. The superomedially located optic foramen transmits the optic nerve and ophthalmic artery and is located 6 mm posterior to the posterior ethmoidal foramen. The superior orbital fissure (SOF) transmits structures from the middle cranial fossa and is split in two by the origin of lateral rectus located in the annulus of Zinn (Fig. 43.3). The relationship of structures transmitted through the SOF relative to the origin of the lateral rectus defines them as either intra- or extraconal. The superior extraconal neurovascular structures include the lacrimal (V1 branch), frontal (V1 branch), trochlear (IV) nerves, and superior ophthalmic vein. Intraconal nerves include the superior and inferior divisions of the oculomotor (III), nasociliary (V1), and abducens (VI) nerves (3). The inferior orbital fissure provides a passageway into the pterygopalatine fossa and transmits the maxillary nerve (V2), infraorbital artery, and inferior ophthalmic vein (4).

No discussion of the orbit is complete without a discussion of cranial nerve II. The optic nerve is segmented into four parts including the intracranial, intracanalicular, intraorbital, and intraocular segments. From the chiasm, the intracranial component courses approximately 10 mm before entering the optic foramen. The next 8 mm of the optic nerve, called the intracanalicular segment, courses through the optic canal and is the only portion of the nerve confined within bone. The nerve then emerges from the optic canal and extends 30 mm to the globe as the intraorbital segment. The last portion of the nerve is the very small intraocular segment that lacks the three meningeal sheaths and is not myelinated (5).

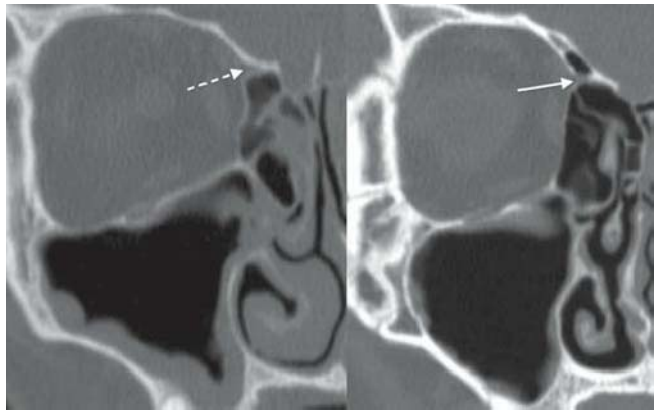


Figure 43.2 Coronal bone-window CTs of the right orbit in two different patients showing the AEA in two configurations. *Dotted arrow* shows an AEA attached to the skull base and not at risk for damage during clearance of the ethmoid skull base. The solid *arrow* shows a mesenteric AEA that is at risk for damage during sinus surgery.

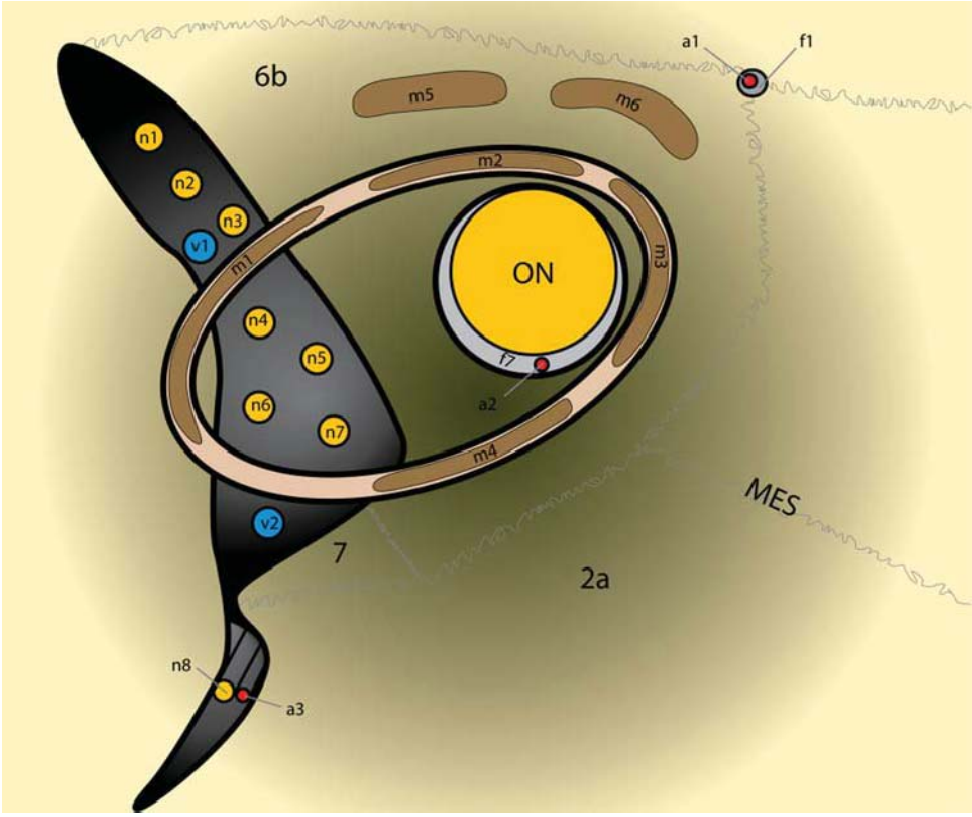


Figure 43.3 Right orbital apex. (*n1*) Lacrimal branch of V1; (*n2*) Frontal branch of v1; (*n3*) Trochlear nerve; (*n4*) Superior division of oculomotor nerve; (*n5*) Nasociliary nerve; (*n6*) Abducens nerve; (*n7*) Inferior branch of oculomotor nerve; (*n8*) Maxillary nerve—V2; (*v1*) Superior ophthalmic vein; (*v2*) Inferior ophthalmic vein; (*a1*) Posterior ethmoid artery; (*a2*) Ophthalmic artery; (*a3*) Infraorbital artery; (*m1*) Lateral rectus; (*m2*) Superior rectus; (*m3*) Medial rectus; (*m4*) Inferior rectus; (*m5*) Levator palpebrae superior muscle; (*m6*) Superior oblique; (*ON*) optic nerve; (*f1*) Posterior ethmoidal foramen; (*f7*) Optic foramen; (*MES*) Maxilloethmoid suture; (*2a*) Maxilla, orbital surface; (*6b*) Sphenoid bone, Lesser wing's orbital surface; (*7*) Palatine bone, orbital process.

Lacrimal Anatomy

The lacrimal system lies just anterior to the medial insertion of the orbital septum and therefore is by definition extraorbital although typically discussed in conjunction with orbital topics (6). The overall flow of tears derives from the combined output of the two lobes of the lacrimal gland (orbital and palpebral lobes), the major reflex lubricators of the eye, and small conjunctival glands responsible for basal secretion. After moisturizing the eye, tears enter the superior or inferior lacrimal puncta, course through the superior or inferior canaliculi into the common canaliculus, and emerge into the lacrimal sac through the valve of Rosenmuller. Ten percent of patients will not have a common canaliculus so that the inferior and superior canaliculi penetrate the sac separately. Approximately one-third of the lacrimal sac lies above the common canaliculus (6). This superior lacrimal sac region, known as the fundus, extends above the axilla of the middle turbinate, which becomes important when attempting to marsupialize the entirety of the lacrimal sac. Inferiorly, the sac transitions into the lacrimal duct before emerging under the inferior turbinate through Hasner valve. The lacrimal system is driven by the pump action of blinking, thereby forcing tears through the horizontally oriented canalicular anatomy (Fig. 43.4).

ADULT DACRYOCYSTORHINOSTOMY

Background

The most common patients considered for DCR are females in their early 60s complaining of continuous tearing of a single eye (7). The causes of epiphora are diverse but predictable relative to the patient's age. Children typically will have a congenitally imperforate Hasner valve effectively treated with short-term lacrimal intubation. Young adults' epiphora is most likely caused by either trauma related anatomical disturbances or herpetic inflammation with stenosis of the canalicular system. Epiphora in middle-aged women is generally caused by a dacryolith formed in the lacrimal sac. Finally, the etiology in elderly women is usually from idiopathic stenosis of the distal lacrimal duct. The two etiologies typical of middle-aged and elderly women are the only ones amenable to DCR. Incomplete obstructions of the lacrimal system will differ from typical

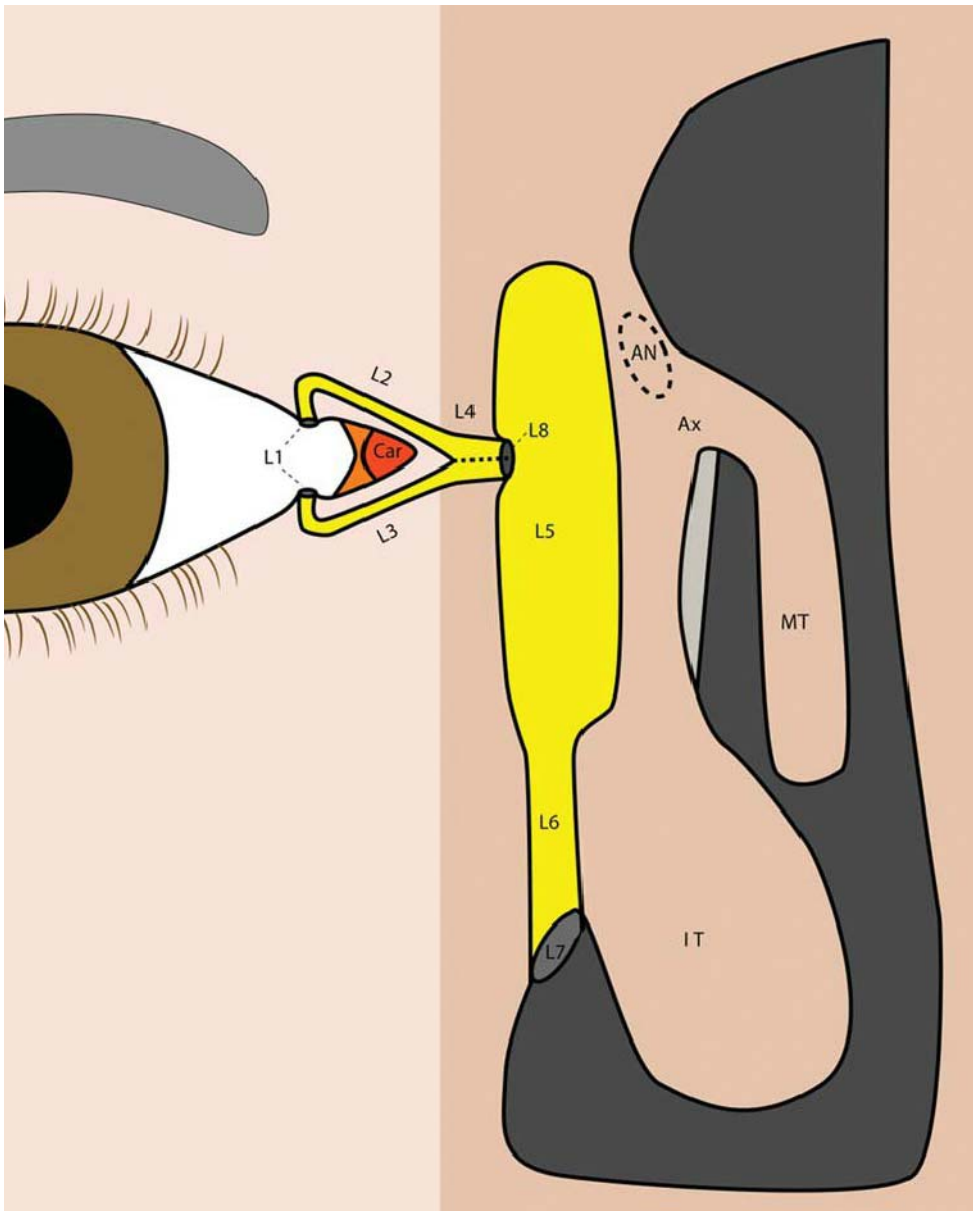


Figure 43.4 Right lacrimal system. Lacrimal puncta in the center of the mounded papilla (*L1*); Superior (*L2*) and Inferior (*L3*) canaliculi merge into the common canaliculus (*L4*). *Dotted line* reminds us that 10% of patients do not have a common canaliculus and separately enter lacrimal sac (*L5*) through the common internal punctum (*L8*) also called the valve of Rosenmuller. A substantial amount of the sac extends above the axilla (*Ax*) of the middle turbinate (*MT*) and often requires extensive drilling through the frontal process of the maxilla and entry into the agger nasi (*AN*) cell to open fully. Lacrimal duct (*L6*) drains through Hasner valve (*L7*) under the inferior turbinate (*IT*) to enter the inferior meatus.

presentations as they tend to only have epiphora in cold or windy weather, but fail to have tearing when inside, and may not develop the infections that are common with complete obstructions.

The purpose of the lacrimal system is to protect and hydrate the cornea through the continuous production, movement, and drainage of tears. The tear film is a delicately balanced multilayered conglomeration of three different liquid components. The largest contribution comes from the central aqueous layer largely produced by the two lobes of the lacrimal gland with minor contributions from the glands of Wolfring and Krause found within the eyelids. The deep layer of the tear film consists of mucus produced by conjunctival goblet cells that cause the aqueous layer to adhere to the cornea. The superficial layer of tear film is a very thin layer of oil produced by the meibomian glands that prevents evaporation of the aqueous layer.

Evaluation

In true epiphora, tears run down the face, which is to be distinguished from a "watery eye" in which tears do not

drain onto the skin. This distinction is important because epiphora is usually caused by obstructions within the canalicular system or nasolacrimal duct and is treated with surgery, while disorders that cause a watery eye are generally treated medically. While watery eyes also drain through the lacrimal system, the cause is usually an excessive accumulation of tears on the surface of the eye due to heterogeneous tear distribution from ineffective blinking or deficits in tear film layering, which leads to ocular irritation and reflex tearing.

A comprehensive examination of epiphora begins with careful study of the lids. The position of the punctum should approximate the globe. Ectropion or entropion will lead to abnormal punctal position and prevent normal drainage of tears. The eyelashes should also be inspected to make sure they are not rotated and causing ocular irritation. Evaluation of lacrimal pump problems includes assessment of lid deformities, incomplete blink due to facial nerve weakness, or lid laxity. Lid laxity is tested with the two-part snap test that involves gently pulling the lid away from the eye and releasing it. A normal lid cannot be pulled 6 mm away from the conjunctiva and quickly snaps back into normal position.

The lacrimal system is studied by means of the dye disappearance test, probing of the canaliculi, and irrigation. The examination is begun by anesthetizing the eye topically, followed by placement of a large drop of 2% fluorescein in both eyes. In a normal eye, the fluorescein should clear from the eyes within 5 minutes. Recovery of dye from the nares with a cotton-tipped applicator (CTA) or nose-blowing (the primary dye or Jones 1 test) also indicates functional patency of the lacrimal drainage system. Any sign of dacryocystitis on exam suggests obstruction.

If the above tests reveal the presence of obstruction, further testing can identify the location of the obstruction. Lacrimal probing is performed with a 0 or 00 Bowman probe through the canaliculi with care not to create a false passage during probing. A normal exam threads the probe along the canaliculus of interest into the common canaliculus, through the common internal punctum (valve of Rosenmuller), and "hard-stops" when it impacts the mucosa-covered bone of the medial lacrimal sac. If the probe cannot pass soft tissue in the common canaliculus or in the sac, the probe is said to have had a "soft-stop" implying proximal lacrimal system pathology. Finally, lacrimal irrigation is performed with a lacrimal irrigation cannula through the lower or upper canaliculus. It should be easy to irrigate and cause flow into the nose that the patient can taste. Reflux around the needle or out of the opposite canaliculus is abnormal. Probing and irrigation performed after the Jones 1 test is known as the Jones 2 test, and can help to localize the level of lacrimal system obstruction. Reflux of clear fluid from the same punctum being irrigated indicates obstruction proximal to the common canaliculus; reflux of clear fluid from the opposite punctum indicates obstruction of the common canaliculus or common internal punctum; and reflux of fluorescein-stained fluid through the opposite punctum indicates nasolacrimal duct obstruction. A final element of the exam includes a thorough nasal exam to exclude obstructing intranasal pathology (8).

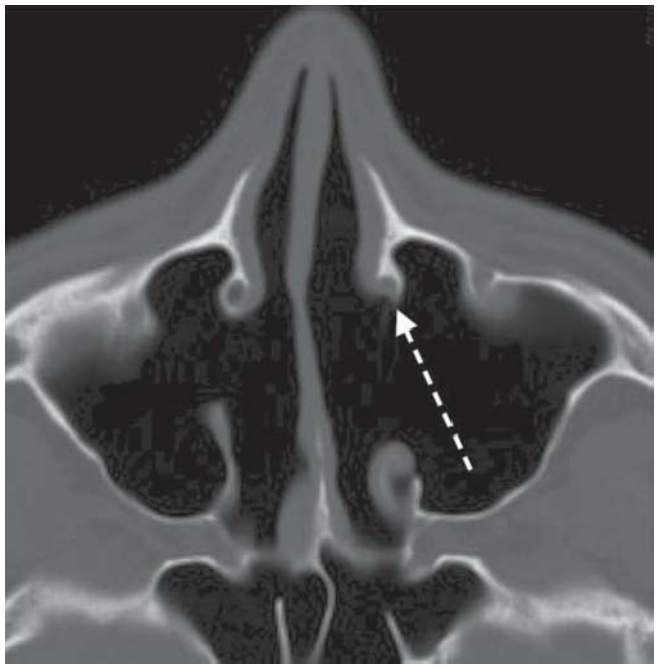


Figure 43.5 Axial bone-window CT of lacrimal duct trauma and stenosis caused by excessive back-biting during maxillary antrostomy. The posterior wall of the nasolacrimal duct is absent (*arrow*). Endoscopic intranasal exam was able to identify the pathology during the initial patient evaluation leading to rapid effective treatment with DCR.

An abnormality detected on this exam suggests lacrimal obstruction, and coupled with appropriate symptoms, is justification for DCR. However, sometimes patients complain of epiphora, but the exam is not convincing for obstructive pathology. In these cases, lacrimal scintillography is indicated to identify those cases with partial obstruction that can still benefit from DCR. Dacryocystogram has also been described as a useful study for identification of complete anatomic blockages; however, this study may be considered redundant to a high-quality exam (Fig. 43.5).

Technique Options

Lacrimal duct and sac obstructions are commonly treated by three procedures including external, endoscopic, and laser-assisted DCR. Outcomes with endoscopic procedures are highly dependent on how the sac is managed, thus any discussion on endoscopic DCR must specify extent of sac marsupialization. The two most commonly discussed variations on endoscopic technique involve either complete preservation and marsupialization of the medial sac or medial lacrimal sac wall excision. Unsuccessful options to be avoided include placement of a grommet through the medial sac wall or a vertical sac slit without

TABLE 43.1 EXTENSIVE REVIEW OF THE LITERATURE BY LEONG ET AL. (7) SUMMARIZED TYPICAL OUTCOMES OF POPULAR DCR TECHNIQUES

Procedure	Immediate Success Rate (%)	Long Term Success Rate
Endoscopic (11)	84–94	92% at 6 y
External (12)	65–100	94% at 4 y
Endonasal Laser-Assisted (13)	47–100	38% at 5 y

marsupialization, both associated with over 65% failure rates (9). Less common techniques include transcanalicular laser-assisted, balloon dacryoplasty, and conjunctivodacryocystorhinostomy (CDCR).

Procedure outcomes vary widely, with typical success rates for the most commonly reported procedures summarized in Table 43.1. Success rates are similar for endonasal and external DCR (10) and decisions regarding choice of procedure are highly dependent on surgeon experience. Laser-assisted DCR suffers from worse long-term results than the other two popular techniques. For atrophic sacs, an alternative technique maintains permanent silastic tubes through an opened sac. If the patient can tolerate the tubes, success rates approximate sac marsupialization (9). However, most patients will complain of foreign body sensation that requires frequent stent adjustment swaying surgeons toward a nonstented option in a majority of these patients.

Adjunctive therapies widely used at the conclusion of DCR including the use of antimetabolite agents and postoperative silicone tubing of the lacrimal system may not be beneficial. Research now suggests that antimetabolites including Mitomycin C or 5-Flourouracil most likely do not improve results (7); however, a few controversial studies have reported better outcomes (14,15). Stenting the proximal lacrimal system with silicone tubing for 1 to 6 months has been a standard postoperative measure to encourage the system to heal in a patent configuration. However, recent reports suggest that tubing may be considered optional with little added benefit to outcomes (16,17).

Endoscopic Technique (18,19)

Endoscopic "access" septoplasty is performed in a majority of cases prior to beginning DCR. This limited septoplasty selectively addresses the anterior-superior septum allowing full exposure to the axilla of the middle turbinate. Additional preparatory work includes utilizing a 30-degree scope for the procedure angled in an upward/lateral direction, injection of the middle turbinate axilla with 1:100,000 epinephrine, and placement of 1:1,000 epinephrine-coated pledgets in the anterior nasal cavity to create vasoconstriction for hemostasis (Fig. 43.6).

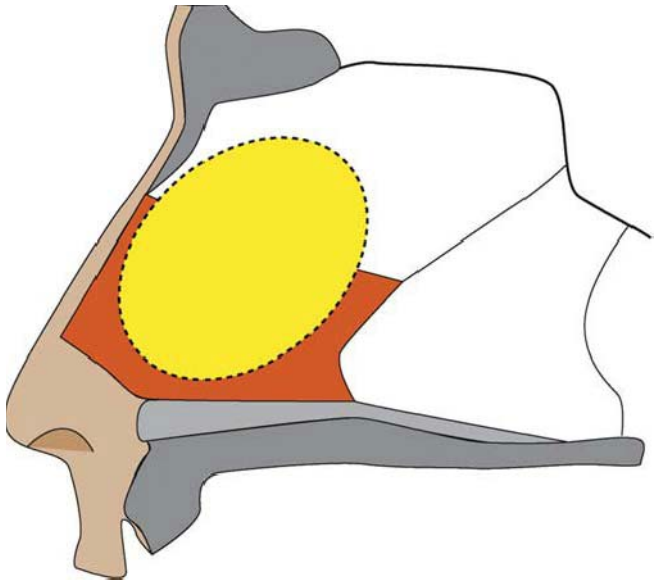


Figure 43.6 Dotted line represents the section of septum (bony and cartilaginous) removed in an "access septoplasty," which optimizes access to the axilla of the middle turbinate. Note that this limited septoplasty avoids the inferior portions of the septum, which are time consuming to remove.

The DCR flap is started posterosuperiorly at a point 3 mm posterior to and 8 to 10 mm above the axilla. The incision is developed 10 mm anterior to the axilla and then dropped inferiorly down to the level of the insertion of the inferior turbinate. A final horizontal incision is created at the level of the insertion of the inferior turbinate from the uncinate to the base of the existing incision. A sharp suction freer is used to elevate this flap over the frontal process of the maxilla, off of the lacrimal bone, and on to the uncinate where it will remain posteriorly pedicled throughout the case. It is also important to elevate the flap off of the axilla. The mucosal flap is protected during the case by rolling it medial to the middle turbinate. Hemostasis is maintained by periodically placing pledgets with 1:1,000 epinephrine (Fig. 43.7).

A round knife or Woodson elevator is used to flake off the very thin lacrimal bone of the posterior lacrimal fossa. A finger pressed on the ipsilateral medial canthus will help identify the lacrimal sac. A forward biting Hajek-Koeffler punch or a forward biting 2 or 3 mm Kerrison is used to remove the anterior half of the lacrimal fossa made of the extremely thick frontal process of the maxilla. The rongeur is carefully positioned between the sac and bone and can remove the majority of this bone. Finally, a DCR diamond drill bit is used to remove any bone that was ergonomically impossible to remove with the rongeur. Drilling is also carried out circumferentially around the sac saucerizing this bone to create a crater in which the lacrimal sac is prominently exposed. Often, the agger nasi cell is entered during this process due to the superior extent of the natural

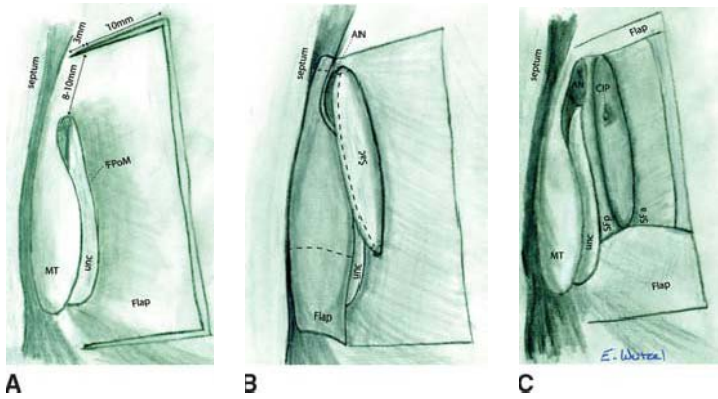


Figure 43.7 Left DCR. Diagram **(A)** shows the dimensions of a typical DCR flap relative to the frontal process of the maxilla (FPOM), uncinate (unc), and middle turbinate (MT). In **(B)**, the flap has been elevated and rolled medial to the middle turbinate. The bone over the lacrimal sac has been removed and saucerized producing a "proud" sac that prominently emerges from the surrounding bone. Bone removal superiorly usually opens the agger nasi (AN) cell. Dotted lines represent incisions to be made on the DCR flap (for removal of the central portion) and the lacrimal sac (for marsupialization). In **(C)**, the DCR is complete (without intubation tubes) showing the marsupialized anterior (SFa) and posterior (SFp) lacrimal sac flaps covering exposed bone and primarily approximating surrounding mucosa.

position of the high lacrimal sac. Once entered, adequate additional bone and mucosa should be removed so that this cell does not obstruct during the healing process. It is imperative during the use of the rongeur or drill that the delicate lacrimal sac is not damaged.

Lacrimal puncta are dilated if necessary prior to insertion of Bowman lacrimal probes. The probe is carefully routed either superiorly or inferiorly (whichever is easier) along the canalicular system to emerge into the sac. Intranasal inspection will reveal a pinpoint medial tenting of the sac if the probe has passed the common internal punctum. If the probe gets caught within the canalicular system, the sac will have a broad ballooned movement and should not be incised. Once the lacrimal probe is holding only the medial wall on tension, an angled knife blade (Beaver blade no. 66) is used to create a vertical incision to the top and bottom of the sac. A ball probe can be inserted into the sac at this point to check the full vertical height to ascertain that the entire medial sac has been cleared of bone. Belucci scissors are used to release the posterior flap at its superior and inferior limits whereas a highly recurved sickle knife, a no. 12 blade, or a thin backbiter can be used to release the anterior flap in a similar fashion. If the surrounding bone has been properly saucerized, the medial sac mucosa will naturally fall and lay open without curling up. The common internal punctum should be visible in the center of the sac. The lateral nasal wall flap lifted at the beginning of the case is now trimmed of mucosa to accommodate the now opened sac. This usually results in leaving only a small band of mucosa superiorly and inferiorly to cover exposed bone.

For procedures that require temporary or permanent stenting with silicone lacrimal tubes, a wide variety are available that can accomplish this task. The tubes are inserted through both the superior and inferior canalicular pathways to emerge through the common canaliculus. Individually, they are withdrawn from the nose. While a cotton swab is placed in the medial canthus to reduce tension on the lacrimal puncta, a 1 cm piece of gelfoam is slid up the tubes to hold the flaps in good position. A short segment of a 14°F catheter is slid up the tubes as well to hold the gelfoam in place. Finally, a medium clip secures the tubes together just behind the catheter segment (disposable clip appliers create too much force and will cut the tubes). The tubes are trimmed to keep the intranasal portion of the tube from bothering the patient.

Patients are sent home on oral antibiotics for 10 days, antibiotic eye drops, and pain medications. Patients follow up at 6 weeks for tube removal, which is accomplished by cutting the tubes at the medial canthus while retracting the looping tube segment between the lacrimal puncta with a right-angled ear hook. The tubes are then grasped and removed through the nose. Fluorescein dye placed in the ipsilateral eye should show excellent nasal penetration through the marsupialized sac.

Complications

Perioperative

Endoscopic DCR has a highly variable reported rate of complication. Wormald's seminal description of the technique reported one delayed epistaxis in 44 patients (18). However, an extensive literature review showed much higher reports of complication with endoscopic DCR than external or laser-assisted techniques (7). The most common intraoperative complication is reported as wound hemorrhage followed by orbital fat exposure (7). However, fat exposure should be an uncommon complication as it can only occur when the dissection is taken posterior to the uncinate, which is an easily identifiable posterior landmark (18). Postoperative complications of endoscopic DCR are most frequently periorbital hematoma followed by synechiae.

Surgical Failures

Silicone stents placed under too much tension may cause "cheese wiring" of the lacrimal puncta and lead to iatrogenic epiphora due to misaligned puncta relative to the conjunctiva. This has been reported in up to 0.1% of cases and is easily prevented by placement of the cotton swab end of a CTA in the medial canthus and looping the lacrimal tubes around it while it is secured intranasally.

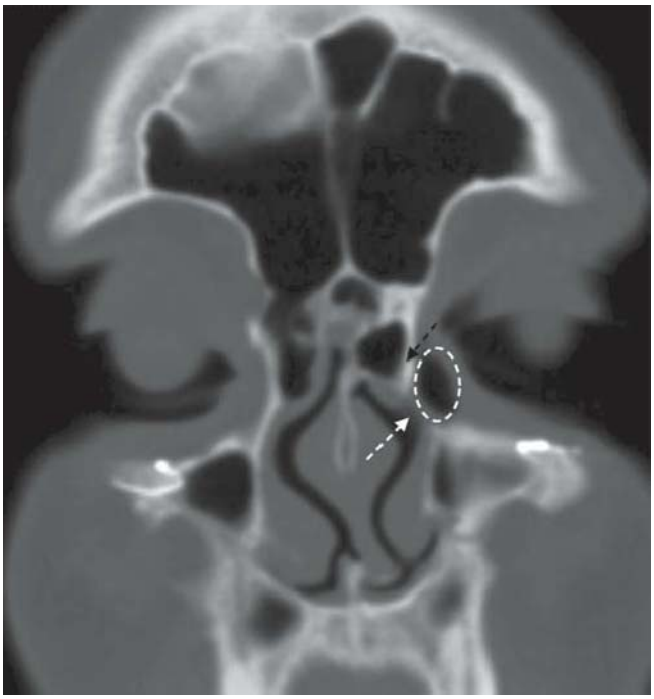


Figure 43.8 Failed left DCR. Coronal bone-window CT shows that the lacrimal sac (white dotted oval) has inadequate bone excision, creating a small inferomedial fistula (*white arrow*). The *black arrow* highlights a large segment of bone making up the lateral wall of the agger nasi cell that when removed at revision surgery cured the patient's symptoms.

A properly placed tube will place no tension on the puncta but not drift on to the cornea. Another common reason for surgical failure and need for revision is inadequate bony removal. As seen in Fig. 43.8, the previous surgeon has removed only a small portion of the bone inferomedial to the sac. This results in a chronic fluid meniscus due to a so-called sump-syndrome and lacrimal pump failure due to increased system resistance. Good outcomes in DCR mandate complete bone removal medial to the lacrimal sac and saucerization of the surrounding bone to allow the lacrimal sac flaps to lay open when marsupialized.

Revisions

Revision DCR is unchanged from the primary technique. However, attention must be paid to the sac available for marsupialization. Prior surgeons may have inadequately opened the existing sac leading to the symptomatic failure, where the ample remaining mucosa makes the revision quite simple. Outcomes in this circumstance are expected to be similar to primary DCR. If however, the available sac is highly scarred or small, outcomes will be compromised. Free mucosal grafts circumferentially covering damaged mucosa around the common internal punctum have been described to encourage primary wound healing. These can be placed as a free graft strung along the silicone tubes into the nose at the completion of surgery and placed under the gelfoam, which will hold it in place (20). Overall outcomes of revision endoscopic DCR tend to still be quite good regardless of sac configuration with 89% success rates reported (19,21).

Conjunctivodacryocystorhinostomy

Epiphora due to obstruction or loss of the canalicular system can be particularly challenging to treat. Causes include trauma, tumors, surgery, chronic inflammation, herpetic disease, topical medications, and chemotherapeutic agents (e.g., Docetaxol). Depending on the level and severity of obstruction, punctal/canalicular probing, dilation, trephination, reconstruction, or intubation have widely variable but often disappointing results. CDCR is considered by most surgeons a last resort, but in many cases can effectively reestablish lacrimal outflow.

The CDCR procedure bypasses the entire normal lacrimal outflow system by creating a direct communication between the medial tear lake and the nose using a Pyrex (Jones) tube (Gunther-Weiss Scientific Glassblowing, Portland, OR). It can be performed following failed external or internal DCR, or in conjunction with a primary DCR. Although the Jones tube can be placed without creating a formal DCR ostium (as described below), many surgeons feel that the presence of an ostium improves the chances for long-term success. After infiltrating the caruncle of the affected eye and the ipsilateral nasal mucosa with 2% lidocaine with 1:100,000 epinephrine, the caruncle is partially or completely excised to create room for the flange of the Jones tube. A Henderson guide needle is then placed through the medial fornix and directed in an inferomedial direction into the nose under endoscopic visualization, or under direct visualization if a primary external DCR is also being performed. Ideally, the needle should enter the nose anterior to the middle turbinate. Once the proper guide needle position has been established, a Henderson trephine is passed over the needle to widen the tract. The trephine itself can be placed into an optimal position in the nose, with the tip sufficiently past the lateral nasal wall but well clear of the septum, and measured at this point to determine the length of the Jones tube. Additional endonasal procedures such as septoplasty or partial turbinectomy may be indicated to ensure that the distal end of the Jones tube does not become obstructed. The trephine is withdrawn and the appropriately selected Jones tube is passed over the guide wire into the nose. Various design modifications of the Jones tube are available, such as frosting, Medpor coating, angling, multiple flanges, and suture holes, all with the intent of decreasing the risk of postoperative tube migration. With the Jones tube in position, a drop of irrigation solution is placed within the medial fornix, which should be observed to quickly disappear through the Jones tube.

Postoperatively, the patient is instructed to daily place tears within the medial fornix and sniff. While a functioning Jones tube can work extremely well, the long-term

propensity for occlusion or migration can make postoperative management a chore for many individual patients and their surgeons.

ORBITAL DECOMPRESSION (22)

Background

Orbital decompression had been performed for over a century prior to the description in the 1950s by Walsh and Ogura (23) of a new technique that approached the medial wall and floor of the orbit through a Caldwell-Luc. The next major advancement occurred in the 1990s with introduction of endoscopic techniques when Kennedy (24) and Michel (25) independently described medial wall decompression. The improved exposure of the medial orbital apex with the endoscopic approach quickly made this the more popular approach for otolaryngologists.

Indications

Endoscopic orbital decompression is utilized to diminish pressure within the orbit and cause globe recession for Graves orbitopathy, retro-orbital hemorrhage, and orbital cellulitis/abscess. Specific indications include compressive optic neuropathy, exposure keratitis, or aesthetic concerns.

Dysthyroid orbitopathy resulting from Graves' disease-related inflammation of orbital contents is the most common reason to utilize orbital decompression. The orbital inflammation with Graves disease is due to a combination of T-cell infiltration and deposition of glycosaminoglycans in both the orbital fat and the extraocular muscles. The clinical presentation of dysthyroid orbitopathy is highly variable, with some patients manifesting primarily orbital fat expansion, while others suffer predominantly from extraocular muscle enlargement. The tendency is for the former to exhibit proptosis and exposure keratopathy, and the latter group strabismus and compressive optic neuropathy.

Dysthyroid orbitopathy develops in an acute stage with active inflammation over 18 months and then stabilizes through fibrosis into a chronic stage. It is preferable to perform surgery after the disease process has stabilized. Acute-stage manifestations can be treated medically with intravenous (IV), oral, injected steroids, orbital radiation, or immunomodulatory agents until the active orbitopathy stage resolves. However, vision-threatening complications that are unresponsive to medical therapy may necessitate surgery during the active phase. Surgical treatment of dysthyroid orbitopathy has been classically performed in a staged fashion, with orbital decompression performed first, followed by strabismus surgery, upper and/or lower lid recession, and blepharoplasty. The choice of decompression should be based upon the degree of proptosis and/or exposure keratopathy, and the presence of compressive optic neuropathy (Fig. 43.9).



Figure 43.9 8mm of proptosis reduction (before [**A**] and after [**B**]) was achieved with bilateral lateral orbital decompression and upper and lower lid recessions. This patient's results show the dramatic aesthetic improvement that can be achieved with this procedure.

Retrobulbar or orbital hemorrhage is generally a traumatic or iatrogenic complication that can result in vision-threatening orbital compartment syndrome. Orbital decompression can be utilized if initial lateral canthotomy and cantholysis do not effectively decrease intraorbital pressures. If enophthalmos develops, delayed floor or medial wall reconstruction can be performed after hematoma resolution.

Orbital cellulitis can require decompression if medical management doesn't adequately control orbital pressures. Since orbital cellulitis typically results as a complication of acute sinusitis, total sphenoethmoidectomy performed prior to endoscopic decompression will generally resolve the underlying disease process as well. Due to active inflammation, these cases tend to have extremely poor surgical fields heightening their difficulty. Periorbital abscesses unresponsive to medical management benefit from localized orbital decompression to drain the purulence (Fig. 10). This procedure is made fairly simple with the use of image guidance, a malleable suction freer, and a neuropatty to dissect between the periorbita and orbit (Fig. 43.11).

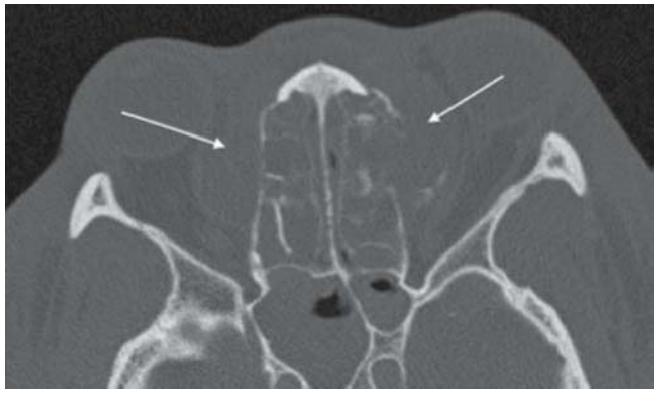


Figure 43.10 Axial bone-window CT showing bilateral retrobulbar hematomas (*arrows*) caused by blunt trauma. Note the associated lamina papyracea fractures and bilateral proptosis.

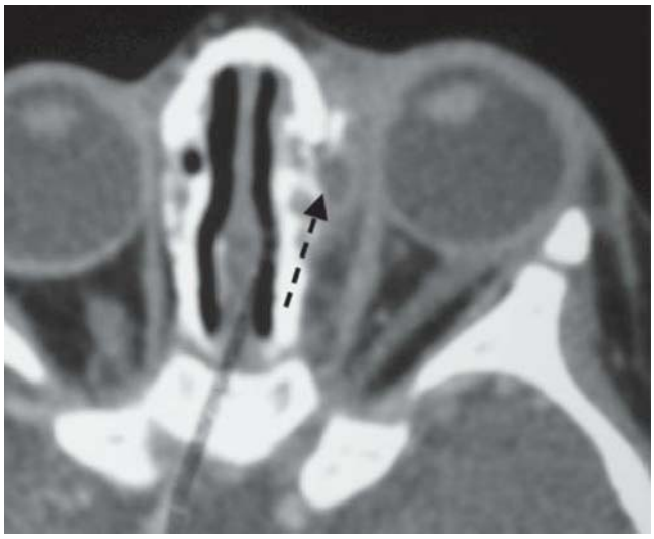


Figure 43.11 Axial contrast-enhanced CT of a child with left ethmoid sinusitis resulting in periorbital cellulitis and orbital subperiosteal abscess (*arrow*).

TYPES OF DECOMPRESSIONS

Medial

The true medial wall of the orbit consists of the lamina papyracea, a paper-thin portion of the ethmoid bone. Removal of this bone is accomplished either through a transnasal endoscopic approach, transcaruncular, medial lid crease, or Lynch incision. Some rhinologists consider isolated removal of the lamina papyracea inadequate and additionally remove the orbital floor medial to the infraorbital nerve. Although this is commonly termed "medial wall decompression" in our literature, the removal of the floor component technically makes this a hybrid procedure. Confusion around these descriptions makes it imperative that rhinology and oculoplastic teams preoperatively discuss common surgical expectations. Both procedures require a total ethmoidectomy and wide maxillary antrostomy to prevent postoperative obstructive sinusitis and allow greatest possible medial decompression into the nose (Fig. 43.12). Modifications of this technique exist that selectively decompresses the posterior orbit for isolated optic neuropathy (26).

Lateral

Lateral orbital decompression includes removal of the greater wing of the sphenoid bone via either a lateral canthotomy, lateral lid crease, or extended lateral canthal incision. Lateral decompression can be used either alone or in conjunction with a medial decompression to provide a "balanced" decompression. Studies suggest a lower rate of diplopia with this procedure while achieving similar or even greater amounts of recession compared to medial floor/medial wall removal (27–29). The lower rates of postoperative new-onset diplopia are thought to be due to preservation of natural vectors of globe movement by allowing the orbital contents to spill over the orbital confines in a balanced medial and lateral fashion (Fig. 43.13). Although medial decompression has traditionally been advocated as the surgery of choice for thyroid-related compressive optic neuropathy, lateral decompression has also been shown to be efficacious for this condition (30).

Floor (Posterior/Anterior)

The orbital floor is accessible through endoscopic, transantral, and translid approaches and historically was the workhorse of decompression until supplanted by medial and

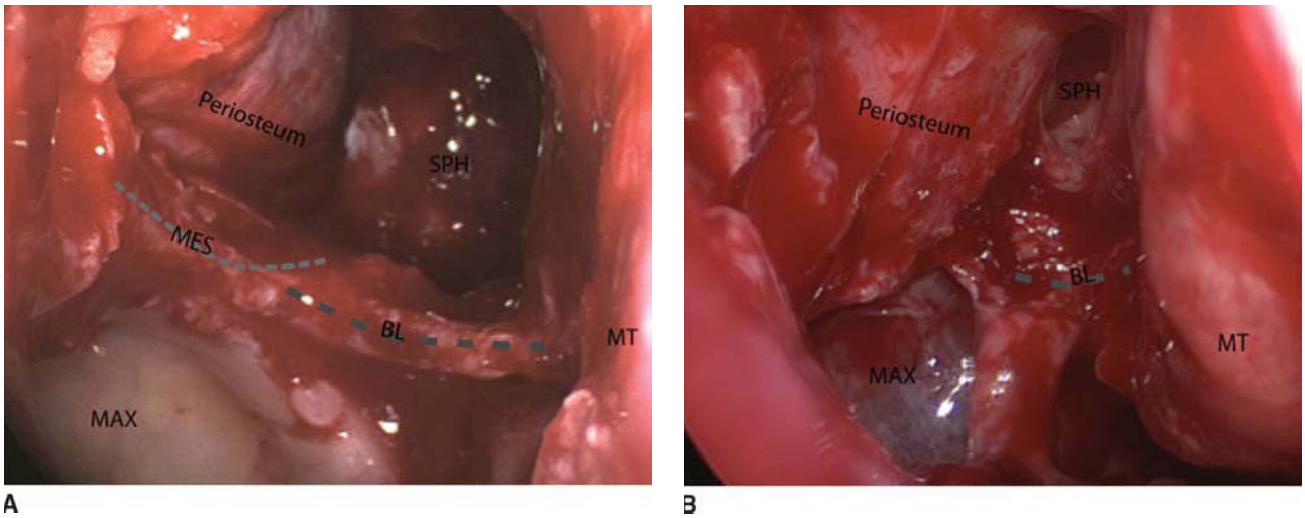


Figure 43.12 Right endoscopic view after **(A)** isolated medial wall and **(B)** medial/floor decompression. Note the increased exposure of the orbital periosteum in **(B)** due to removal of the maxilloethmoid suture (MES) and orbital floor lateral to V2. View includes maxillary (MAX) and sphenoid (SPH) sinuses as well as the middle turbinate (MT) and the base of the basal lamella (BL).

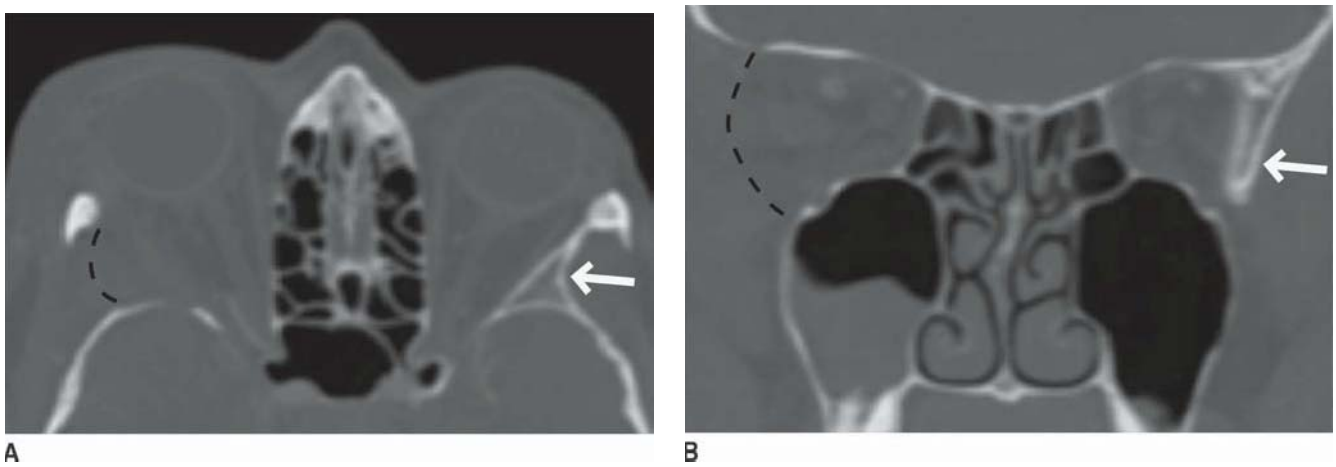


Figure 43.13 Postoperative axial **(A)** and coronal **(B)** bone-window CT of a right lateral wall decompression. The *white arrow* marks the intact bone whereas the black dotted lines show the edge of the orbital contents that have herniated through the decompression defect.

lateral options. Currently, it is rarely utilized as a standalone procedure due to its propensity to cause hypoglobus and enophthalmos. The portion of the orbital floor that typically is removed is that component medial to the infraorbital groove. In extreme cases, highly aggressive floor removal also can include the segment lateral to the infraorbital nerve, but this inevitably places the function of the nerve at risk. The medial floor component should additionally be distinguished into a posterior and anterior segment. Posterior segment removal is performed specifically for treatment of optic neuropathy from apex congestion and increases the radial arc of bone removed from 66 degrees with isolated lamina papyracea removal to 117 degrees when adding the floor component (unpublished data). This increased bone removal has been shown to be advantageous for optic nerve decompression in Graves disease (26). The anterior floor segment is removed to create globe recession for the purpose of addressing proptosis (Fig. 43.14).

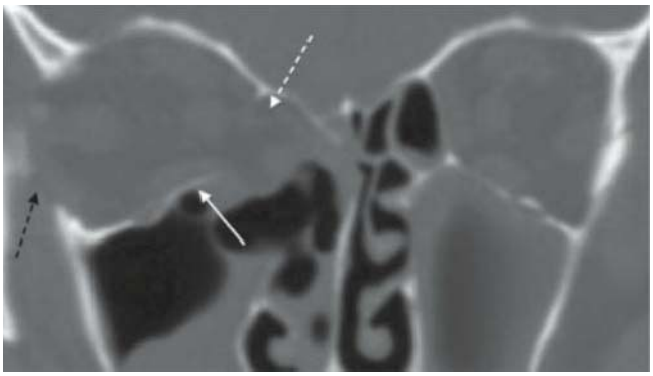


Figure 43.14 Postoperative coronal bone-window CT shows balanced orbital decompression. The lateral wall (*black dotted arrow*) and medial wall (*white dotted arrow*) decompressions have resulted in significant herniation of orbital contents. The orbital floor has been preserved in this example (*white solid arrow*).

Superior

Decompression of the orbital roof is only performed in the most recalcitrant cases requiring additional decompression after three-wall decompression has failed. Superior orbital decompression is performed through a frontal craniotomy with elevation of the frontal lobe in conjunction with a neurosurgical team. Severe complications have been reported including intracranial hemorrhage, frontal lobe trauma, meningitis, and pulsatile proptosis (28,31–33).

Fat

Through transconjunctival or other orbitotomy approaches, selective fat removal of the anterior orbit can be accomplished to achieve additional decompression in order to "fine-tune" a result.

Orbital Approaches for Endoscopic Access

Endoscopic Transnasal

Typical preparations for functional endoscopic sinus surgery (FESS) can be utilized for this approach; however, an ophthalmologic prep solution (5% Betadine paint) is required for the face to protect the cornea. Lacrilube or other hydration of the cornea must additionally be accomplished throughout the case. An "approach septoplasty" is helpful in all orbital surgery. As described by Wormald (40), this targeted submucosal resection removes the high cartilaginous and bony septum to improve access to the axilla of the middle turbinate. Access septoplasty is performed in over 70% of DCR cases (19) as it creates potential space in the anterior nasal cavity to accommodate additional space for endoscope movement, which is advantageous for anterior orbital inspection.

Maxillary Trephination

A canine fossa trephination (CFT) provides an alternative vector for approaching the anterior orbital floor. The procedure has been described in detail (40), but concern for Caldwell-Luc type chronic postoperative complications shrouds the wide acceptance of this procedure. To address this concern, Singhal et al. studied the procedure noting that 40% of patients undergoing CFT develop postoperative symptoms including facial tingling/numbness/pain, cheek pain/swelling, teeth numbness, and gingival problems. The immediate severity of these complaints can be quite high, but resolve quickly and do not require treatment. By 3 months after surgery, only 5% of patients have ongoing minimal symptoms, which in this large series included two patients with very mild paresthesias (41).

Transcaruncular

This minimally invasive approach avoids skin incisions while allowing extensive medial orbital exposure. It was originally described as a direct approach for repairing medial orbital fractures (42). The approach is worthy of mention as it has been utilized with increasing frequency in conjunction with endoscopic rhinologic approaches to the posterior-medial orbit while avoiding ethmoid dissection. This can be especially useful as a hidden approach to the anterior ethmoid neurovascular foramen. Additionally, the approach is extremely useful for repairs of orbital defects prior to drilling near the orbit (Fig. 43.15), thereby minimizing the risk of winding orbital tissue around a drill.

The caruncle is an ectodermal structure that lies just lateral to the medial commissure and contains adnexal skin structures covered by nonkeratinized stratified squamous epithelium. The approach can be made as a vertical incision, either directly through the caruncle or between the caruncle and adjacent plica semilunaris. Blunt dissection is carried posteromedially to the posterior lacrimal crest. Sharp incision then opens the periorbita allowing lateral retraction of intact periorbita. It is common for the periorbita to be weak and fat to herniate into the field during this procedure, necessitating the use of numerous malleable retractors. Measurement of 24 mm from posterior lacrimal crest to the anterior ethmoid artery is useful for verification of the correct foramen.

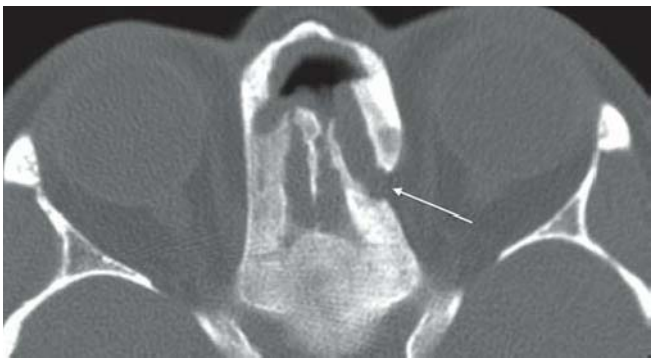


Figure 43.15 Axial bone-window CT from a patient who required extensive drilling on the skull base for fibrous dysplasia. There is a large left orbital dehiscence (*arrow*). Temporary placement of a medial orbital wall implant during surgery will protect the orbital contents from such injury.

Endoscopic Orbital Decompression

A wide maxillary antrostomy and total sphenoethmoidectomy with a complete frontal dissection precedes the start of the procedure (Fig. 43.16). It is helpful to widen the sphenoid ostium to have excellent visualization of the thickened lateral prominence also known as the optic tubercle. This bone corresponds to the medial attachment of the annulus of Zinn. The maxillary ostium should have the widest possible diameter to prevent postdecompressed herniated orbital fat from obstructing the neo-ostium. A middle turbinectomy is reported to be beneficial (22) to accommodate additional herniated fat from medial decompression. The procedure is begun by removing the lamina papyracea in its entirety with a Freer elevator. A 1 cm portion of lamina is left at the base of the frontal ostium to prevent herniating fat from creating postobstructive frontal sinusitis. The range of decompression that can be accomplished endoscopically varies from medial wall decompression to removal of the medial wall and medial orbital floor (to the infraorbital groove). If working with an ophthalmologist, it is imperative to have similar preoperative expectations of what bone is to be removed as "balanced" decompression may be interpreted as strictly ethmoid bone removal (no floor component). Once the bone is removed, periorbita will be exposed holding back orbital fat from obscuring endoscopic view. Due to the tendency of herniating fat to obscure endoscopic visualization, periorbita must be incised from a posterior to anterior direction. A 1-cm strip of periorbital "sling" left over the medial rectus is reported to minimize postoperative diplopia (22,39). The ipsilateral eye is then repeatedly compressed to encourage additional medial herniation of fat. The process can be encouraged by use of a ball probe to break up small fascial bands holding the fat together. Care must be taken to not damage the medial rectus during this process if employed. Consensus differs on the order of wall removal in balanced decompression and likely is irrelevant since both are removed safely as isolated procedures.

Perioperative care includes antibiotics, steroid taper, and low-pressure irrigations. No packing should be used after these cases for fear of artificially increasing intraorbital pressures with either the packing itself or development of a loculated hematoma lateral to the packing (22).

Surgical Risks

The main surgical risk from orbital decompression as documented by numerous publications is new onset diplopia. The incidence of this appears to vary dramatically

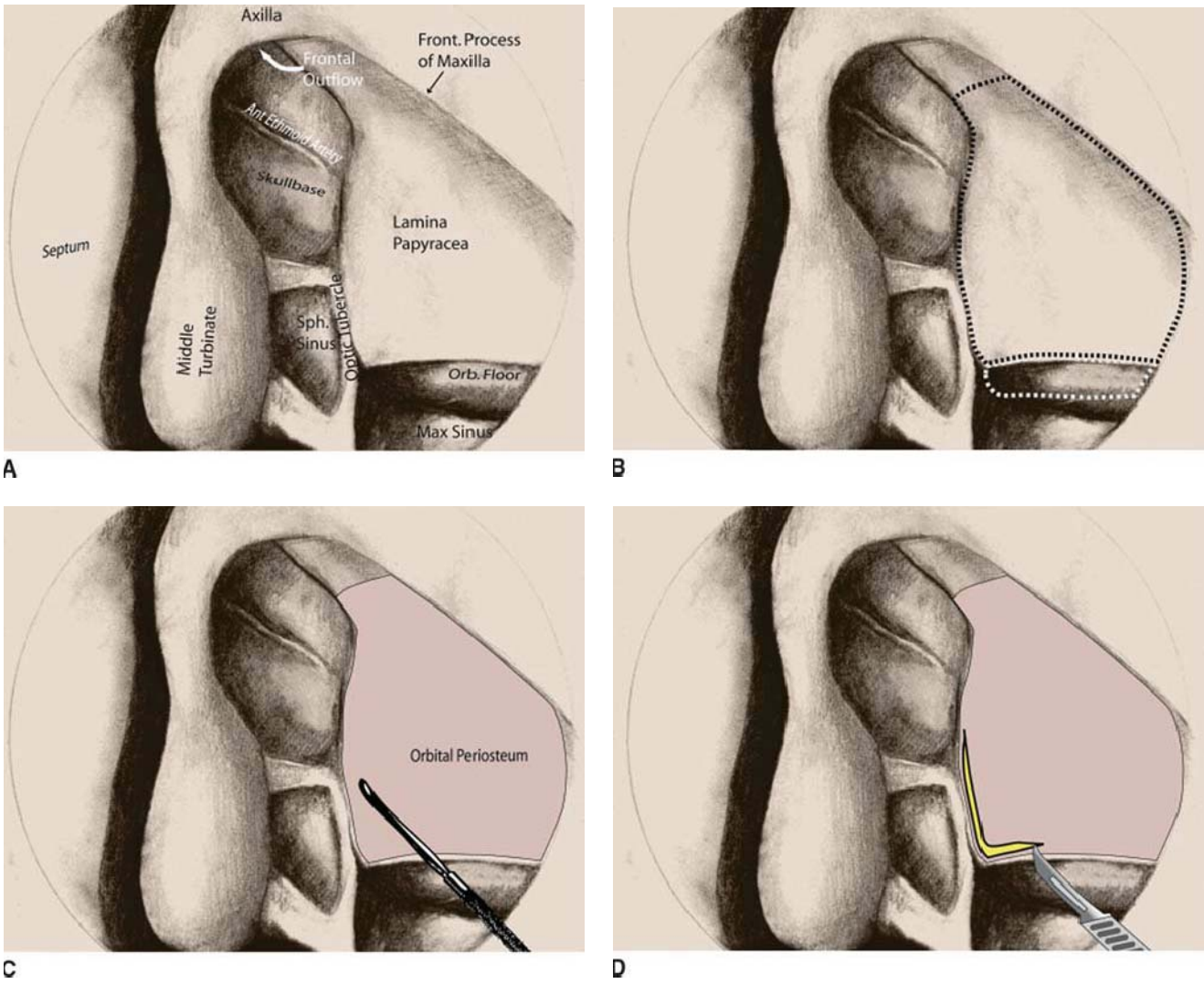


Figure 43.16 Left middle meatus diagram after full house FESS. All major structures are annotated in **(A)**. In **(B)**, *black dotted lines* denote the bone to be removed for a strict medial wall decompression, sparing 1 cm of bone to protect the frontal outflow tract from obstruction. The white dotted line is the floor component that can be removed medial to V2. In **(C)**, orbital periosteum has been exposed in preparation for a medial wall decompression. Using a 12 blade, the periosteum is being incised and removed from posterior to anterior in **(D)**. The medial rectus is hidden just below a shallow layer of fat, so extreme care is required for this maneuver. Artist acknowledgment: Andria M. Caruso, MD.

depending on technique (Table 43.2). Many patients have diplopia as a result of Graves orbitopathy, and there is an additional risk that this diplopia will not be improved by the surgery. Patients with diplopia will frequently require further strabismus surgery for this problematic complication (22). Less than 5% of patients will experience deterioration in vision from orbital decompression. Additional risks include postoperative epistaxis, which should be managed with bipolar suction, and new onset frontal or maxillary ostial obstruction from herniated fat. Maxillary obstruction requires further ostial enlargement with either maxillary antrostomy or mega-antrostomy. Frontal obstruction (Fig. 43.17) generally requires frontal drill-out after temporary medial orbital implant placement to protect the orbital contents during surgery.

TABLE 43.2 LITERATURE COMPILATION OF COMMON OUTCOME MEASURES ASSOCIATED WITH ORBITAL DECOMPRESSION

Walls Removed	Recession (mm)	New Postop Diplopia
Lateral (30,34)	3.5–6.3	8%
Medial (30,35)	2.6–4.9	38%
Medial + Floor (36,37)	5	100%
Balanced, No Floor (36,38)	0–10	10–40%
Balanced + Floor (28,36)	3–10	0–29%
Balanced + Floor w/ Sling (39)	5.1	0%
Four Wall Removal (32)	10–17	N/A

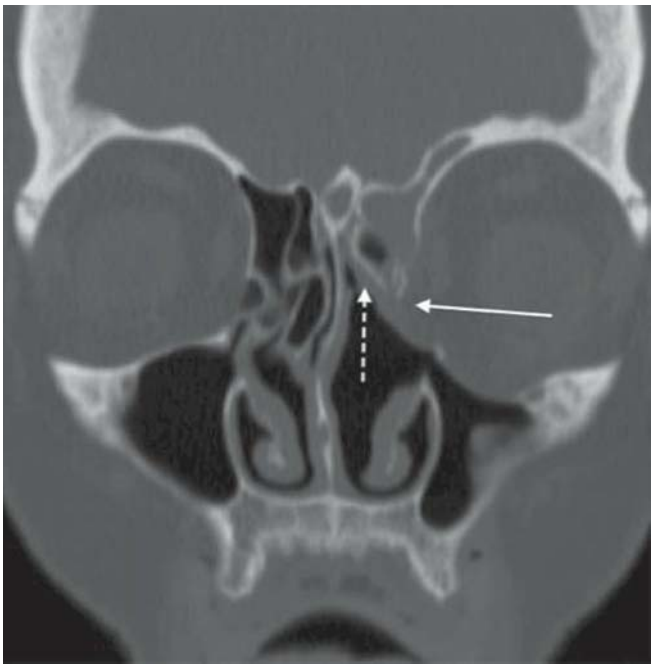


Figure 43.17 Coronal bone-window CT from a patient with Graves disease who has undergone left orbital decompression. Because the previous surgery did not include an adequate frontal dissection (*dashed arrow*) prior to the medial decompression, the herniated orbital fat (*solid arrow*) is now obstructing the frontal sinus.

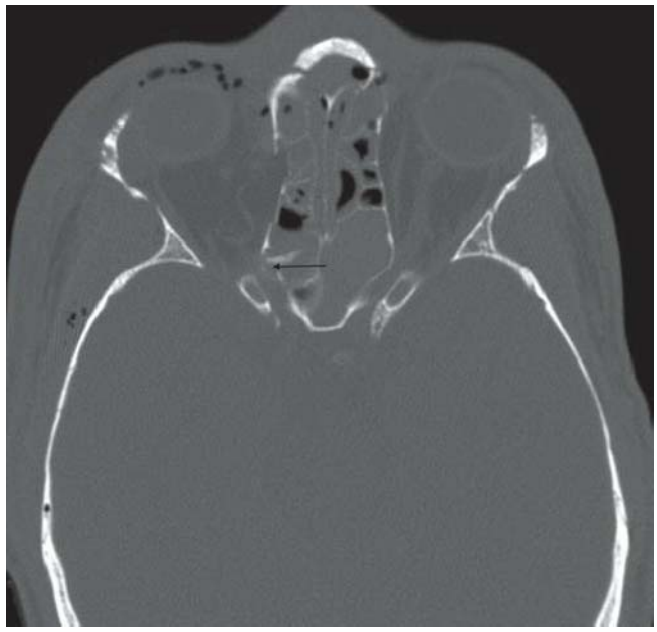


Figure 43.18 Caption: Axial bone-window CT of a patient who sustained blunt trauma to the right globe with a piñata stick. The trauma force was transmitted posteriorly, resulting in fracture of the optic canal (*arrow*). Visual acuity loss recalcitrant to high-dose steroids prompted optic nerve decompression.

OPTIC NERVE DECOMPRESSION

Background

Unlike the previous topics of discussion, optic nerve decompression is far more controversial. Due to the rarity of the need for such a procedure and the dire circumstances under which it is performed, there is limited and conflicting data to ascertain its value. The procedure is most often utilized under the diagnosis of traumatic optic neuropathy (TON) for which it has the most controversial indications. Specifically, a meta-analysis of low-quality evidence (43) gave opposite recommendations to the 1999 Optic Nerve Trauma Study (44) regarding the value of this procedure.

Accepted indications include the need to reduce excessive pressure on the edematous optic nerve from trauma (Fig. 43.18), pseudotumor cerebri, fibrous dysplasia, and compressive tumors. Endoscopic approaches appear to offer a more limited risk profile relative to intracranial decompressions due to reduced risk of CSF leak and elimination of the need to cut the falciform ligament and anterior clinoid process while achieving similar bony decompression throughout the optic canal (5). A temporizing measure that can be effective in acute traumatic settings where temporary nerve edema is causing compressive optic neuropathy is administration of high-dose methylprednisolone (30 mg/kg bolus) followed by a continuous infusion of 5.4 mg/kg/h given for 48 hours (22).

Patients may present with vague visual symptoms noting loss of color perception or peripheral vision prior to changes in visual acuity. Involvement of an ophthalmologist is mandatory for all cases of suspected optic neuropathy for definitive diagnosis (22). Measurement of ocular pressures, a high-quality ophthalmologic exam, and an orbital computed tomography (CT) are prerequisites to surgical therapy (22).

The position of the ophthalmic artery relative to the optic nerve is highly relevant to safe endoscopic surgery of the optic canal. Disruption of this artery will cause irreversible blindness. In the intracranial segment of CNII, the ophthalmic artery typically runs inferomedial to the nerve. However, in the optic canal, the ophthalmic artery will typically switch to an inferior position. This means that decompression with nerve sheath incision can be performed safely from a medial approach; however, the relationship of the artery to the nerve is highly variable along its length becoming more vulnerable as the surgery proceeds toward the intracranial segment (5).

Technique

A complete sphenoethmoidectomy provides adequate exposure for this procedure. The anterior face of the sphenoid should be removed as extensively as possible in a lateral direction over to the thickened bony ridge marking the posterior aspect of the orbit known as the optic tubercle (40). Using a diamond drill bit and irrigation, this bone and the bone along the optic canal is thinned

to egg-shell thickness. Care is taken to avoid damage to the internal carotid artery, which is most at risk inferior to the nerve at the opticocarotid recess. An elevator is used to remove bone starting on the posterior orbit about 1 cm anterior to the optic tubercle and working posteriorly until the entire medial portion of the optic canal is dehiscent.

At the conclusion of the procedure, a medial, longitudinally oriented nerve sheath incision may be performed. Again, quality evidence to support this incision is lacking with proponents suggesting improvement in visual outcomes due to release of compartment syndrome pressure on venous drainage and detractors citing increased risk of CSF leak with potential damage to nerve fascicles, pial vasculature, or the ophthalmic artery (45).

HIGHLIGHTS

- DCR by either the endoscopic or external approach with complete sac marsupialization is a highly successful treatment for epiphora due to obstructions of the lacrimal sac or duct.
- The lacrimal sac is located within the lacrimal fossa (anteriorly thick frontal process of the maxilla and thin posteriorly lacrimal bone) with a significant portion of the sac located above the axilla of the middle turbinate.
- New onset diplopia after orbital decompression is a common and troublesome complication that appears to be correlated to the technique of decompression.
- Complete ethmoidectomy and wide ostial enlargement of all sinuses with preservation of 1 cm of lamina papyracea around the frontal outflow tract minimizes risk of postobstructive sinusitis after orbital decompression.
- Optic nerve decompression is controversial in the setting of TON and should only be performed in consultation with an ophthalmologist.
- Endoscopic optic nerve decompression provides an ideal approach to the entire bony optic canal and minimizes risk of damage to the ophthalmic artery, which typically runs inferior to the nerve in the canal.

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44 Complications of Sinus Surgery

James A. Stankiewicz *Kevin C. Welch*

Risk is inherent with any surgical procedure. Fortunately, most surgeries performed to relieve sinus disorders are uncomplicated and result in high patient satisfaction. Complications resulting from sinus surgery can be divided into two categories: (a) intraoperative complications and (b) postoperative complications. Intraoperative complications can be devastating and include both vascular and neurologic injury, not the least of which includes catastrophic bleeding, visual loss, and cerebrospinal fluid (CSF) leaks with ascending meningitis. Postoperative complications are typically less severe and can be considered functional complications leading to poor long-term surgical outcomes, patient dissatisfaction, or need for revision sinus surgery. Despite intense preparation and experience, complications resulting from sinus surgery do occur. With early recognition, many complications can be controlled early and reversed.

Sinus surgery should never be considered routine; the surgeon must be thoroughly prepared prior to the operation and constantly alert, anticipating complications as the procedure ensures. It is important to understand the nature of these complications to increase awareness and prevention. This chapter reviews the relevant anatomy; discusses the complications of specific sinus procedures; and evaluates specific complications, pathophysiologic mechanisms, and management.

RELEVANT ANATOMY OF THE ORBIT

Soft Tissue and Bony Anatomy

A thorough understanding of sinonasal anatomy is crucial to performing safe and successful sinus surgery. It cannot be understated; however, that knowledge of the regional anatomy is critical to avoiding the complications discussed in this chapter. Orbital complications resulting from sinus surgery are fortunately rare, and this stems from understanding the relationship of the orbit and its internal structures with the sinuses themselves. The orbit comprises seven bones: maxilla, zygoma, frontal, lacrimal, sphenoid, palatine, and ethmoid. The seven bones together form a conical-shaped structure that is approximately 4 cm wide by 5 cm long. The contents of the orbit are divided into the anterior and posterior compartments, which are divided anatomically by the orbital septum and the globe. The orbital septum is the reflection of the periorbita into the tarsal plates. Separating the anterior and posterior eye chambers, the septum is tough and holds the orbital contents in place. To its detriment, the orbital septum also holds orbital effusions such as hemorrhage and infection within the orbit, preventing the fluid from passing directly into the preseptal space and instead allowing potentially dangerous increases in orbital pressure. The anterior compartment of the orbit contains the lids, orbital soft tissue, and the lacrimal apparatus. The posterior orbital compartment, or retrobulbar space, is subdivided into the intraconal and extraconal spaces, which are separated by a fascial sling that envelops the extraocular muscles.

The intraconal space contains the vital orbital structures, including the optic nerve, portions of the ophthalmic artery, branches of the ophthalmic artery (central retinal artery, long and short ciliary arteries, lacrimal artery, portions of the anterior ethmoidal artery, and the posterior ethmoidal artery), the ophthalmic veins, and orbital fat. The blood supply to the retina, chiefly the choroid choriocapillaris (outer half) and the central retinal artery and branches, lies within the intraconal space as well. The blood supply is protected by various compensatory mechanisms so that retinal blood flow is maintained even if the entire system is under stress.

The extraconal space can be subdivided into superior, inferior, medial, and lateral compartments. The superior extraconal space contains the levator muscle, supratrochlear and supraorbital nerves, the trochlear nerve, and the supraorbital artery. The lateral extraconal space is not as relevant in sinus surgery; however, it contains the lacrimal gland, the lacrimal neurovascular structures, and fat. The inferior extraconal

space contains fat and the infraorbital nerve and vessels. The medial extraconal space is the most relevant space in sinus surgery and contains a plethora of vascular structures: distal portions of the posterior ethmoidal artery, the distal portion of the ophthalmic artery, and the anterior ethmoidal artery as well as fat. Of extreme importance is the relationship of the ophthalmic artery and the anterior ethmoidal artery. The ophthalmic artery courses anteriorly in the extraconal space just inferior to the superior oblique muscle before giving rise to the anterior ethmoidal artery near the anterior ethmoidal foramen along the medial orbital wall. Radiographically, this is best identified in the coronal plane along the convergence of the medial rectus muscle and the superior oblique muscle (Fig. 44.1). In approximately 10% of cases, this neurovascular bundle can be suspended from the anterior ethmoid skull base in a bony mesentery, often associated with a supraorbital ethmoid air cell (1). Considering the *limen nasi* as a fixed landmark, the artery is located approximately 55 degrees from the nasal floor and at 50 mm.

Superficial to the orbital fat in the extraconal space is the orbital periosteum, or periorbita. The periorbita is tough and fibrous but can be elevated easily except at the suture lines, where it passes through to fuse with the periosteum on the opposite side. Medial to the periorbita is the *lamina papyracea* of the ethmoid bone, which is paper thin and is easily susceptible to injury during sinus surgery. The *lamina papyracea* is the lateral-most extent of the ethmoid sinuses. Finding the *lamina papyracea* is essential to preventing orbital complications. The orbit and the paranasal sinuses are intimately related on three sides.

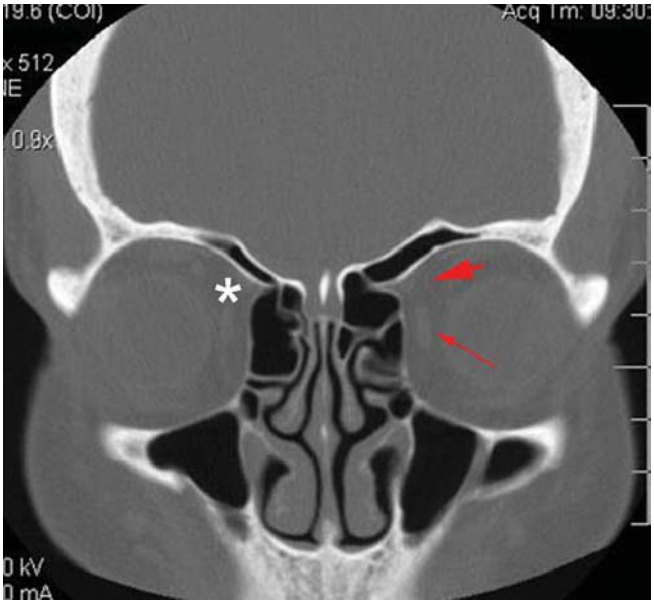


Figure 44.1 A coronal CT of the paranasal sinuses featuring the location of the anterior ethmoidal artery (*asterisk*) near the convergence of the medial rectus (*arrow*) and superior oblique (*arrowhead*) muscles. Note that in this patient, the anterior ethmoidal artery (*asterisk*) is located within a bony mesentery, suspended from the skull base.

Posteriorly, the orbit converges and permits passage of neurovascular structures through the superior orbital fissure, the inferior orbital fissure, and the optic canal. Through the optic canal traverses the optic nerve and ophthalmic artery, as well as various vasa nervosa that supply the optic nerve itself. Posteriorly, this optic canal narrows and can form an indentation in the sphenoid sinus at the junction of the cavernous carotid artery known as the opticocarotid recess (Fig. 44.2), which anatomically relates to the anterior clinoid process of the sphenoid bone. This region is notable for dehiscence of the carotid artery and optic nerve, which can occur in 4% to 22% (2–5) and 4% to 8% (3,5) of cases, respectively.

Practical Application of Orbital Anatomy

The lamina is curved and gives way superiorly to the supraorbital ethmoidal cells and inferiorly to the maxillary sinus. It is important to define the lamina surgically when working in the ethmoid and maxillary sinuses to avoid entrance into the orbit via compromise of the *lamina papyracea* and periorbita and injuring the vasculature or musculature. It is appropriate to stay near the superior part of the inferior turbinate when making a middle meatal antrostomy and to not open the true ostium any more anteriorly than the anterior end of the middle turbinate. Specifically, the true ostium of the maxillary sinus is situated along the inferior half of the maxillary line in 94% of specimens and *just* inferior to the mid-point of the maxillary line in 60% of cases (Fig. 44.3). The os is obliquely oriented and less than 5 mm posterior to the lacrimal duct. Dissecting anterior to the true ostium only encounters the blind bony pouch of the infundibulum and does not provide any additional functional improvement in maxillary sinus mucociliary clearance. Moreover, dissection more anteriorly than this places the lacrimal duct at risk of injury. After the antrostomy is made, the inferolateral aspect of the *lamina papyracea* can be identified superior to the ostia and if the opening is large enough, the floor of the orbit can be identified as well. Proceeding through the maxillary os in a lateral or superolateral direction will likely result in injury to the orbit; therefore, once the os is identified, entry in the maxillary sinus is performed in an inferolateral direction to safely avoid the *lamina papyracea*.

The structures of the orbit viewed through an endoscope appear different on the right and left sides (6). The actual right nasal and meatal structures lie visually straight back. On the left, the ethmoid sinuses are actually more medial in location, especially anteriorly and superiorly. Because of altered perception, a *right-handed* surgeon operating on the left side who takes the same straight-back approach as on the right, especially during an endoscopic procedure, contacts *lamina papyracea* and enters the orbit, particularly in the superior and lateral orbit area. It is important to stay in the medial aspect against the middle turbinate. See Table 44.1 for a tabulation of important orbital anatomy.

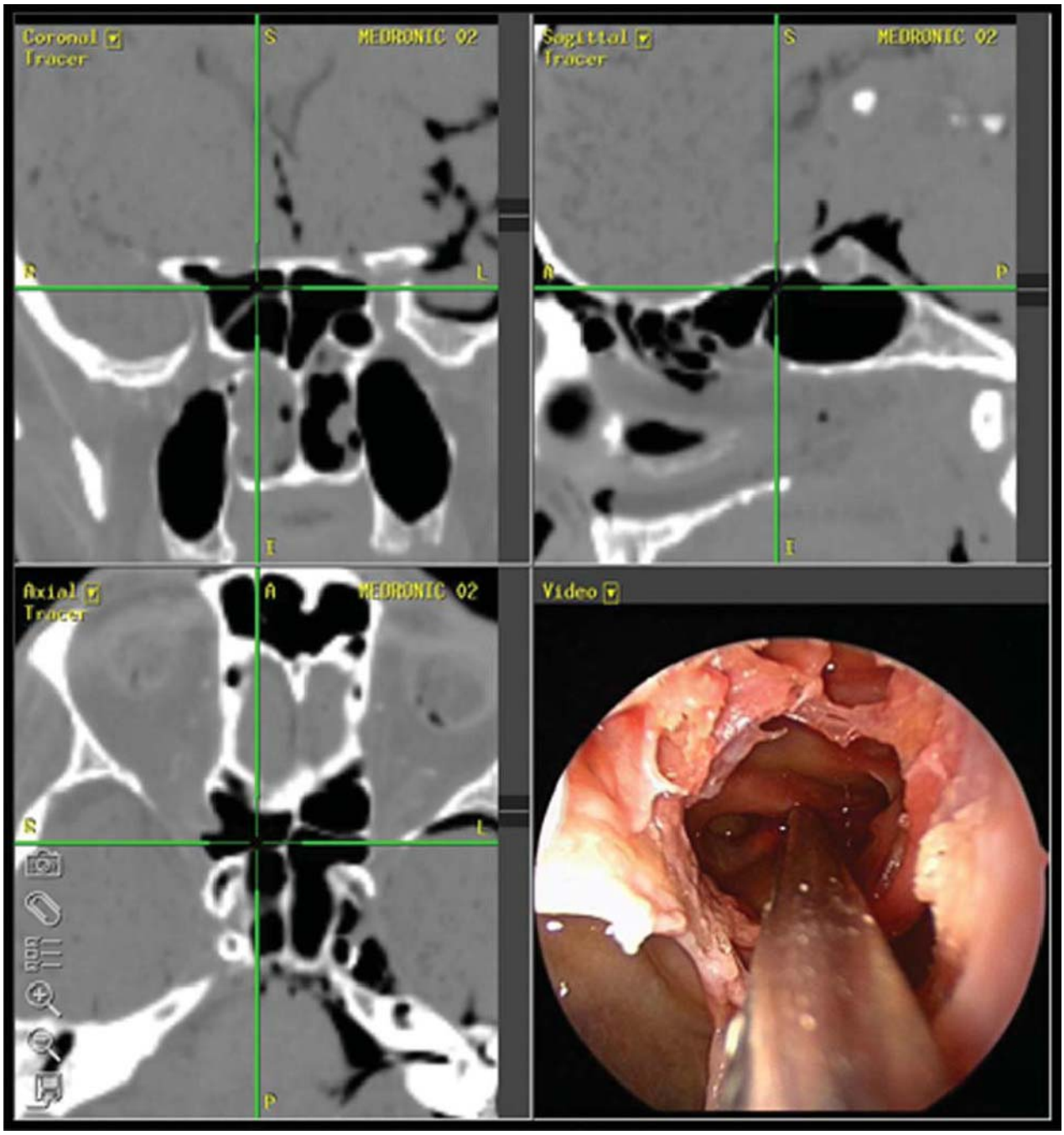


Figure 44.2 Triplanar images of an endoscopic dissection performed on a cadaver. The probe is pointing to the location of the opticocarotid recess where the carotid artery and the optic nerve are prominent within an Onodi (sphenoethmoid) cell.

RELEVANT ANATOMY OF THE ANTERIOR SKULL BASE

Bony Anatomy

The surgeon should be aware that the skull base slopes downward beginning at the frontal recess and terminating at the *planum sphenoidale* (Fig. 44.4). It is a mistake to assume that this slope is both smooth and two-dimensional. Anteriorly, the skull base is variable in structure as described by Keros (7), as the ethmoid roof (a.k.a. *fovea ethmoidalis*) is generally higher laterally than it is medially where the cribriform plate is identified. The anterior ethmoidal artery can pierce the cribriform plate and even be intracranial as it travels medially toward the septum. The bone at this point is 10 times thinner than in other areas of the cribriform plate and thus can be easily violated. Surgeons need to beware of a low skull base or cribriform plate, as found at computed tomography (CT).

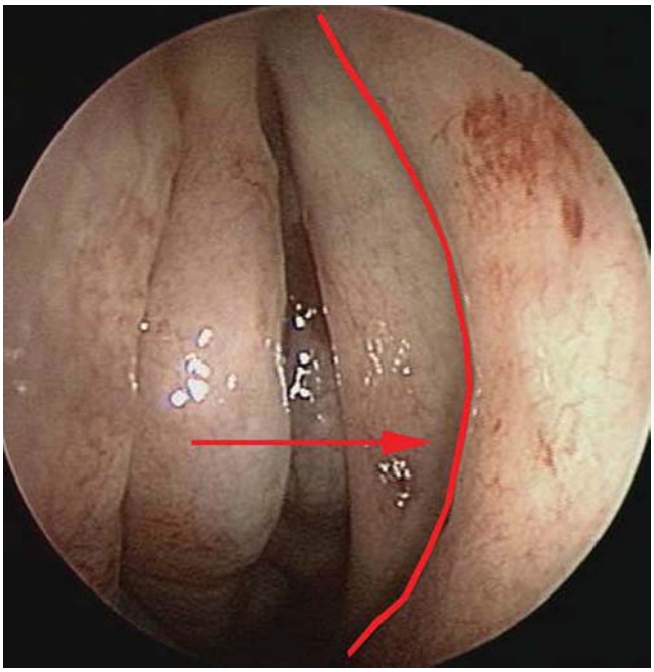


Figure 44.3 An endoscopic view of the middle meatus. The middle turbinate is medialized. A curvilinear line can be imagined at the junction of the uncinate process and the lacrimal bone. The maxillary sinus ostium (*arrow*) is located (in two-thirds of cases) at the junction of the inferior one-third and the superior two-thirds of this line.

TABLE 44.1 SUMMARY OF IMPORTANT ANATOMIC RELATIONS

- The *lamina papyracea* is superior to and just lateral to the natural ostium of the maxillary sinus.
- Ethmoid dissection is performed lateral to the middle turbinate, never medial or superior.
- The maxillary antrostomy is performed just superior to the inferior turbinate with the surgical instrument lying on top of the inferior turbinate.
- The maxillary antrostomy should not be more anterior than the anterior end of the middle turbinate. A backbiter is used to incise the uncinate process and create an "uncinate window." The natural ostium of the maxillary sinus is in the lower half of the infundibulum behind the uncinate process.
- The maxillary antrostomy is at the level of the inferior orbital rim.
- The frontal recess lies at 6–6.5 cm from the *limen nasi*.
- In adults, the anterior ethmoidal artery and base of the skull (posterosuperior *fovea ethmoidalis*) are 6 cm from the nasal opening or 5.5 cm from the *limen nasi*.
- In adults, the sphenoid sinus ostium is 7 cm from the nasal opening.
- In adults, the basal lamella of the middle turbinate is 6 cm from the nasal opening (posterior ethmoid bones lie behind this).
- The nasopharyngeal wall approximates the posterior sphenoid wall to within 1 cm.
- The surgeon should identify and cannulate the sphenoid ostium, if possible. The superior turbinate is the gateway to the sphenoid sinus since the ostium is just medial to the vertical midline of the superior turbinate. The ostium lies one-third of the way up the anterior wall from the choana just next to the septum.
- If the middle turbinate must be removed, the surgeon should remove only the inferior or anterior part of the turbinate and preserve the superior part as an anatomic landmark.

Two excellent articles relating to anatomic variations on CT scanning important to the sinus surgeon describe and enhance this anatomic discussion and are highly recommended (8,9). As the skull base transitions posteriorly to meet the *planum sphenoidale*, the ethmoid roof can be identified at the same level as the cribriform plate.

The sphenoid sinus is the key to identifying the skull base. The sphenoid sinus is bounded anteriorly and superiorly by the sphenoid crest, which articulates with the perpendicular plate of the ethmoid bone. Inferiorly and anteriorly, the sphenoid bone converges into the rostrum, which articulates with the vomer of the septum. Lateral to the sphenoid crest are the two sphenoid ostia, both of which measure approximately 2mm in dimension. Each ostium is located approximately 15-20mm above the choanal arch. The ostia are the anatomic keys to the skull base. These ostia can be obstructed by posterior ethmoidal disease making them difficult to directly visualize. However, a beaded probe or image-guidance probe placed onto the sphenoid ostium safely identifies the appropriate area for opening into the sphenoid sinus, which is anatomically inferior and medial. The sphenoid ostium can be approached in a position medial to the middle turbinate (transethmoid) or approached laterally in a plane between the superior turbinate and the septum, just superior to the choanal bridge (transnasal). The superior turbinate is a well-established landmark for the ostium of the sphenoid sinus since it is typically medial to the lower one-third to one-half of the superior turbinate. Viewed in an axial plane, the anterior wall of the sphenoid sinus approximates the posterior wall of the maxillary sinus. The only intervening anatomic structure is the pterygopalatine fossa, which is thin and permits the sphenopalatine artery and it branches to enter the sinonasal cavity. The anterior aspect of the sphenoid bone usually is extremely thin, but thickens both medially near the rostrum and sphenoid crest and laterally near the orbital apex. If resistance is felt, the bone should not be penetrated blindly, rather entered cautiously with a drill or other instrument after the anatomy is confirmed radiographically. The posterior ethmoidal cells can be opened in a medial direction through the posterior middle turbinate to allow visualization of the sphenoid ostium, which safely identifies the lateral aspect of the sphenoid and posterior ethmoidal cells that can be penetrated.

Anterior to the planum sphenoidale, the bone transitions into the cribriform plate, the lateral cribriform lamella, and the *fovea ethmoidalis* (ethmoid roof). This anatomy is best considered in the coronal plane despite its

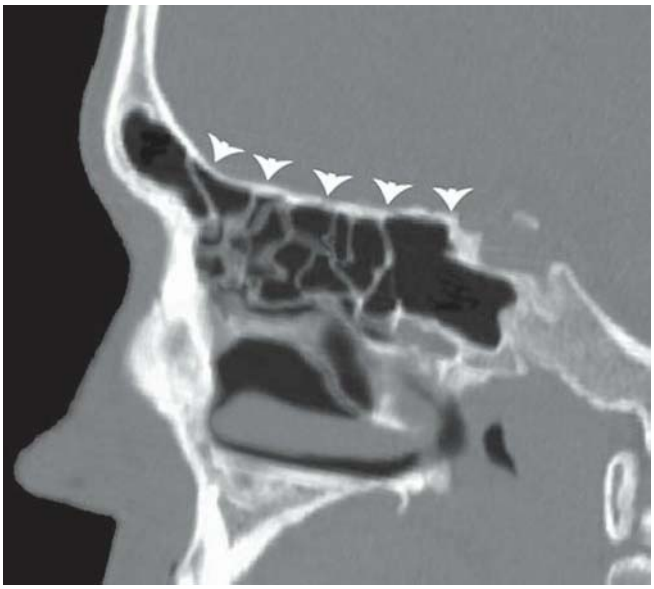


Figure 44.4 A sagittal reconstruction of the paranasal sinuses and anterior skull base. Note that the skull base (*arrowheads*) slopes in a downward fashion starting at the frontal recess and terminates at the *planum sphenoidale* (sphenoid roof). It is important to note this when operating within the posterior ethmoid sinuses.

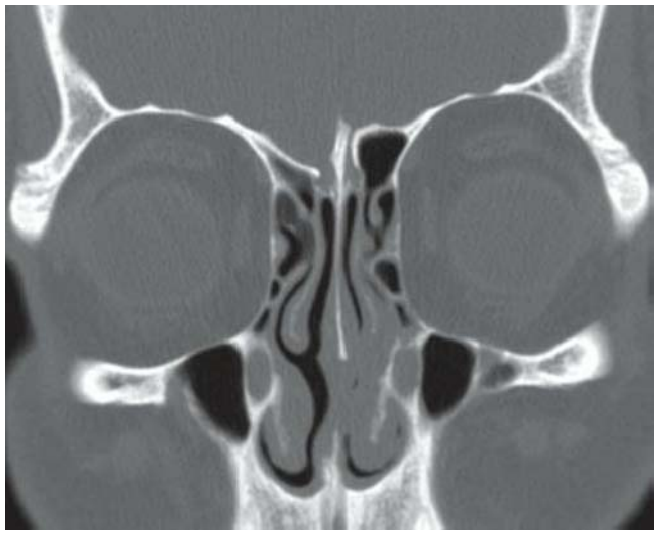


Figure 44.5 A coronal CT of the paranasal sinuses and anterior skull base. Keros categorized three types of skull base anatomy based on the length of the lateral lamella. However, the length of the lateral lamella may be different on each side. Therefore, the surgeon should always note any asymmetry in the skull base anatomy.

three-dimensional variance. The cribriform plate represents the lowest midline structure in the medial aspect of the nasal vault. The lateral mass of the ethmoid is suspended from the *fovea ethmoidalis* or ethmoid roof. Intervening between the ethmoid roof and cribriform plate is the lateral cribriform lamella, or simply lateral lamella. The length of the lateral lamella (and hence the depth of the cribriform plate) was noted by Keros (7) in several anatomic dissections. Keros classified the anterior skull base depth based upon the length of the lateral lamella: 1 to 3 mm (type I), 4 to 7 mm (type II), and 8 to 16 mm (type III). The skull base may also be asymmetric in design (Fig. 44.5). Some (10) have shown that type II anatomy is encountered most frequently and that patients with a lower skull base depth (i.e., type I) have a lower incidence of skull base injury.

Suspended from the articulation of the lateral lamella and the cribriform plate is the sagittal attachment of the middle turbinate; therefore, it is clear that the middle turbinate is an important landmark. In addition to directing the surgeon to the transition between the cribriform and the lateral lamella, the anterior most portion of the middle turbinate marks the anterior limit of maxillary dissection, marks the medial-superior extent of the lacrimal sac, and is important in identifying the frontal recess. The sagittal portion of the middle turbinate transitions posteriorly as the (third) basal lamella and is visualized in coronal and horizontal planes. The basal lamella identifies the transition between the anterior and posterior ethmoidal sinuses, and the lower half of the middle turbinate and its insertion into the choana help to identify the entrance into the sphenoid sinus. These characteristics, not to mention its host of olfactory neurons, make the middle turbinate a structure worth preserving. However, turbinates that are mechanically obstructive, such as concha bullosa or those with significant polypoid degeneration, may need partial or total removal (Table 44.1).

Measuring the anatomic structures is important to avoiding complications. The distance from the nasal spine or nasal opening to the frontal recess is 6 cm, to the base of skull is 7 cm, and to the anterior wall of the sphenoid is 7 cm in adults of normal size. The nasopharyngeal wall approximates the back wall of the sphenoid sinus, usually to within 1 cm. The choanal bridge (just above the choana and below anterior wall sphenoid) is 7 cm. The basal lamella of the middle turbinate is 6 cm. In children, these dimensions are variable, and the surgeon needs to exercise caution. However, one can always find the distance to the sphenoid bone and the base of the skull by measuring the distance to the choanal bridge just above the choana (Fig. 44.6).

Practical Application of Skull Base Anatomy

The relationship between the maxillary and ethmoid sinuses should be examined in the coronal and sagittal planes on CT imaging prior to the start of surgery. In particular, the ratio of the posterior ethmoid to maxillary sinus height should be assessed. In patients with a vertical height ratio of 1:1 (maxillary sinus height to posterior ethmoid height) are less likely to incur skull base injury. However, in patients with a 2:1 or greater than 2:1 maxillary sinus height to posterior ethmoid height (Fig. 44.7), the posterior ethmoid skull base is encountered rather quickly due to the sloping nature of the skull base in this region. Inadvertent injury to the skull base may occur once

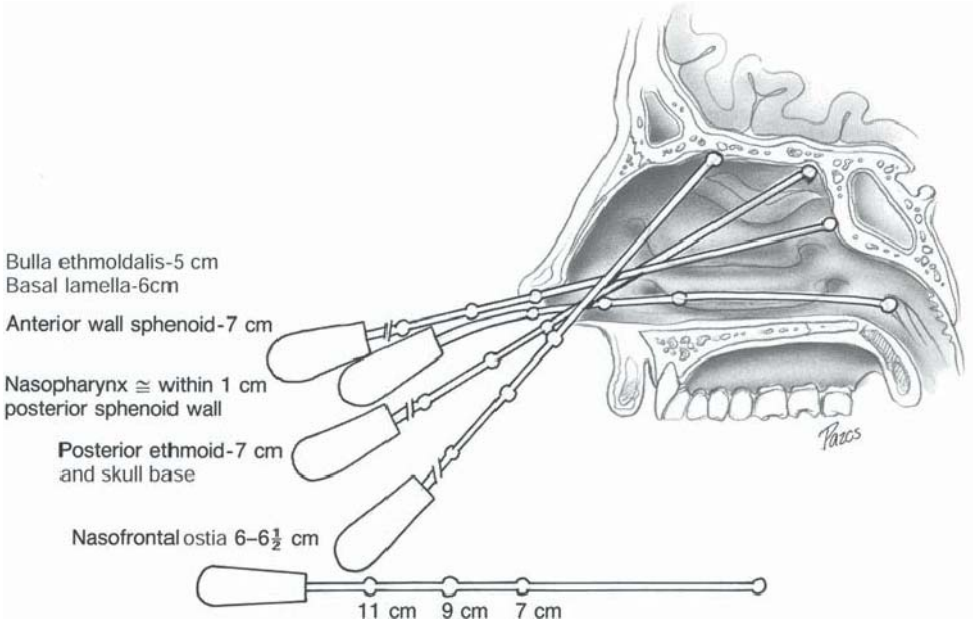


Figure 44.6 Beaded probe measurements to various areas of the nose from the nasal opening (nasal spine). (From Stankiewicz J. Complication of endoscopic sinus surgery. *Otolaryngol Clin North Am* 1989;22:749, with permission.)

proceeding through the basal lamella if the patient has a 2:1 or greater than 2:1 ratio. Therefore, the surgeon must consider this "angle of attack" when penetrating the basal lamella and entering the posterior ethmoid cavity. Entering the posterior ethmoids via the medial-inferior aspect of the coronal face of the basal lamella, along the roof of the maxillary sinus or floor of the ethmoid bulla, will provide a much safer avenue toward the sphenoid sinus and away from the skull base (Fig. 44.8).

COMPLICATIONS OF OPEN SURGICAL PROCEDURES

Specific complications of sinus surgery are numerous. Several can be catastrophic because of the proximity of the paranasal sinuses to the orbit and brain. All otolaryngologists should be familiar with work of Harris P. Mosher (11), who described the ethmoid labyrinth in great detail in his 1929 publication. Mosher described intranasal

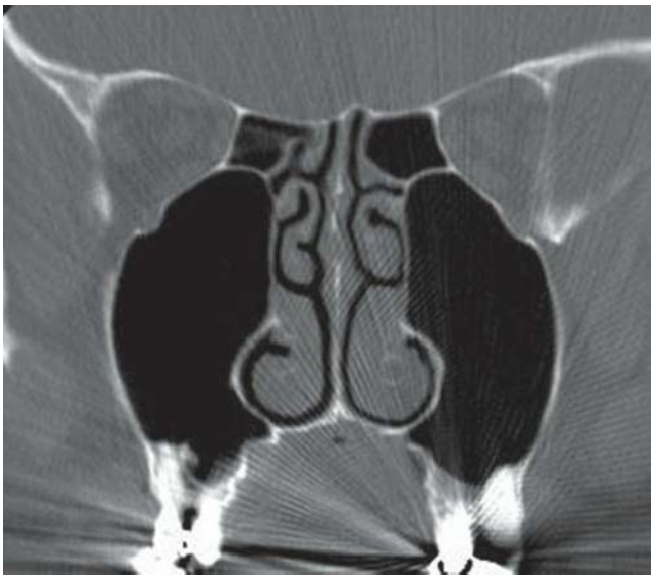


Figure 44.7 A coronal CT of the paranasal sinuses reveals significant asymmetry of the height of the maxillary sinus when compared to the height of the posterior ethmoid sinuses. A ratio (maxillary sinus height:ethmoid sinus height) ≥2:1, such as in this patient, places the posterior ethmoid skull base at high risk for injury when proceeding through the basal lamella.

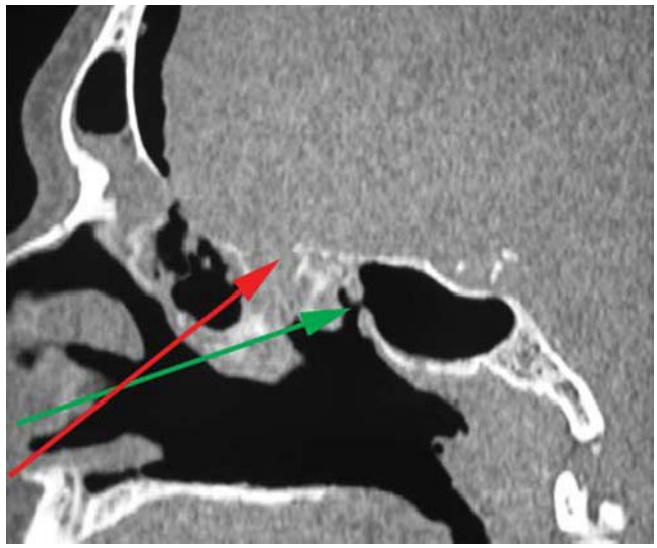


Figure 44.8 A sagittal reconstruction of the paranasal sinuses. This patient sustained an injury to the skull base that resulted in CSF rhinorrhea and pneumocephalus. This injury was due to high penetration of the basal lamella (*red arrow*). An angle of attack that penetrates the basal lamella at the roof of the maxillary sinus or base of the ethmoid bulla (*green arrow*) is safer when entering the posterior ethmoid sinuses.

TABLE 44.2 COMPLICATIONS SINUS SURGERY

Vascular injury
- Carotid artery
- Anterior communicating artery
- Carotid cavernous fistula
- Ethmoidal arteries (anterior and posterior)
- Sphenopalatine artery
- Septal branch of the sphenopalatine artery

Nerve injury
- Infraorbital hypesthesia
- Infraorbital pare sthesia
- Supraorbital and supratrochlear hypesthesia
- Supraorbital and supratrochlear paresthesia
- Inferior alveolar hypesthesia
- Inferior alveolar paresthesia

Facial disorders
- Facial edema
- Subcutaneous emphysema

Orbital disorders
- Blindness
- Diplopia
- Nasolacrimal duct injury
- Nasolacrimal sac injury
- Injury to Hasner valve
- Orbital hematoma
- Orbital emphysema
- Periorbital ecchymosis
- Lid edema
- Anisocoria

Brain and neurologic
- Cerebrospinal fistula
- Meningitis
- Frontal lobe injury
- Hyposmia, dysosmia, anosmia
- Pneumocephalus
- Anterior cerebral artery injury
- Subarachnoid hemorrhage
- Brain abscess
- Death

Packing related
- Displaced packing
- Aspiration
- Infection
- Increased orbital pressure
- Toxic shock syndrome
- Myospherulosis
- Scar tissue formation

ethmoidectomy as "one of the easiest operations with which to kill a patient." Most of the catastrophic complications are related to ethmoidectomy and frontal sinus surgery. Table 44.2 lists the complications of sinus surgery. May et al. (12) studied the complications of sinus surgery among large populations of patients noting CSF leak and blindness were the common major complications; orbital hematoma the most common minor complication.

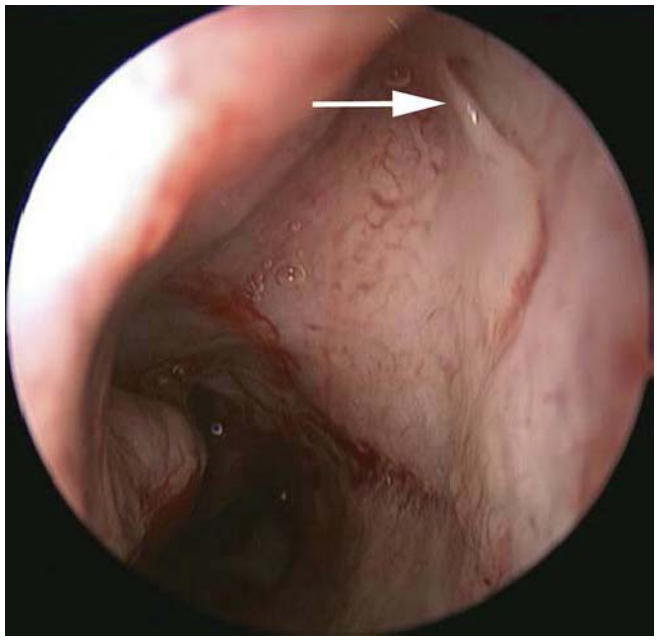


Figure 44.9 An endoscopic view of the inferior meatus. Hasner valve (*arrow*) is the termination of the lacrimal apparatus. Injury to Hasner valve can occur when performing an IMA as well as other procedures (turbinate fracture, turbinate resection, and endoscopic medial maxillectomy).

Inferior Meatal Antrostomy

Complications of inferior meatal antrostomy (IMA) include bleeding due to injury to the greater palatine artery, injury to Hasner valve (Fig. 44.9) and the lacrimal apparatus, dental injury, and functional complications due to synechia, or recirculation of infected mucus. IMA must be performed with great care in children since injury to the developing canines within the bony walls of the maxillary sinus can occur. The canine impression in the lateral nasal wall should be viewed before performing an IMA on children.

It appears that, although complications related to the development of the teeth, especially among children, and occasional bleeding can occur during IMA, the risk of permanent injury is low if care is taken during the procedure. Inferior meatal antrostomy is not commonplace in the era of endoscopic sinus surgery; however, it can be useful for obtaining cultures in the ICU setting, aid in removal of polyps or fungal disease, or aid in clearance of benign maxillary sinus tumors, such as inverted papilloma.

Caldwell-Luc Procedure

Complications of the traditional Caldwell-Luc operation are facial swelling, cheek discomfort, hemorrhage, facial asymmetry, facial paresthesia, oroantral fistula, gingivolabial fistula, dacryocystitis, devitalized teeth, recurrent polyps, and recurrent sinusitis. The most common immediate complications are facial swelling and cheek discomfort, which occur after almost 90% and 33% of procedures,

respectively (13) and resolve within 1 to 2 weeks of the procedure. DeFreitas and Lucente (13) reviewed 670 Caldwell-Luc procedures and found a 9.1% and 3% incidence of facial paresthesias and dacryocystitis, respectively. Yarington (14) reported on 271 Caldwell-Luc procedures with a 3% overall complication rate. The most common complications were postoperative hypesthesia, devitalized teeth, and postoperative ethmoiditis. Blindness can occur with the Caldwell-Luc procedure if the orbit is entered, but this is a rare complication. DeFreitas and Lucente (13) also noted a recurrence of sinusitis and polyps in 12% and 5% of patients as well.

Major long-term complications of chronic pain and numbness are not as common as one might believe (13,14). Modification in surgical technique, including the use of a triangular flap in the buccal mucosa and the use of a drill rather than an osteotome or rongeur to open the canine fossa, resulted in a decrease in long-term numbness and pain according to Yarington (14). DeFreitas and Lucente (13) found that paresthesia, numbness, and other complications such as facial asymmetry, oroantral fistula, dehiscence, and devitalized teeth persisted for about 1 year and then resolved or necessitated minor surgical procedures. Low (15) reviewed 216 Caldwell-Luc operations and found that facial swelling, facial pain and numbness, and dental pain and numbness were the most common complications among 30% to 60% of patients. Facial paresthesias can be minimized by understanding the regional anatomy of the infraorbital nerve, which is described nicely by Robinson et al. (16) and Singhal et al. (17).

Intranasal Ethmoidectomy

Intranasal ethmoidectomy can be performed with a headlight, microscope, or endoscope. As previously implied through the work of H. P. Mosher, ethmoidectomy has been described as perhaps the most dangerous of all otolaryngologic operations. Catastrophic complications such as blindness, permanent diplopia, CSF fistula with meningitis, brain injury, and major vessel injuries have been described. In more than 1,000 ethmoidectomies, Freedman and Kern (18) reported overall complication rates of less than 4%. Factors that contributed to complications included extensive sinus disease and factors that led to revision surgery included loss of landmarks. The most common complications were hemorrhage and orbital hematoma with an overall complication rate of 2.8%.

Lawson (19) also found a low (1.1%) incidence of complications following 1,077 intranasal ethmoidectomies over a 15-year period, the worst complications being three CSF fistulae. Included in this review of ethmoidectomy was an extensive review of complications of all ethmoid procedures.

Complications of endoscopic sinus surgery mirror those of traditional surgery. Stankiewicz (6), however, reported a 17% complication rate in 150 ethmoidectomies and indicated that endoscopic ethmoidectomy is extremely difficult for inexperienced surgeons. This discordance between endoscopic and traditional ethmoidectomy procedures most likely relates to the deployment of new surgical techniques at the time. Moreover, Stankiewicz (20) demonstrated in a group of 150 *subsequent* ethmoidectomies a decrease in complication rate to less than 2%, thus indicating that with experience, endoscopic surgery is safe and results in complication rates comparable to traditional ethmoidectomy and other endoscopic procedures. Stankiewicz (6,20) also found that CSF fistula specifically and orbital complications in general are more common among patients who are under general anesthesia for endoscopic ethmoidectomy. No experienced surgeon claims to have had a patient with blindness or double vision, although management of these patients certainly does occur. CSF fistulae with meningitis also are rare.

A meta-analysis of 6,801 patients reveals that the most serious complication of ethmoidectomy was CSF rhinorrhea. Serious complications occurred among almost 1% of patients. Orbital penetration was the most common minor complication. Complication rates were similar for endoscopic and traditional techniques except for a higher rate of orbital penetration in traditional surgery (12).

Intranasal ethmoidectomy in the hands of experienced surgeons has an overall complication rate of 4% or less (12,21). When comparing traditional and endoscopic ethmoidectomy, the rates of complication appear to be equivalent. Factors that appear to decrease ethmoidectomy-related complications include preservation of the middle turbinate. However, middle turbinate preservation may increase the risk of intranasal synechiae and iatrogenic obstruction of the ethmoid and frontal recess, ultimately leading to revision sinus surgery. Revision ethmoidectomy, advanced disease (particularly long-term chronic disease, polyps, or fungal disease), intraoperative hemorrhage, operations by a right-handed surgeons on the right side of the head, endoscopic procedures by a right-handed surgeons on the left side of the head and inexperience of the surgeon all appear to increase the risk of ethmoidectomy complications in some fashion.

Transantral Ethmoidectomy and External Ethmoidectomy

Complications of transantral ethmoidectomy and external ethmoidectomy are the same as for intranasal ethmoidectomy. However, because direct vision with or without a microscope is used, fewer major complications are found. Transantral ethmoidectomy necessitates a Caldwell-Luc operation; therefore, the complications include those of a Caldwell-Luc procedure (see earlier). It is also important that the distance to the ethmoidal and sphenoid sinuses through a transantral approach is half that of an intranasal approach. In 158 transantral ethmoidectomies on 98 patients, Malotte et al. (22) found increased blood

loss (average 384 mL) and an average hospitalization of 3.6 days. A total of 20.4% of patients had complications.

The adverse events of external ethmoidectomy really should be divided into expectations and risks. Because external ethmoidectomy produces an external scar, patients should expect some deformity, especially if the incision is extended for frontoethmoidectomy. Almost all patients have ecchymosis from an injury to the angular vessels and lid edema from the incision. Most complications are minor orbital problems such as periorbital edema and forehead anesthesia, which can occur via injury to the supratrochlear and supraorbital neurovascular bundles. Other problems include hemorrhage and wound infections that resolve in the majority of cases. Injury to the lacrimal apparatus can happen as well. Complications such as intracerebral hemorrhage, pneumocephalus, and CSF fistula occurred among 3.1% of patients (22). Minor complications such as infraorbital nerve numbness and pain, atrophic rhinitis, facial edema, crusting, epistaxis, diplopia, and epiphora also were found. Infraorbital nerve injury with numbness was the most common complication.

Neal (23) found optic nerve injury, corneal abrasions, exposure keratitis, trochlear and medial rectus injury, and diplopia from enophthalmos as potential orbital complications from external ethmoidectomy. The need for possible scar revision, especially if webbing of the incision occurs, was also mentioned in this study. In 41 frontoethmoidectomies, Dedo and Broberg (24) had no complications and a 97% success rate. Although complications occur frequently in transantral and external ethmoidectomy, most are minor and resolve. Major complications such as CSF leak and transcranial hemorrhage are rare owing to the excellent exposure afforded by these procedures but seem to be more common than with intranasal surgery.

Sphenoidotomy

Thirteen important structures, including the carotid artery, the cavernous sinus, the optic nerve, and the brain, are contiguous with the sphenoid sinus (Fig. 44.10). Many of these structures can be injured during sphenoidotomy, regardless of whether the operation is external, transantral, intranasal, or transseptal. These injuries can be catastrophic but rare. Malotte et al. (22) found no sphenoidotomy-related problems in 158 sphenoidotomies in conjunction with transantral ethmoidectomy. The sphenoid wall in transantral sphenoidotomy is only 4 to 5 cm from the antral opening compared with 7 cm in transnasal sphenoidotomy (Fig. 44.6). CSF leaks can occur when a sphenoidotomy is improperly performed, and these leaks can be repaired with a number of intrasphenoidal techniques. Injuries to the cavernous sinus and/or carotid artery are rare but can be fatal. Immediate management can be successful, and this includes packing the sphenoid sinus and nasal cavity and involving a neuroradiologist who is skilled at performing endovascular occlusion of the carotid artery either in the operating suite (if the patient is unstable) or in the interventional suite (25–27). Delayed formation of carotid artery pseudoaneurysm is uncommon but may also be treated with endovascular techniques. Sphenoidotomy can cause major complications, but these are rare. Minor complications include bleeding from the septal branch of the sphenopalatine artery, which is controlled with electrocautery, as well as mucus recirculation around a false ostium, ostial stenosis, and late mucocele formation.

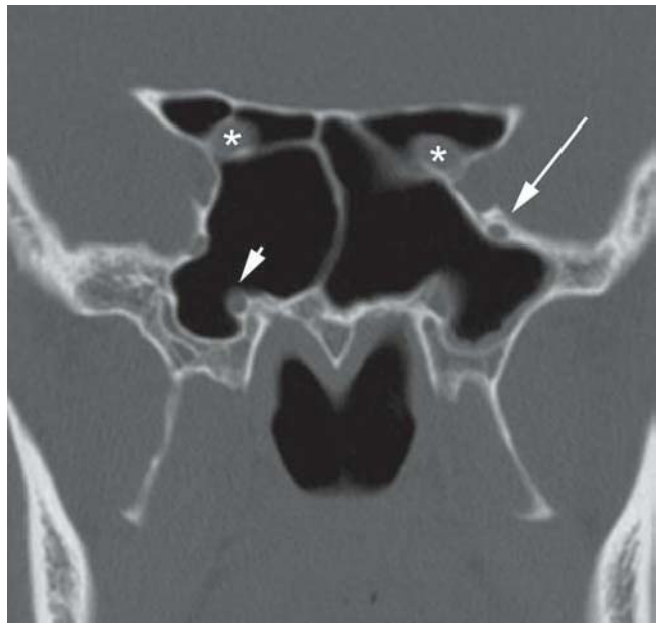


Figure 44.10 A coronal CT of the paranasal sinuses featuring the anatomy that relates to the sphenoid sinus. The optic nerve (*asterisk*), Vidian nerve (*arrowhead*), and maxillary nerve (*arrow*) can be easily seen in this image. Not as easily seen are the carotid arteries and the cavernous sinuses, which contain branches of the trigeminal nerve, the occulomotor nerve, the trochlear nerve, and the abducens nerve.

Frontal Sinus Trephination

Surgery on the frontal sinus varies in complexity. The simplest form of frontal sinus surgery is via external trephination, which was described by Ogston (28) and Luc (29) in the late 1800s as evacuation of the frontal sinus through a hole the size of a "six penny piece" (a.k.a. sixpence or half-shilling, 19 mm or 0.75 inch), which is typically larger than the modern day trephination. Trephination requires a small incision along the medial/superior brow line, and the sinus is entered with the aid of an osteotome or drill. Bleeding and numbness of the overlying skin are the most common adverse outcomes of this procedure; however, injury to the supratrochlear neurovascular bundle may occur or even injury to the orbital trochlea. The depth of the posterior table of the frontal sinus has been studied relative to the location of the anterior table, and while trephination is considered a safe procedure, up to 15% of patients may have relative radiologic contraindications (30).

Open Frontal Sinus Surgery

More advanced surgery of the frontal sinus requires either an extended Lynch, gullwing, mid-brow, or coronal incision. There are benefits and disadvantages to each type of incision. Obviously, the Lynch, gullwing, and mid-brow approaches require incisions that are visible on the face, some of which (i.e., gullwing, mid-brow) can lead to unsightly scars as well as numbness in the area. The coronal incision offers the distinct advantage of being hidden in the hair line, although considerations for future hair loss or existing hair loss in men must be made prior to choosing this approach. The major complication of this incision is hair loss around the area of the incision as well as numbness of this region of the scalp. Other complications related to this approach include those acquired during the elevation of the scalp flap: injury to the frontal branch of the facial nerve, injury to the supraorbital and supratrochlear neurovascular bundles, and laceration of the pericranial flap. Nevertheless, the coronal incision provides the surgeon with unprecedented access to the frontal sinus. It is through this approach that the surgeon can perform either a unilateral or bilateral ablative or osteoplastic frontal sinus procedure.

Various ablative frontal sinus procedures have been described throughout the late 1800s and early 1900s as means of treating chronic frontal sinusitis. The complete removal of the anterior table of the frontal sinus with removal of all diseased mucosa was originally described by Riedel-Schenke (31). This resulted in the often times unsightly collapse of the forehead skin into the frontal sinus defect. To avoid this rather hideous result, Killian (32) proposed leaving a 1 cm supraorbital bar to minimize the cosmetic defect; however, his procedure was criticized for high rates of recidivism, presumably due to retained mucosa posterior and inferior to the retained frontal bar. Both procedures suffer from all the usual complications related to the approach: scar, bleeding, and paresthesias. Long-term failures were criticisms mainly of the Killian procedure; however, incompletely ablated mucosa during the Reidel procedure would result in disease recurrence as well. To mitigate the poor cosmetic result and long-term failures, the osteoplastic frontal sinusotomy more or less replaced these procedures.

Ironically, the osteoplastic frontal sinusotomy was described only shortly after the Reidel procedure by Schonborn (33) in 1894. However, what we now consider to be the modern osteoplastic frontal sinusotomy was described by Macbeth (34) and popularized through the publication and follow-up performed by Goodale, and Montgomery (35–38). Osteoplastic frontal sinus surgery with or without fat obliteration is an extensive procedure performed most frequently on patients with refractory chronic sinusitis, frontal sinus fractures, mucoceles, or CSF rhinorrhea. Any procedure involving the ablation of the frontal sinus in which an allograft is taken obviously involves morbidity associated with the harvest procedure. Common donor sites include the scalp, abdomen, and lateral thigh.

Hardy (39) reviewed a series of 250 patients and found that 47 patients (18%) had early complications, including abdominal wound complications related to the fat graft harvest, such as hematoma, seroma, or abscess. Hematoma, seroma, or abscess also occurred within the frontal wound. In these reviews (37,39), Hardy and Montgomery found that some osteotomies intended to be within the sinus were in fact craniotomies that resulted in dural exposure without brain injury. Four cases of dural exposure were found when the mucous membrane was stripped, suggesting areas of dehiscence. Five dural lacerations occurred, two of which had to be repaired. Other complications included necrosis of the skin of the dorsum of the nose, anosmia, temporary ptosis, and temporary dysfunction of the frontalis muscle. After 8 years, 6% of 208 patients had persistent postoperative pain, and 1% had persistent neuralgia. These complications occurred most often with brow incisions, in which the supraorbital nerves usually are incised, as opposed to coronal incisions, in which the supraorbital nerves usually are preserved. Poor appearance of the incision scar occurred among less than 1% of patients. Six percent had depression or elevation (a.k.a. frontal bossing) of the osteoplastic flap. This complication can be avoided by beveling the osteotomies and by closing the wound meticulously with semi-rigid or functionally rigid fixation. Only 6% of patients needed revision surgery (37). Because of this low revision rate, frontal sinus obliteration with osteoplastic flap was considered the gold standard for treatment of chronic frontal sinus disease for many years until the era of endoscopic sinus surgery.

Hypesthesia and wound infection are the most common complications after osteoplastic flap surgery. Postoperative pain persists among 6% of patients, and almost 7% have scarring or forehead abnormalities. Although exposure of dura does occur, CSF leak, meningitis, or brain injury is unusual. After operations on 43 patients, Ulualp et al. (40) found that 6 patients had decreased sensation and 1 had CSF leak.

COMPLICATIONS SPECIFIC TO ENDOSCOPIC SURGICAL PROCEDURES

Middle Meatal Antrostomy

The complications of middle meatal antrostomy are bleeding, blindness, facial pain, numbness, nasolacrimal duct injury, and synechiae. Davis et al. (41) performed 310 middle meatotomies endoscopically with no serious surgical complications. Epiphora developed in 1 patient and synechia in 20 patients. However, Bolger et al. (42) found up to a 15% incidence of *occult* injury to the lacrimal apparatus during middle meatal antrostomy. A few anecdotal reports exist of temporary pain and numbness due to endoscopic

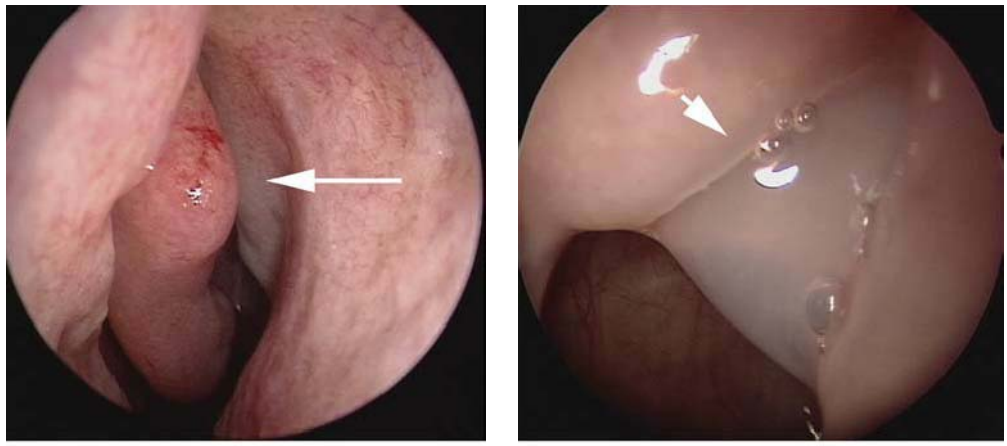


Figure 44.11 An endoscopic view of the middle meatus during revision sinus surgery for chronic maxillary rhinosinusitis. Inspection with a 0-degree telescope reveals a partially resected uncinate process. This middle meatus looks otherwise healthy; however, an inspection of the surgical antrostomy with a 45-degree telescope reveals recirculation of cloudy mucus (*arrowhead*) from the true ostium of the maxillary sinus into the surgical antrostomy.

middle meatal antrostomy. These complications were most likely caused by injury to the alveolar nerves lining the meatal wall of the maxillary sinus.

In 300 antrostomies, Stankiewicz (20) found two cases of epiphora. Today endoscopic middle meatal antrostomy is a relatively complication-free procedure with sporadic reports of numbness and pain. Although blindness is possible, it is usually associated with ethmoidectomy.

Improper identification of the true ostium of the maxillary sinus can result in the formation of a surgical ostium that does not properly treat maxillary mucosal disease. In his review of surgical failures, Parsons et al. (43) revealed that the largest cause of revision maxillary sinus surgery was the presence of a missed maxillary ostium. Missing the natural ostium can result in recirculation of mucus, potentially infected mucus; typically this is the result of incompletely removing the uncinate process and failing to identify the natural ostium prior to performing maxillary sinus surgery (Fig. 44.11).

Sphenoidotomy

Perhaps not unique to endoscopic sinus surgery, but certainly mistaken quite frequently during endoscopic sinus surgery is the sphenoethmoidal (a.k.a. Onodi (44)) cell. The sphenoethmoidal cell is an ethmoid cell that pneumatizes lateral and superior to the true sphenoid sinus. It may be identified preoperatively on coronal CT imaging where a transverse partition within the sphenoid sinus heralds the possibility of this cell (Fig. 44.12). The sphenoethmoidal cell is closely, if not intimately, associated with the optic nerve and the carotid artery. Mistaking the Onodi cell for the sphenoid cell, or proceeding distally to the Onodi cell with the assumption that the sphenoid sinus is directly behind this ethmoid cell are recipes for disaster. If the surgeon proceeds through the ethmoid and if he or she can see the floor easily of what he or she believes to be the sphenoid sinus, this is more likely to be an Onodi cell. Therefore, the superior turbinate can be used as a landmark for safe and successful entry to the sphenoid sinus. Bolger et al. (45) described a means by which the posterior ethmoid cavity was outlined by an imagined parallelogram with the boundaries being the skull base superiorly, *lamina papyracea* laterally, basal lamella of the superior turbinate inferiorly, and the superior turbinate and septum medially. Entry into the sphenoid sinus through the

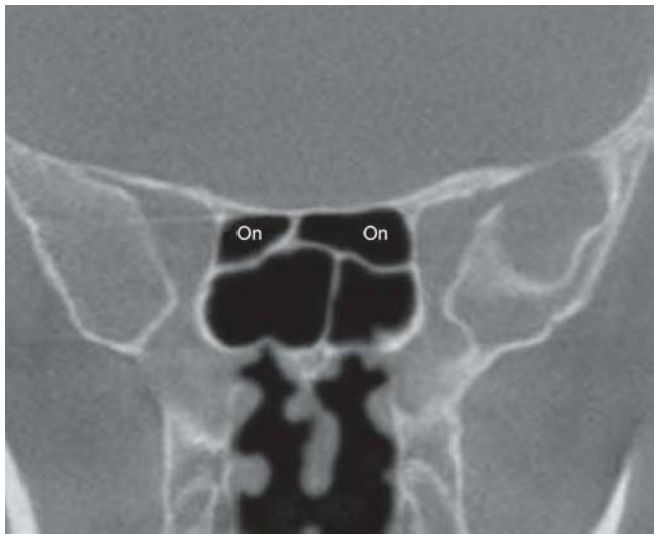


Figure 44.12 A coronal CT of the sphenoid sinus. Transverse partitions within the sphenoid sinus may indicate the presence of Onodi (sphenoethmoid) cells (*asterisk*). These ethmoid cells pneumatize the sphenoid bone lateral to and superior to the sphenoid sinus. They are typically related to the optic nerve and may feature the optic nerve prominently (see Fig. 44.2).

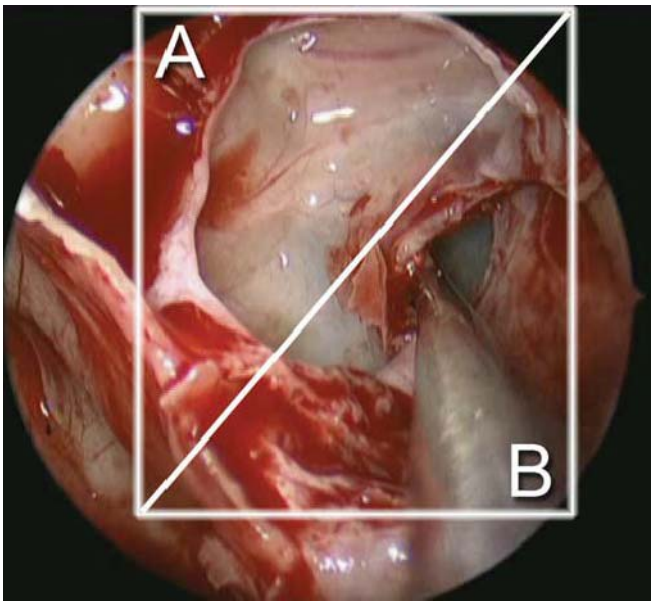


Figure 44.13 An endoscopic view of a patient undergoing primary endoscopic sinus surgery of the sphenoid sinus. Safe entry into the sphenoid sinus may be performed through the inferior and medial aspect of "Bolger's Box," which is an imagined box with the following boundaries: lateral being the *lamina papyracea*, superior being the skull base, inferior being the ground lamella, and medial being the septum and superior turbinate.

natural os or through the inferior and medial half of this "box" is considered safe and unlikely to injure the carotid artery or optic nerve (Fig. 44.13). Distances to the sphenoid sinus can be marked with a beaded probe (recalling that the distance to the os is ~7 cm) or with image-guidance probes.

Frontal Sinus Surgery

Postoperative synechiae, or ostia scarring due to middle turbinate lateralization or ostia manipulation are the most common complications resulting from endoscopic frontal sinus surgery. The more significant intraoperative complications, such as CSF leak, intracranial injury, hemorrhage, or orbital injury, are much less common, however. Of particular note is the increased incidence of complications associated with the use of the high speed drill, particularly during the transseptal frontal sinusotomy or Draf III (46) procedure. Because of the widespread surgery on the floor of the anterior skull base from orbit to orbit that is necessary, the potential for major complications, which include CSF leak, brain entrance with hemorrhage, smell loss, and orbital hematoma, is present. Samaha et al. (47) in a large series of 100 procedures had no intraoperative complications and 4 postoperative hemorrhages. The use of stereotactic navigation during these drill-out procedures is very helpful and ultimately may reduce complications in surgery on the frontal sinus, especially during revision cases.

Balloon Catheter Dilation Procedures

The use of balloon catheters as instruments to dilate the sinus ostia for treatment of medically refractory chronic rhinosinusitis is a relatively new phenomenon. Balloon catheter dilation can be performed via either the transnasal or transantral route, although the application of transantral balloon catheter dilation is more limited. Bolger et al. (48) reported the initial results of balloon catheter dilation on patients with 24 weeks of follow-up and no significant adverse events were noted. Vaughan (49) reviewed a number of uncontrolled studies pertaining to the use of transnasal balloon catheters and surmised that the number of serious complications was low; however, scattered reports (50,51) do indicate the possibility of catheter-related complications.

Transantral balloon catheters dilate the maxillary sinus os and infundibulum; however, they require a mini-trephination in the canine fossa. Therefore, the approach is subject to similar risks and complications as those previously described in the section pertaining to Caldwell-Luc procedures. Stankiewicz et al. (52) reported no significant adverse events after initial use after 1-year follow-up (53) in patients undergoing mini-trephination and transantral dilation of the maxillary os and infundibulum.

Therefore, when used as prescribed balloon catheters do not appear to carry with them a significant risk of major surgical complications; however, the long-term functional outcomes and minor complications have been incompletely described. The rates of revision surgery following balloon catheteronly surgeries have not been described either.

Powered Endoscopic Sinus Surgery

The use of the microdebrider (tissue shaver) is commonplace in endoscopic sinus surgery, as it accelerates the process of sharply removing diseased sinus tissue and bone while providing the surgeon with a relatively dry field through its suction capabilities. Ironically, the speed with which the microdebrider functions as well as its relative lack of tactile sensation can be considered two of its largest shortcomings. The microdebrider does not discriminate: It will aggressively resect orbital fat, muscle, and brain just as efficiently as it resects polypoid mucosa (Fig. 44.14). The onset of diplopia due to medial rectus injury has been attributed to microdebrider misadventures, and horror stories of parenchymal dissection and bilateral blindness are certainly present in discussion of these complications. Practically speaking, the microdebrider is a tool and is best used by a surgeon who is acutely aware of the location of the cutting blades. Therefore, the teeth of the microdebrider should *always* be in view so the surgeon can confirm what tissue is being resected. The microdebrider should never lead into unknown tissue and should never be operated in a pool of blood. When dissecting close to the orbit, the teeth should be pointed away from the *lamina papyracea*, especially if dehiscent areas are identified. Otherwise,

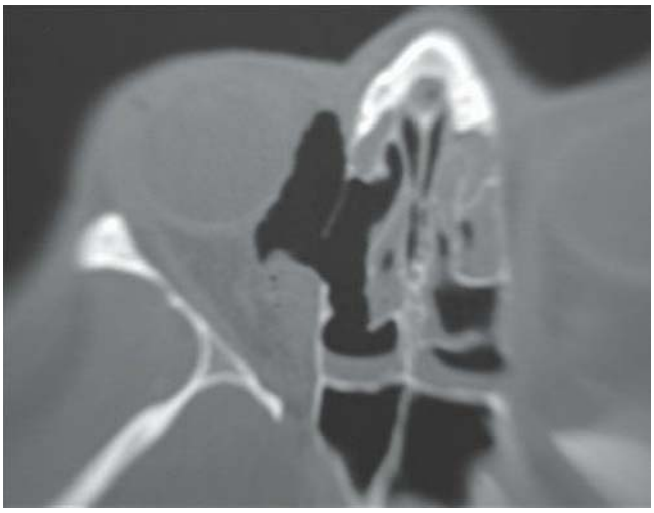


Figure 44.14 An axial CT of a patient who underwent endoscopic sinus surgery who complained of postoperative diplopia. The CT reveals a large dehiscence of bone along the right orbit and evacuation of the orbital contents. This injury was sustained when the surgeon violated the *lamina papyracea* with a microdebrider, which has strong suction and dissection capabilities. In this situation, the suction power of the microdebrider drew orbital fat as well as extraocular muscle far beyond the reaches of the microdebrider into the field of dissection.

in a few seconds, orbital tissue can be suctioned into the microdebrider, exposing or removing orbital fat, occasionally injuring the medial rectus muscle. Techniques for identifying the *lamina papyracea* and dehiscence have already been discussed in the Relevant Anatomy section and are further discussed under the upcoming Blindness section. Additionally, the microdebrider should be used only in short bursts along the skull base, and there is rarely any good reason to debride within the sphenoid sinus.

Image-Guided Endoscopic Sinus Surgery

Image-guided endoscopic sinus surgery (IGSS) was developed in the early 1990s. Truly practical systems for use with endoscopic sinus surgery were not available until the mid-1990s. There are two types of systems currently available: line-of-sight models and electromagnetic models. Line-of-sight models rely on the placement of headgear with reflective spheres that with an infrared emitter triangulate the position of a probe within the sinonasal cavity. Electromagnetic models rely on the creation of a magnetic sphere around the field and uses wired technology to track the position of a probe within the sinonasal cavity. Excellent review of this technology is described by Citardi (54,55).

The expansion of image-guidance systems is such that IGSS is commonplace (56,57). The American Academy of Otolaryngology—Head and Neck Surgery has drafted a policy statement (http://www.entnet.org/Practice/policyIntraOperativeSurgery.cfm) that describes the indications for computer-aided sinus surgery. The indications include the following: (a) revision sinus surgery; (b) distorted anatomy that is postoperative or traumatic in origin; (c) extensive polyposis; (d) frontal, posterior ethmoid, and sphenoid sinus disease; (e) disease of concern abutting skull base, orbit, optic nerve, or carotid artery; (f) CSF rhinorrhea or skull base defect/encephalocele; and (g) benign and malignant tumors.

Image-guided sinus surgery has the ability to reduce complications if used correctly (56), but the level of evidence supporting what is commonly maintained by surgeons is lacking (58). Truly long-term studies to evaluate outcomes would be very difficult to perform; therefore, the image-guided surgery is considered state of the art rather than standard of care, even for difficult or revision cases. Two problems have emerged that contribute to complications related to the use of image guidance. First, surgeons with marginal skills may use these systems to perform surgeries in areas in which they have little experience and are technically not experienced enough to avoid or deal with complications. Second, many surgeons may rely heavily on the accuracy of the computer and may not verify the computer images with what is observed. This is obviously hazardous and can lead to disastrous mistakes. The image-guidance systems should always be properly calibrated. Calibration errors can begin with the preoperative computerized CT scan, at the time of surgery registration, or during surgery. A protocol for CT scanning should be set in place at a surgeon's institution, and this protocol should be followed to the letter each and every time an image-guided protocol CT is performed. If using surface registration, the CT should be performed as close to surgery as possible to avoid minor changes in skin appearance, swelling, weight gain/loss, etc. If surface registration is performed on a patient, it should be performed prior to placement of eye tape and nasal pledgets, both of which may distort facial anatomy. Care must be taken to not place too much tape or traction on the endotracheal tube, as this may distort the facial anatomy as well. During the procedure, especially when changing instruments, verification of bony landmarks (frontozygomatic suture, anterior nasal spine, axilla of the middle turbinate, or posterior maxillary sinus wall) should always be performed. These systems are susceptible to registration errors and fiducial localization errors such that three-dimensional localization may contain a 1 to 2 mm margin of error (59–61). So the skull base or orbit should be given at least 2 to 3 mm as a buffer zone of safety. Any discrepancy between anatomic endoscopic visualization and the computer requires repeat registration and, if necessary, system recalibration. If still inaccurate, the computer should not be used for guidance and the surgeon should decide whether proceeding is essential under the circumstances.

ORBITAL COMPLICATIONS

Orbital Hematoma

Orbital hematoma is caused by entrance through the *lamina papyracea* and can occur whether or not the periorbita is injured. The risk of orbital hematoma with blood retention

in the retrobulbar space increases greatly with penetration of the periorbita. However, ecchymosis can occur in either situation if the *lamina papyracea* has been violated. Orbital hematoma is by definition a postseptal injury of the retrobulbar space (intraconal or extraconal). There are two types of orbital hematoma—fast (arterial) hematoma and slow (venous) hematoma (62,63). Orbital hemorrhage is caused most frequently by trauma to the orbital veins lining the *lamina papyracea* and rarely by injury to the anterior and posterior ethmoidal arteries (6,18,20,62,63). The difference between the two is the speed at which the clinical signs and symptoms of retrobulbar hematoma develop. Hematoma from ethmoidal artery injury occurs immediately. Orbital hematoma can be caused using forceps or a microdebrider (powered instrumentation).

The difference between postseptal and preseptal (such as hematoma from injury to the angular vessels with a needle injection) ecchymosis is that the preseptal hematoma is darker, is more diffuse, and produces more lid edema or evidence of subcutaneous emphysema (Fig. 44.15). A postseptal (or retrobulbar) hematoma, when clinically significant, is marked by proptosis, conjunctival changes such as chemosis (edema of the conjunctiva), and pupillary changes, such as mydriasis or a dilated pupil. Anisocoria (unequal pupillary size) can be caused by topical or injected local anesthesia and is self-limited. Proptosis is not present, and the eye is soft, unlike the situation with hematoma. Ecchymosis due to Caldwell-Luc external ethmoidectomy with a frontal osteoplastic flap usually is preseptal but can be postseptal if the orbit is entered. Ecchymosis related to intranasal ethmoidectomy is almost always postseptal. Most cases of orbital hematoma do not have associated proptosis and pupillary changes, but patients have to be observed closely so that these findings do not develop. These findings signal increased orbital pressure and potential damage to the optic nerve. Ecchymosis usually resolves in about 7 to 10 days.



A



B

Figure 44.15 Photographic depictions of patients who sustained injuries to the *lamina papyracea.* The patient featured on the top **(A)** developed orbital emphysema after blowing his nose. The patient on the bottom **(B)** developed superior lid ecchymosis due to a bony and soft tissue injury of the orbit. The outline of the ecchymosis extends along the arcus marginalis, which is contiguous with the orbital septum and periorbita.



Figure 44.16 A photograph of a patient about to undergo endoscopic sinus surgery. The surgeon gently presses on the orbit to accomplish two ends: (a) to determine how tense the globe is prior to surgery and (b) to view the middle meatus endoscopically to see if any orbital dehiscence is present. Areas suspicious for orbital dehiscence should be confirmed with CT imaging prior to the start of surgery. This bulb test can be performed at any time during the procedure. Also note that the patient's eyes are taped closed at the lateral canthus. This is preferred over placing the tape transversely across the lids or placing a bio-occlusive dressing, as a strip of tape along the lateral canthus often does not have to be removed to take a quick look at the sclera and pupil.

It is important to check the eyes with a simple bulb test (Fig. 44.16) prior to surgery to assess how much tension is present prior to the procedure. Therefore, there will be no confusion when the surgeon suspects a retrobulbar hematoma and the globe is tense. If an orbital hematoma does occur, there are multiple medical and surgical maneuvers to treat this complication. The normal intraocular pressure ranges from 10 to 20 mm Hg; a rise in the pressure to within the range of 30 to 40 mm Hg is extremely worrisome and implies hematoma until proven otherwise. General anesthesia lowers intraocular pressures; therefore, the surgeon should not rest assured if the reading on the tonopen is borderline. When the pressure is elevated in this range, orbital massage, administration of mannitol (2 g/kg of a 15% to 25% solution over 30 minutes), and 10 mg of dexamethasone are indicated. In an awake patient, one to two drops of timolol may be administered. These conservative measures are adjunctive and do not replace an active investigation of the site(s) of bleeding and immediate relief of the intraocular pressure. If necessary, the surgeon should not hesitate to perform a lateral canthotomy and cantholysis. This single maneuver can save a patient's vision. To perform this, a 1 to 2 cm incision is fashioned from the lateral commissure through the lateral canthal soft tissue. This will relieve pressure by itself and give approximately

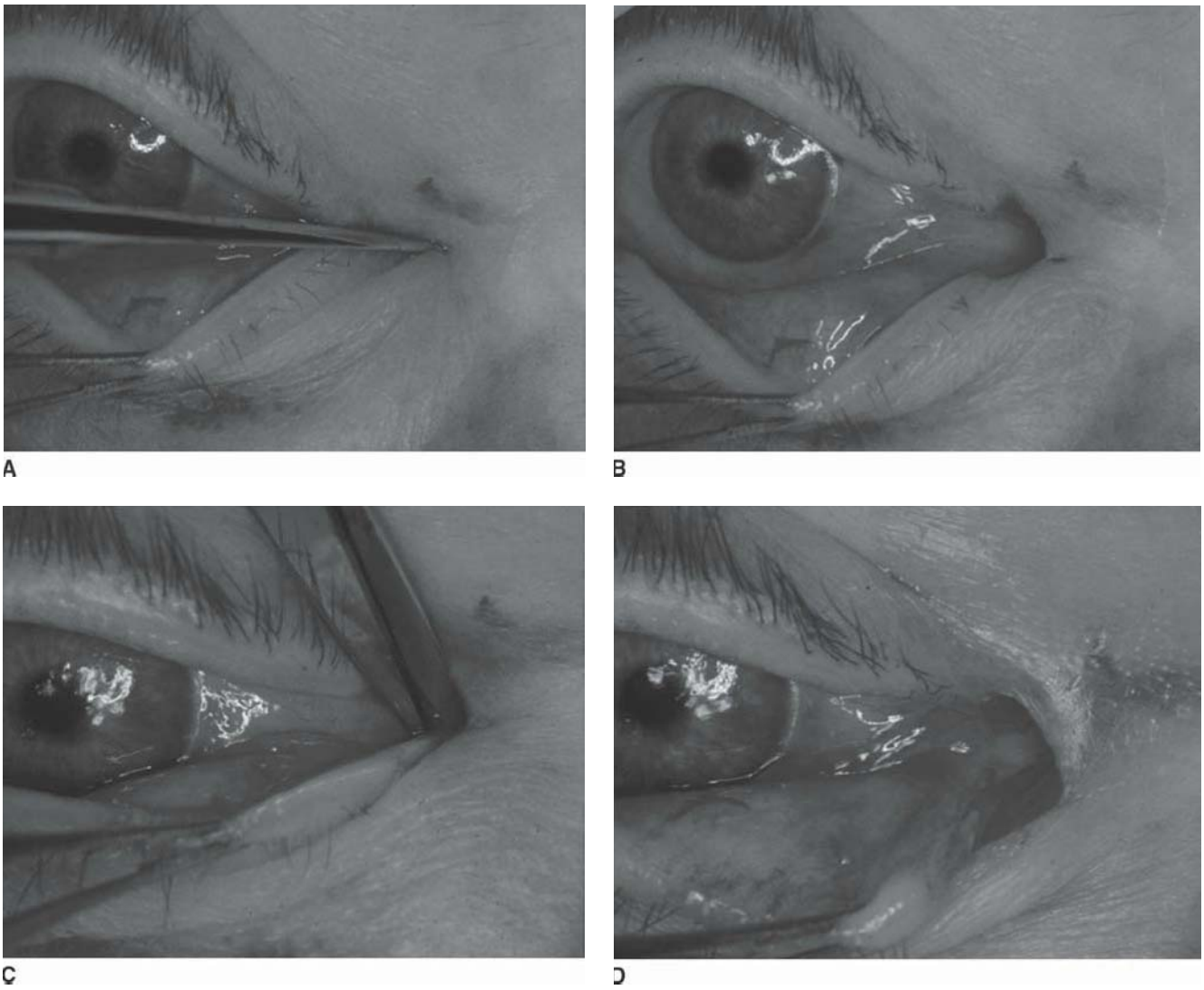


Figure 44.17 Photographic steps of a lateral canthotomy and cantholysis. Scissors or a blade is used to incise from the lateral commissure through the lateral canthus **(A)**. With the lid retracted **(B)**, this maneuver alone with help achieve up to 15 mm Hg release. If further relief of pressure is required, the superior and inferior ligaments are divided **(C)**. The result is a lateral canthotomy and cantholysis **(D)**, which can relieve up to 20 mm Hg of additional pressure. This maneuver can be performed in less than 1 minute. All surgeons performing endoscopic sinus surgery should know how to perform this relatively simple procedure, as it can save a patient's vision.

15 mm Hg leeway. If additional pressure needs to be relieved, a cantholysis should be performed; the superior and inferior portions of the lateral canthal ligament and their attachments to Whitnall tubercle are divided. This maneuver can attain up to 20 mm Hg relief (Fig. 44.17). If further relief of pressure is still necessary, an endoscopic orbital decompression can be performed by removing the *lamina papyracea* and incising transversely the periorbita to allow prolapse of extraconal fat into the sinonasal cavity.

Once the pressure is relieved, the source of bleeding should be identified. Any nasal packing should be removed to prevent pressure on the orbit and that would otherwise delay egress of orbital fluids into the nose. Monopolar cautery should absolutely be avoided around any dehiscent areas of the orbit, since the spread of cautery may injure the neurovascular structures or extraocular muscles. If necessary, bipolar cautery of bleeding from the periorbita or extraocular fat is preferred. If bleeding is suspected to have arisen from the anterior or posterior ethmoidal arteries, an attempt to ligate these vessels with bipolar cautery can be performed endoscopically. If the vessels are embedded within the skull base, as they are greater than 90% of the time, the surgeon may have to make an external excision to ligate the vessels with surgical clips or bipolar cautery.

It is advised that an ophthalmologist be involved in the steps of this process whenever feasible. If possible, an ophthalmologist may even perform these procedures. However, no delay in action should be taken by the sinus

TABLE 44.3 MANAGEMENT OF SUDDEN LOSS OF VISION

Immediate (fast arterial hematoma: >30 min decompression time)				
1. Orbital injury	Proptosis[a] Pupillary change[a] Vision loss[a] Yes ↓	No	→	Observe
2. Medical treatment	Eye consultation Mannitol[b] Orbital massage High-dose steroid[d] No success	Success	→	Observe; bed rest; sedation; acetazolamide[c]; ophthalmology follow-up
3. Surgical treatment	Lateral canthotomy Medial external (Lynch) Decompression Endoscopic decompression Control bleeding artery	Success	→	Observe as in medical treatment
Delayed (venous slow hematoma: 60–90 min decompression time)				
	Proptosis Vision loss Yes ↓	No	→	Observe
	Medical treatment (same as above) No success ↓	Success	→	Observe
	Surgical treatment (same as above)			

[a]Local or general anesthesia.
[b]Intravenous dose of mannitol, 1–2 g/kg.
[c]Acetazolamide used at discretion of ophthalmologist.
[d]High-dose steroid works within a few minutes.
Adapted from Stankiewicz JA. Blindness and intranasal endoscopic ethmoidectomy: prevention and management. *Otolaryngol Head Neck Surg* 1999;120:841, with permission.

surgeon in order to wait for the ophthalmologist to arrive, and certainly any delay caused by confirming a hematoma by CT or MR imaging may ultimately result in a patient who has lost his or her vision. See Table 44.3 for the steps related to treatment of orbital hematoma.

Blindness

Blindness is a catastrophic complication of sinus surgery and can be temporary or permanent. Temporary blindness can be caused by injection of vasoconstrictive agents (especially if via the transoral, pterygopalatine route since the pterygopalatine fossa freely communicates with the inferior orbital fissure) or by orbital hematoma that has expanded to such an extent that it increases orbital pressure, consequently compromising vascular supply to the optic nerve, which is sensitive to ischemia. Studies with laboratory animals have shown that increased intraocular pressure gradually returns to normal within 2 to 3 hours. However, light perception may not return for several more hours and the pupillary reflex for 24 to 48 hours (62,63). In blindness caused by retrobulbar venous hematoma, the retina can tolerate these extreme pressures perhaps for 60 to 90 minutes; however, irreversible changes in vision may occur in 30 minutes or less if there is an arterial bleed. Intervention must take place within this time limit (63). In the case of fast arterial hematoma usually due to anterior ethmoid artery injury and retraction into the orbit, immediate high pressure on the optic nerve must be reduced in less than 30 minutes to avoid blindness.

Although compensatory mechanisms protect retinal blood flow, neural tissue is vulnerable to ischemic injury. Even transient interruption of the blood supply can cause neural tissue in the retina to become nonfunctional and unresponsive to light. Venous outflow obstruction of the vessels supplying the optic nerve induces hypoxia. Prevention of blindness begins preoperatively with a history and physical examination that exclude potential problems (previous surgery, complicated surgery, or long-standing disease) and patients who have bleeding problems or are taking medications such as aspirin that can affect bleeding. Inquiries should be made regarding pathologic conditions of the eye that can be related to blindness, such as glaucoma, amblyopia, diabetic retinopathy,

and retinal vascular disease. Scrutiny of radiologic studies, primarily CT scans, for evidence of dehiscence or other problems is important.

Surgical planning commensurate with the ability and experience of the surgeon is necessary. Operative prevention involves selection of appropriate anesthesia. Surgeons operating on the ethmoid sinus should keep the eye taped closed at the lateral canthus and be scrutinized frequently in order to detect any early proptosis, ecchymosis, or eye movement during the surgical procedure. Although with an external procedure structures are apparent under direct vision or with stereoscopic (binocular) vision, the use of an endoscope can distort anatomic features and misrepresent depth of field, allowing entrance into the orbit.

A technique helpful for endoscopic ethmoidectomy but also practical for microscopic or traditional intranasal ethmoidectomy is the intraoperative bulb press test or simultaneous eye palpation and intranasal examination (62,63) (Fig. 44.18). This simple maneuver readily identifies movement of the periorbita or orbital contents and prevents entrance into the orbit. This test should be performed prior to the procedure and during the procedure. This is also useful for identifying the lacrimal sac when removing agger nasi cells. Identification of the maxillary sinus ostium and proceeding with the maxillary antrostomy before performing the ethmoidectomy also help with delineation of the *lamina papyracea* early in the procedure. An assistant or scrub nurse/technician can be asked to monitor the eye as an additional layer of protection.

Tissues such as fat float in fluid, whereas others such as those encountered in sinus disease and polypoid disease do not. The instrument nurse always should place fluid in the specimen containers and should immediately inform the surgeon whether anything floats. It should be noted that extraocular muscles, especially the medial rectus muscle, will sink. Before any biopsy of the lamina papyracea is taken, one should perform the bull test to determine if there is any dehiscence and fat is visible. If orbital fat is found, it should be left alone and not tampered with. In most cases, ecchymosis forms intraoperatively or

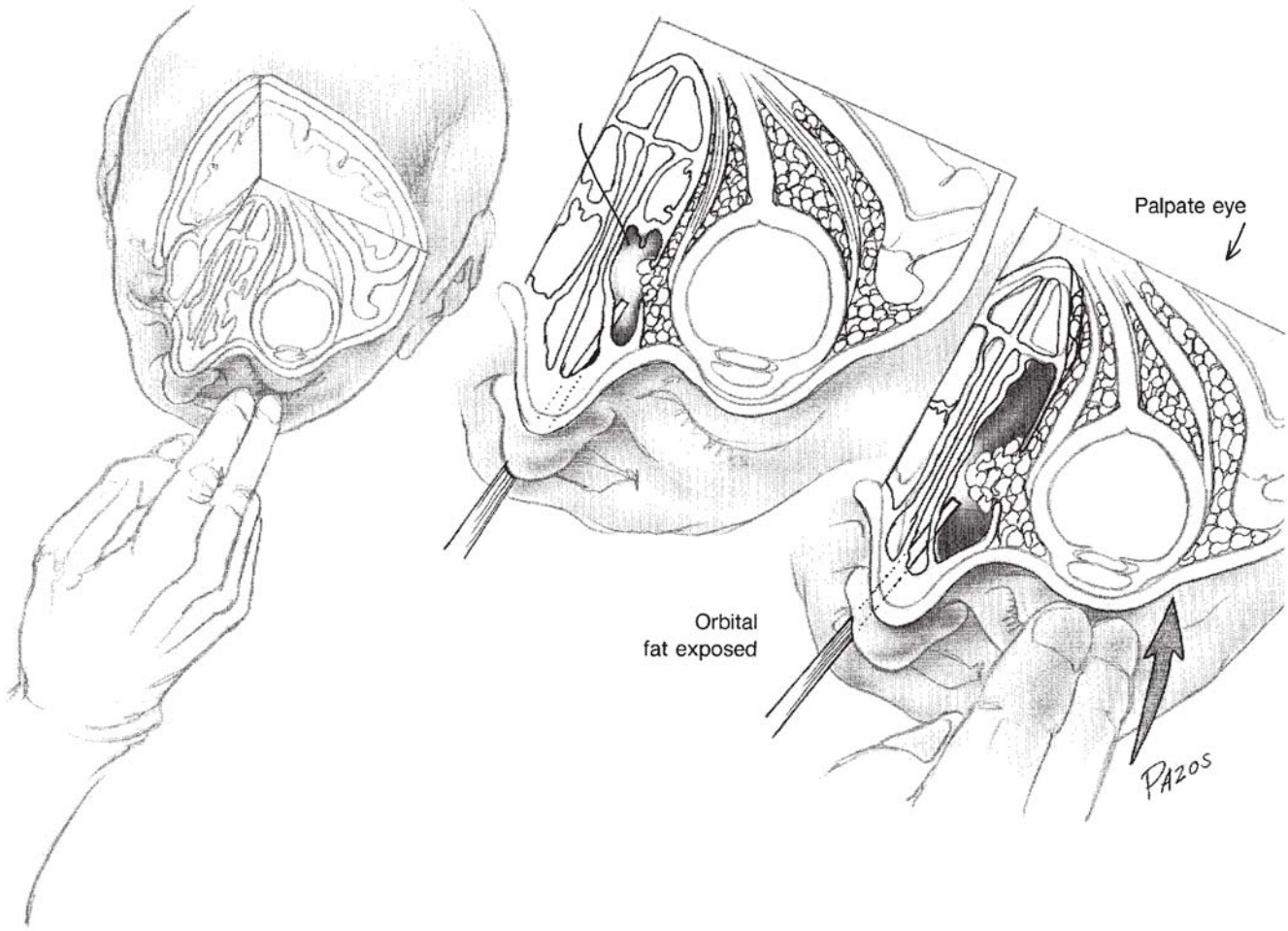


Figure 44.18 Bulb press test. Endoscope is in place for examining the middle meatus and the lateral wall of the ethmoid sinus. A hole in the lamina papyracea is visible. Simultaneous eye palpation and endoscopic visualization to find periorbital fat or fat exposure as early as possible. (Redrawn from Stankiewicz JA. Blindness and intranasal endoscopic ethmoidectomy: prevention and management. *Otolaryngol Head Neck Surg* 1989;101:320, with permission.)

postoperatively, and the patient should be watched closely for orbital hematoma. The nose should not be overly packed; in fact, it may be advisable to instill a hemostatic gel or paste within the nasal cavity to perform hemostasis. If a dehiscence is present, the packing itself can press into the periorbita and posterior chamber, increase pressure, and cause proptosis. Frontal sinus procedures, especially with obliteration, often encounter the orbit from above. Orbital hematoma can occur with increased pressure if orbital fat is present. Most eye swelling is otherwise preseptal.

Postoperative prevention revolves around informing the patient, nurse, and family about what to expect and what to do if vision problems occur. Slow venous hematoma can accumulate over 24 to 48 hours. Surgical outpatients need rigid guidelines for monitoring and need inpatient observation if signs of orbital complications develop. When evidence of orbital changes appears during any sinus-related procedure, especially ethmoidectomy, immediate action must be taken. Blindness has been reported as a complication of all forms of sinus surgery. Optic nerve injury is not reversible, but it is sometimes difficult to separate the signs and symptoms of expanding retrobulbar hematoma, which can be corrected, from those of optic nerve injury because in almost all cases there is evidence of orbital hematoma.

Diplopia

Double vision is caused by injury to the extraocular muscles most intimately related to the sinuses, chiefly the medial rectus and the superior oblique muscles (8). The medial rectus is immediately lateral to the periorbita along the transverse midpoint of the *lamina papyracea*. The superior oblique muscle is higher in the orbit just lateral to the ethmoidal roof; it is more difficult to reach via an intranasal approach. However, during an external ethmoidectomy, the periorbita may be violated higher in the orbit and as a result, injury to the superior oblique may occur. (The surgeon should note that the convergence of the superior oblique and the medial rectus muscles is the location of the extraconal portion of the anterior ethmoidal artery and more posteriorly, the take-off of the ophthalmic artery. Injuring these vessels is even more severe than muscle injury.) Muscle injury can be caused by direct muscle injury or injury to the nervous or vascular supply to the eye muscle. Indirect muscle injury theoretically can occur as a result of heat conduction from a cautery or laser through a dehiscence in the *lamina papyracea*; therefore, bipolar cautery is advised when topical thrombotic agents are ineffective. No published reports of this type of injury are known. Unintentional injection of local anesthesia into the orbit can traumatize the medial rectus muscle and cause temporary diplopia or anisocoria. Powered instrumentation has recently been noted to be related to medial rectus injury. If a dehiscence occurs in the *lamina papyracea*, the high suction used by a microdebrider can pull the periorbita, orbital fat, and medial rectus into the microdebrider chamber causing injury (64,65). Persistent diplopia necessitates ophthalmologic evaluation and possibly surgery, which has a poor prognosis.

Epiphora

The lacrimal gland and sac are contiguous with the ethmoidal sinuses in almost 90% of patients. The agger nasi cells are adjacent to the lacrimal sac, whereas the ethmoid sinus and natural maxillary sinus ostia are related to the lacrimal duct. To reiterate, the true maxillary sinus ostium is less than 5 mm posterior to the nasolacrimal duct, and Hasner valve opens the lacrimal apparatus into the inferior meatus within 1 cm of the anterior end of the inferior turbinate or pyriform. As a rule, the ethmoid sinuses or the maxillary ostia should not be opened anterior to the anterior end of the middle turbinate or into the hardened bone separating the maxillary os from the nasolacrimal duct. An IMA is made after identification of Hasner's valve and performed posterior and inferior to this structure.

Patients should be observed initially because most cases of epiphora resolve. However, prolonged epiphora is associated with persistent injury to the lacrimal system. Both intranasal and external ethmoidectomy and inferior middle meatal antrostomy are associated with this complication. Dacryocystitis can be associated with the Caldwell-Luc procedure as well. If recovery does not occur, a dacryocystorhinostomy with or without placement of drainage tubes can be performed endoscopically with little difficulty (66).

SUBCUTANEOUS EMPHYSEMA

When a fracture or perforation occurs in the *lamina papyracea* during external, intranasal, or endoscopic ethmoidectomy, subcutaneous emphysema can occur (6,20). This complication usually is caused by bag ventilation while the patient is emerged from anesthesia, coughing, nose blowing, emesis, or straining, all of which allow air to enter the soft tissue surrounding the eye (Fig. 44.14). Observation for orbital hematoma is necessary, especially if the periorbita has been violated. In rare instances subcutaneous emphysema is considerable, even extending into the mediastinum. Treatment in most cases is simple observation and reassurance. The emphysema usually reabsorbs within 7 to 10 days, but some puffiness can persist for a few months (6,20).

CEREBROSPINAL FLUID FISTULA

CSF fistula occurs with all techniques of ethmoidectomy, frontal sinus procedures (both open and endoscopic) and, in rare instances, sphenoidotomy. During ethmoidectomy the dura can be entered anywhere from the anterior ethmoid sinus base to the sphenoid sinus skull base (*planum sphenoidale*) or *sella turcica*. The variability in skull base anatomy makes certain areas more susceptible

to injury and the complication can be devastating. Along the anterior skull base in the anterior ethmoid region, the cribriform plate is lower than the *fovea ethmoidalis* and the lateral lamella. It is important that the surgeon stay away from the middle turbinate attachment and operate laterally within the ethmoid. The slope of the skull base is in a downward (Fig. 44.4) fashion as one progresses inferiorly and becomes more horizontal as the posterior portion of the anterior skull base (8,9). The medial part of the roof of the base of the skull posterior to the medial portion of the anterior ethmoidal artery to the sphenoid sinus is almost 10 times thinner than the rest of the bone and can be easily penetrated. The dura is tightly attached, and the base of the skull usually tears if bone is removed. The bone of the base of the skull is hard laterally and not easily penetrated above the sphenoid sinus. In the sphenoid sinus, removing disease from the superior wall or roof can cause a CSF fistula. Endoscopic surgery is especially dangerous because of monocular vision and loss of depth of field.

CSF fistula during frontal sinus usually occurs when using a drill during the performance of a Draf IIb or Draf III procedure or during an open osteoplastic procedure when the osteotomies are made outside the boundaries of the frontal sinus or where the depth of the posterior table is shallow (usually at the apex or lateral aspect of the sinus). The bone incision is made outside the frontal sinus. Although a template is made to help delineate the bone cut, the template is subject to human error during the setup of the x-ray (the patient should be 6 feet from the beam), printing, and with surgeon placement. Although safe and accurate, using an inaccurate image-guidance probe can also lead the surgeon outside the confines of the frontal sinus if the anatomy is not fully appreciated. When this occurs, dural exposure is found, but rarely a CSF fistula is present.

CSF fistula as a result of ethmoidal or sphenoid surgery can be repaired transantrally, externally, or intranasally during the operation if the leak is found intraoperatively. Almost any type of living tissue membrane can be used to patch a fistula; examples are fascia temporalis, septal or turbinate mucosa, and fascia lata (67–69). Local flaps of septal mucosa, inferior turbinate or middle turbinate also are successful. An endoscope or microscope provides excellent intranasal visualization. The nature of the injury, including defect size, intracranial complications, and whether the patient has the potential for elevated intracranial hypertension all play a role in selecting the graft type and number.

Delayed fistula identification and location are important. CT with intrathecal contrast agent helps to localize an active leak. Alternately, the injection of 0.1 mL of 10% fluorescein mixed with 10 mL of autologous CSF or bacteriostatic saline can be located with an endoscope after 20 to 30 minutes to help locate a CSF fistula (67,69). Endoscopic examination alone may suffice to localize a CSF fistula. Delayed fistulae can be repaired in the same fashion as those repaired in the acute setting. Adjunctive help from a neurosurgeon with the placement of a subarachnoid drain may be beneficial along with the mandatory bed rest. A failed closure mandates either a different approach (endoscopic or open), a change in adjunctive therapy, or referral to a more experienced surgeon. Use of antibiotics is controversial and should be used with caution so as not to select out resistant organisms.

HEMORRHAGE

Hemorrhage is one of the most common complications during or after sinus surgery. Transantral or external procedures have more bleeding associated with them than do intranasal procedures, although occasionally intranasal ethmoidectomy bleeding can be profuse. Hemostasis for intranasal surgery has to be controlled before the operation begins. Appropriate sedation, blood pressure control, anesthesia, administration of topical and injectable anesthetics, vasoconstriction, and waiting time before the operation is begun are important to decreasing risk of intraoperative hemorrhage.

Preoperative sedation and vasoconstriction with a topical spray in the surgical preparation area improve blood pressure control and decongestion and diminish any systematic reaction to topical vasoconstrictors. The use of total intravenous anesthesia with remifentanil and propofol with maintenance of bradycardia and relative hypotension can significantly reduce cardiac output and improve venous bleeding within the sinonasal cavity. The patient should be positioned at 15 degrees to decrease peripheral venous pressure. Irrigation with warm saline helps maintain platelet function. Frequent topical decongestion with 4% cocaine, cocaine powder, or 1:1,000 to 1:10,000 epinephrine ±10,000 units of thrombin significantly helps with mucosal bleeding. Greater palatine foramen injections placed prior to surgery can also help to control bleeding (70); the surgeon must take care to aspirate frequently during injection to ensure that the placement of the drug is not intravascular.

Only diseased tissue should be removed rather than widespread mucosal sacrifice (6,20). Although bleeding from the ethmoidal artery usually is not a problem given its location and the infrequent need to perform a skull base dissection in routine disease, the sphenopalatine artery and septal branch of the sphenopalatine artery running along the anterior face of the sphenoid sinus, below the os, can cause marked intraoperative and postoperative hemorrhage. Unipolar and bipolar endoscopic or microscopic cauterization provides good control of these vessels (6,20); however, the effect of cautery can lead to postoperative crusting and if performed near the sphenoid os, stenosis of the sphenoidotomy. If turbinates are removed, the remnant also should be prophylactically cauterized. Visualization is essential (6,20). Epinephrine diluted to 1:10,000 or even 1:1,000 placed topically during surgery often is helpful. Any topical solution should be marked appropriately so it is not inadvertently injected. If bleeding is too great

for intranasal surgery, especially endoscopic surgery, the procedure should be terminated on that side or altogether. Often it is safer to come back another day when bleeding usually is much less of a problem. Packing is placed at the end of the operation if oozing continues. Use of polyvinyl acetal sponge or perforated film absorbent dressing causes much less patient discomfort than does a nose full of petrolatum gauze or iodoform, and both materials are easily removed without significant bleeding.

There are multiple products available as topical dressings that can aid in bleeding control. When needed, these dressings can be helpful. While usually excellent sources of hemostasis, several of these topical hemostatic agents may cause problems with healing (71,72) and can be difficult to debride in the postoperative setting.

SYNECHIA

The most common complication of endoscopic sinus surgery is synechia formation. Synechia is especially common in functional or limited endoscopic sinus surgery with preservation of the middle turbinate. Prevention of synechia involves meticulous surgical technique with minimal manipulation of the middle turbinate and compulsive postoperative care. Even so, the slightest abraded surfaces can form synechiae. Most of these slight synechiae are not troublesome. If the middle turbinate adhesion to the lateral nasal wall is predictable following endoscopic sinus surgery, often the placement of a vinyl-wrapped sponge, gelfilm, or other absorbable or nonabsorbable packing material in the middle meatus or suture medicalization of the middle turbinate should be performed. If the septum appears to be the cause of middle turbinate lateralization, a septoplasty should be performed. The presence of a large symptomatic concha bullosa or polypoid middle turbinate necessitates reduction, which is performed along the lateral side of the concha bullosa. Again, if there appears to be contact between the cut edges of the concha bullosa and the lateral nasal wall, a middle meatal stent should be used or the concha bullosa medialized either with suture or by fashioning a controlled synechia to the septum.

Severely polypoid or atrophic middle turbinates can be part of the disease process and preservation may cause more problems than resolving; on occasion, these degenerated middle turbinates must be partially or completely removed. Spacers are helpful to separate the middle turbinate from the lateral wall. The ideal spacer is not yet available, but perforated film absorbent dressing works well and is fairly nonreactive. Polyvinyl acetal sponge is satisfactory for a few days, but tissue reaction and granulation occur if the material is left in place for a prolonged period. Steroid-impregnated middle meatal stents (73) as well as bioabsorbable sponges, which can be impregnated with steroid solution, are available on the market but can be expensive. Use of bioabsorbable materials can, however, reduce patient discomfort since they do not need to be removed.

Many surgeons routinely amputate the anterior end of the middle turbinate and find this avoids synechia without *sequelae*. It is important to understand that any reduction or undermining of the middle turbinate can predispose it to weakness, giving it a natural tendency to lateralize, blocking the anterior or posterior ethmoidal sinus, frontal recess, or antrostomy and precipitating infection (Fig. 44.19). Patients with turbinate reduction have to be observed for

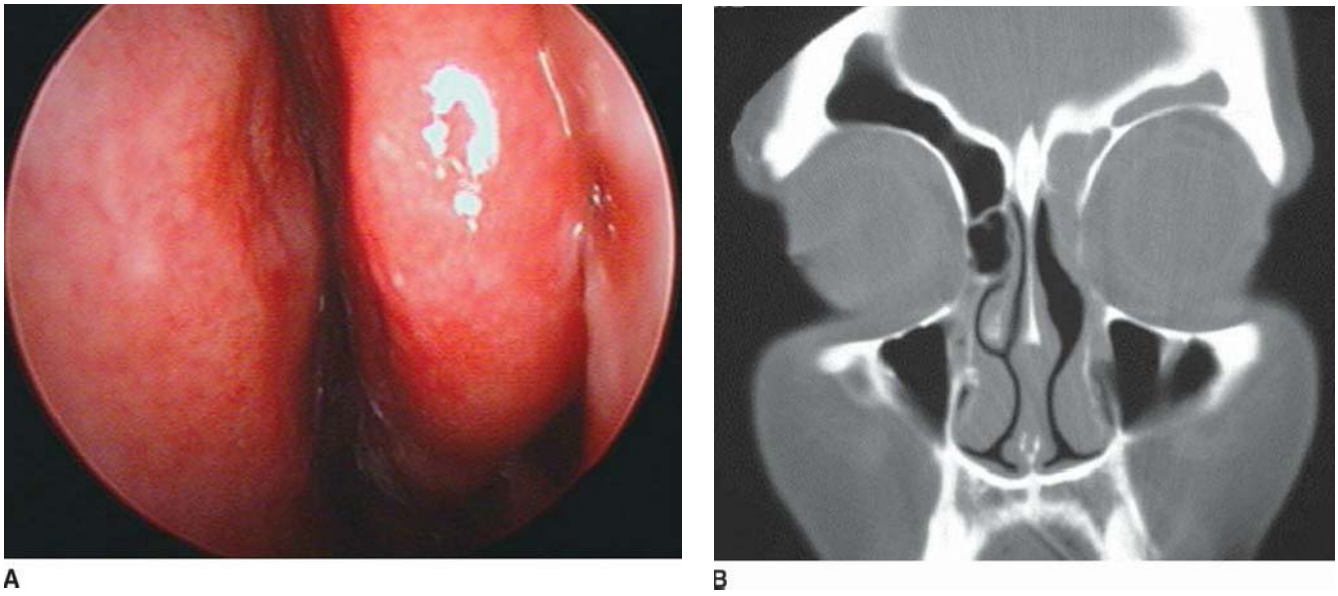


Figure 44.19 An endoscopic view **(A)** of a middle turbinate adhesion to the lateral nasal wall. The adhesion of this middle turbinate has caused frontal sinus obstruction **(B)**. Adhesion of the middle turbinate to the lateral nasal wall can be prevented by placing a middle meatal spacer consisting of absorbable or nonabsorbable material or by suture medialization of the middle turbinates with absorbable suture.

any evidence of lateralization. Removal of the agger nasi cells, if present, often opens the meatus, dramatically reducing the chances of middle turbinate lateralization. Middle turbinates can be attached to the septum by means of light scoring of opposing tissue to set up a scar adhesion, which can be divided after ethmoidal healing has occurred.

An antistaphylococcal antibiotic is used to prevent toxic shock syndrome, which can occur in an acute or delayed manner owing to the presence of packing or retained crust. Gelatin foam sheets, folded polymeric silicone, or hyaluronic acid gel ointment or packing can be helpful in operations on children and adults. These are expensive and often not necessary. Mitomycin-C has been used successfully to control scarring or synechia of the larynx but has had mixed results when topically applied to the nose and sinuses and is not recommended at this time (74–76). It is important for any foreign material to be appropriately anchored to avoid aspiration. Newer studies regarding the use of drug-eluting middle meatus stents (73) may offer promise in the reduction of these adhesions as well. Children may need follow-up examination under anesthesia for debridement of the nose, to take down synechia, and to make sure the maxillary ostium and anterior ethmoids remain open (77).

PARESTHESIA AND HYPESTHESIA

Paresthesia and hypesthesia are two of the most common complications of the Caldwell-Luc procedure, external ethmoidectomy, and frontal sinus surgery (13–15). For the most part, these are temporary complications that resolve 3 to 6 months after surgery. Obvious nerve transection as in frontal sinus obliteration causes permanent numbness. A small percentage of patients who undergo Caldwell-Luc procedures continue to have permanent numbness or paresthesia. This can signal recurrent sinusitis or dental injury, and medical treatment or revision surgery is needed to alter this problem if it is persistent. Medical therapy includes antibiotics, systemic and injected steroids, and medications such as phenytoin or carbamazepine to avoid neurologic problems. Yarington's (14), Low's (15), and Duncavage's modifications to avoid these complications are discussed (78). Paresthesia and/or hypesthesia during endoscopic sinus surgery can be due to injury to the infraorbital nerve or the branch of the fifth nerve supplying the medial wall of the maxillary sinus. Modifications to avoid these complications were discussed earlier.

OLFACTORY LOSS

There have been increasing injuries to the olfactory pathways after intranasal sinus surgery. Removal of the middle turbinate—whole or in part—may contribute to loss of smell. Obviously, direct damage to the cribriform plate(s) will compromise smell. Scarring or synechiae pulling the middle turbinate medially may affect smell. Certainly, the most common cause of smell loss is disease recurrence. Especially, in the case of recurrent nasal polyps and repeated surgeries, smell will diminish over time. The emphasis must be on prevention of olfactory injury and control of disease.

BRAIN INJURY AND MAJOR VESSEL INJURY

Injury to the brain and major blood vessels is rare during sinus surgery. The anterior communicating artery and its feeding vessels can be injured through the cribriform plate. These vessels are surprisingly close once the cribriform is penetrated. They can also go into spasm, resulting in serious central nervous system injury and sometimes death. Frontal lobe syndrome with loss of memory, forgetfulness, and behavioral change also can be caused by entrance through the roof of the nose into the brain (Fig. 44.20). Sphenoid surgery and injury to the carotid artery can occur (79,80). The carotid artery can be dehiscent in as many as 20% of sphenoid sinuses. Carotid cavernous sinus fistulae also can occur.

Prevention of brain and vessel injuries necessitates that the surgeon be aware of anatomic details, especially during operations on patients with structures compromised by disease or previous surgery. If appropriate visualization is impossible because of bleeding, the operation should be terminated. Sometimes radiologic evaluation in the operating room with a cross-table lateral radiograph, fluoroscopy, or computerized stereotaxis can help to establish the precise location of the nasal roof, base of the skull, and sphenoid sinus. Marked hemorrhage during superior or posterosuperior approaches can herald entrance through the nasal roof and brain injury.

All these conditions necessitate neurologic surgical intervention. Slight injury to the brain can be managed quickly and with minimal deficit. Serious injury is always life-threatening. Most patients who survive have a disruption of olfactory fibers with loss of smell and can have persistent neurologic *sequelae*. The more quickly intervention takes place, the better the chances for a good outcome. These types of injuries occur much less frequently under local anesthesia. Neurologic changes with general anesthesia are not found until the patient is awakened and even then can be delayed until the patient is wide awake. In the case of carotid artery injury, action must be taken immediately. A carotid drill should be established to aid in management of this problem (Table 44.4). It is possible that with quick action a life can be saved (79,80).

ABNORMALITY OF FACIAL GROWTH AND SINUS DEVELOPMENT

Although growth disturbance and retarded sinus development have occurred in animals (primarily pigs), no clinical study has shown growth problems (77). Therefore, sinus surgery should be deployed in children on a case-by-case

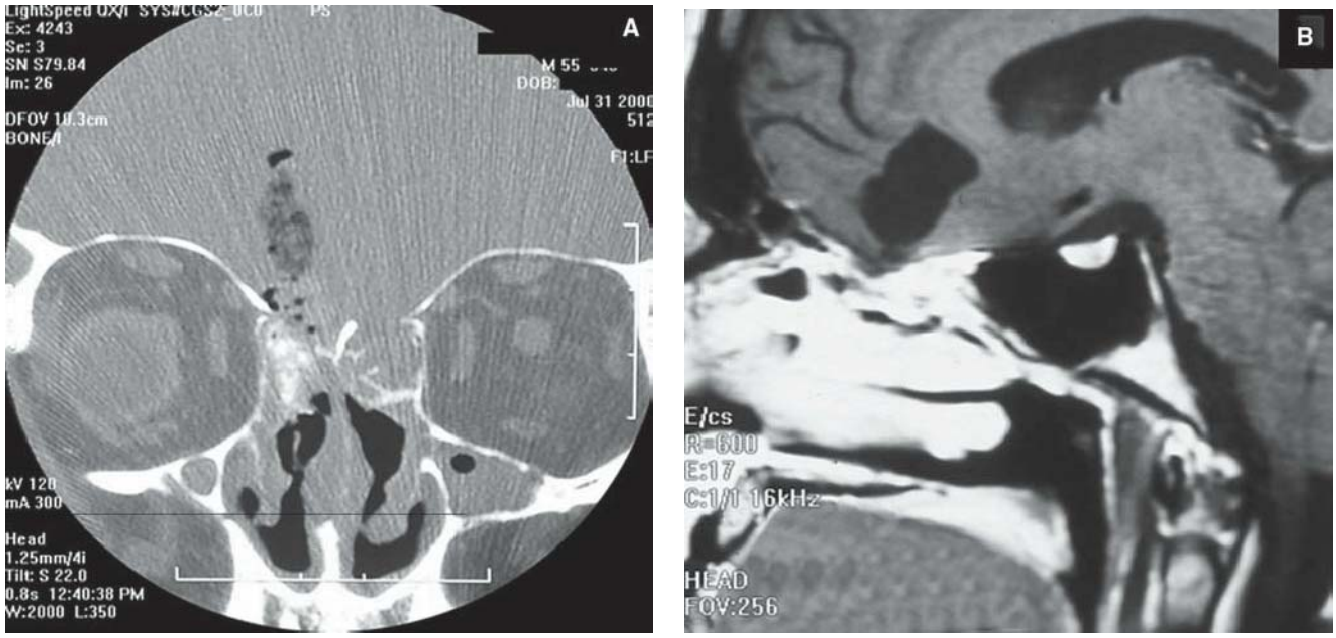


Figure 44.20 CT **(A)** and MR **(B)** images of a patient who sustained bilateral skull base injuries and brain injury during endoscopic sinus surgery performed with a microdebrider. As stated previously, the microdebrider is an excellent instrument for quick, precise removal of diseased sinus tissue; however, the utility of this instrument can be undone by a surgeon who is not present to his location within the sinuses.

TABLE 44.4 ℞ **TREATMENT CAROTID DRILL**

Tertiary care center

1. For every sinus operation, have available, on momentary notice, two long polyvinyl acetate (Merocel) sponges, petroleum-impregnated gauze, two 18F Foley catheters and umbilical clamps for nasal packing.
2. Pack nose immediately at the first sign of severe hemorrhage.
3. Compress the carotid artery in the neck on the affected side.
4. Begin anesthesia to induce controlled hypotension.
5. Ready blood for transfusion.
6. Call neurosurgeon immediately.
7. If the patient's condition is unstable, the neuroradiologist should perform intraoperative arteriography. If the patient's condition is stable, transfer the patient to the neuroradiology suite.
8. Perform balloon occlusion under EEG surveillance.
   a. If there is no evidence of a change in perfusion or lateralization, ligate the carotid artery.
   b. If changes are present on the EEG (dangerous recording), deflate the balloon, maintain packing, and observe.
9. Insert Swan-Ganz catheter. Put the patient in a hyperdynamic state by using high molecular weight starch (hetastarch) to increase cerebral perfusion.
10. After cerebral perfusion has been increased, reinflate the balloon and check the EEG.
    a. If lateralization occurs, try carotid bypass or barbiturate coma.
    b. If bypass is possible, reinflate the balloon and ligate the carotid artery.

Nontertiary hospital

1. Call neurosurgeon.
2. Expose the carotid artery in the neck.
3. Temporarily occlude the carotid artery with a clamp or tape.
4. Ligate the carotid artery.
5. Perform a trapping procedure: Clip the carotid artery below the anterior communicating artery to isolate this segment from blood flow.

EEG, electroencephalogram.

basis, with the full understanding that most children with chronic rhinosinusitis benefit from medical management, allergy management, and adenoidectomy prior to progression to sinus surgery. The previously mentioned anatomic variation related to growth and development of the face (i.e., canine teeth position, molar position) should be investigated prior to surgery.

MYOSPHERULOSIS AND TOXIC SHOCK

Myospherulosis, which is a foreign body reaction to ointment on nasal packing, can occur after sinus surgery and can lead to impaired healing due to increased risk of postoperative adhesion scarring (81). Likewise toxic shock syndrome due to specific staphylococcal organisms can occur in susceptible patients up to 1 month postoperatively even without nasal packing if fixed clot or crust is present (82,83).

HIGHLIGHTS

- There are no easy sinus operations.
- Practical knowledge of anatomy correlated with sinus CT scanning is most important in avoiding complications.
- The *lamina papyracea* and middle turbinate should be identified early in intranasal surgical procedures on the ethmoidal sinus.
- Knowledge of distance relations aids in finding important intranasal structures.
- All sinus procedures have common minor complications that resolve in most cases.
- Major complications in sinus surgery are rare; however, when they occur they often are catastrophic.
- The complications of paresthesia and hypesthesia from the Caldwell-Luc procedure can be avoided with alterations in technique.
- Distances to important structures in transantral sphenoethmoidectomy are less than they are in intranasal procedures.
- Blindness related to retro-orbital hematoma can be reversed or prevented if managed immediately.
- CSF fistula can occur with almost any surgical procedure on the sinuses and can be corrected during the operation.
- Operative or postoperative hemorrhage, especially during or after intranasal surgery, can be prevented if a judicious combination of anesthesia and surgery is used.
- Intracranial or major vascular injury, if managed immediately, can be minimized in some cases.
- Blind trust in image-guided (computerized) surgery without visual anatomic correlation may result in serious injury.

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45 Endoscopic Evaluation and Treatment of CSF Leaks

Pete S. Batra

HISTORY OF CSF LEAK SURGERY

The history of surgery for cerebrospinal fluid (CSF) rhinorrhea has witnessed evolution from an entity historically managed by neurosurgeons via open approaches to one largely in the rhinologic domain amenable to endoscopic techniques. The initial description of CSF leak management was provided by Dandy (1) in 1926, who repaired a case of pneumocephalus resulting from a frontal dural tear suffered from trauma via a frontal craniotomy approach. In 1948, Dohlman (2) reported the first extracranial repair of cribriform plate CSF leak using muscle and nasal mucosa via a nasoorbital incision. In 1952, Hirsch (3) repaired a sellar CSF leak resulting from resection of a pituitary tumor by a transnasal transseptal approach. In 1981, Wigand (4) provided the initial description of endoscopic repair of CSF leaks; he repaired six intraoperative leaks encountered during 300 ethmoidectomy procedures. In 1996, Lanza et al. (5) reported endoscopic repair of 36 skull base defects, codifying the endoscopic technique as the method of choice for treatment of CSF rhinorrhea.

CSF PHYSIOLOGY AND INTRACRANIAL PRESSURE BASICS

Normal CSF is a clear colorless fluid nearly iso-osmotic to plasma. CSF serves several key functions, including protecting the central nervous system, providing an alternate circulation for distribution of micronutrients, and mediating intracranial compliance in physiologic and pathologic states. Majority of CSF is produced from the choroid plexus of the ventricular system (70%). The remainder is produced extrachoroidally by capillary ultrafiltration (18%) and metabolic water production (12%). In an adult, the total CSF volume equals approximately 140 to 150 mL. The ventricles hold about 30 mL, while the brain and spinal subarachnoid spaces contain 80 and 30 mL, respectively. Traditional teaching holds that CSF production occurs at a constant rate of 500 mL daily. However, quantitative magnetic resonance (MR) imaging has estimated daily production rates as high as 650 mL based on variations with circadian rhythm, with maximal production at 2:00 AM and nadir at 6:00 PM. CSF absorption is a hydrostatic pressure–dependent event that occurs at the arachnoid villi juxtaposed to the dural sinuses. These villi act as pressure gradient one-way valves that transmit CSF into the venous system when the intracranial pressure (ICP) increases 3 to 6 cm H_2O greater than venous pressure (6,7).

Normal ICP ranges from 5 to 15 cm H_2O at the lumbar cisterns with the patient in a supine position. ICP is a dynamic measurement with activities, such as change in position, straining, and sneezing, transiently increasing it to 40 cm H_2O. Further, the pressure can vary depending on time of day, patient age, respiratory phase, and cardiac cycle. Sustained increases or frequent spikes in the 20 to 30 cm H_2O range can result in neurologic symptoms and requires measures to reduce the ICP. For example, patients with ICP exceeding 20 cm H_2O in the setting of traumatic brain injury is strongly associated with mortality (6).

ETIOLOGY

A number of important etiologies may result in CSF rhinorrhea. The most common include accidental trauma, surgical trauma, congenital, tumors, and spontaneous (or idiopathic). Though earlier studies cited accidental trauma as the most common etiology, recent reports have noted spontaneous CSF leaks to be the most common cause of CSF leakage. Banks et al. (8) reported on 193 cases repaired over 21 years; the most common etiologies included spontaneous (40%), iatrogenic trauma after endoscopic sinus surgery (ESS) (26%) or endoneurosurgical procedures (20%), accidental trauma (8%), and congenital (4%). Careful understanding of these etiologies is a prerequisite

prior to devising a comprehensive diagnostic and management strategy for effective surgical repair of CSF rhinorrhea.

Accidental Trauma

The reported incidence of posttraumatic CSF leaks ranges from 2% to 4% in cases of blunt head injury. Eighty percent of leaks will occur within 48 hours after injury, and 95% will manifest in 3 months. However, a small but important subset may have a delayed presentation months, or even years, after the initial injury. Though 70% will present with active CSF rhinorrhea, the remainder will only develop pneumocephalus or ascending meningitis as part of the initial presentation. The most common locations of skull base fractures in descending order include the ethmoid–cribriform plate region, posterior table of the frontal sinus, orbital roof, and sphenoid sinus. The fractures can range from linear fractures to massive communication of the entire skull base, based on the extent of traumatic force. Concomitant facial fractures and intracranial lesions, such as cerebral contusion and epidural or subdural hematoma, are not uncommon.

Approximately 60% to 70% of traumatic leaks will close with conservative measures, such as bed rest, stool softeners, and lumbar drain (LD). However, the dura does not regenerate in these cases and the skull base may only be covered by a thin monolayer of nasal mucosa or fibrous tissue. Further, this layer may break down over time by sinonasal inflammatory processes or by the pulsatile effect of the brain. The risk of ascending meningitis in this setting has been noted in 30% to 40% of cases. This underscores the need for a proactive strategy with early detection and repair of persistent posttraumatic CSF leaks. All cases of suspected trauma should undergo high-resolution thin-cut computed tomography (CT) imaging to delineate the extent of skull base fracture. The management strategy should be highly individualized given the heterogeneity of these fractures. Cases with linear disruption of the ethmoid or sphenoid roof are good candidates for an endoscopic approach. Cases with extensive skull base disruption, especially with associated skull fractures or intracranial injury, may require an open neurosurgical approach. Penetrating skull base trauma from gunshot wounds or other projectile missiles can also result in significant skull base comminution and may be associated with extensive granulation tissue in the path of the foreign body (Fig. 45.1A and B). Close multidisciplinary coordination among subspecialty services is imperative to optimize care in these challenging cases (9,10).

Surgical Trauma

Surgical trauma from ESS or neurosurgical procedures represents the most common causes of iatrogenic CSF leaks. With the advances in image-guided surgery and sophisticated surgical instrumentation, the risk profile of ESS

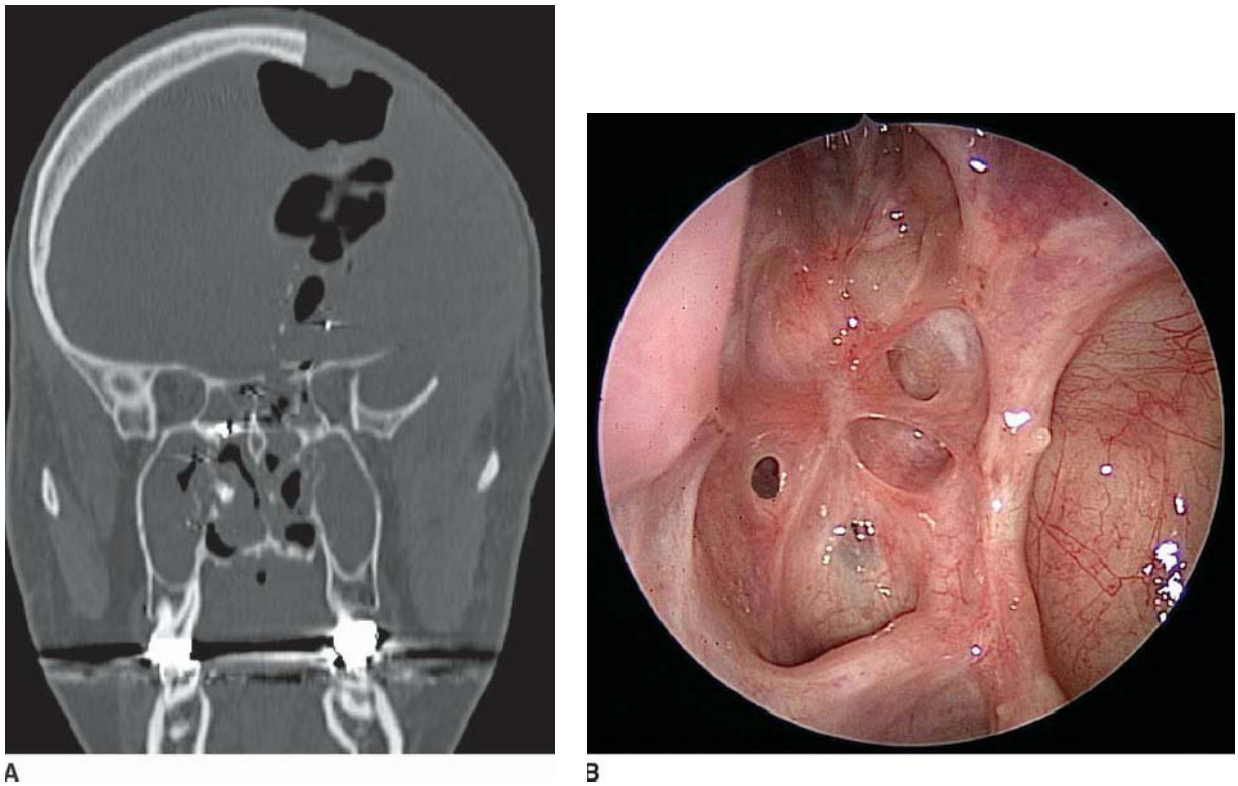


Figure 45.1 **A:** Reformatted coronal bone window CT scan demonstrates disruption of the left posterior ethmoid roof and resulting pneumocephalus from a self-inflicted gunshot wound. **B:** Endoscopic view of the left side with 0-degree endoscope demonstrates a healed posterior ethmoid roof after endoscopic repair 1-year postoperatively.

has improved dramatically with the general incidence in the 0% to 3% range. In a recent review of 6,908 endoscopic sinus surgeries at a single institution, 32 (0.46%) intraoperative CSF leaks were reported (11). Approximately 70% of the leaks were evident at the time of surgery, while 30% manifested postoperatively. The side distribution was right in 56%, left in 41%, and bilateral in 3% of cases. The leaks were commonly to result in hands of residents and novice attending surgeons. Further, asymmetry and low-lying skull base have been recognized as potential risk factors for iatrogenic leaks.

The two most common locations for CSF rhinorrhea include the lateral lamella of the cribriform plate (LLCP) and posterior ethmoid roof as it transitions to the sphenoid sinus. LLCP represents the thinnest portion of the skull base with mean thickness of 0.5 mm; this decreases 10-fold at the ethmoidal sulcus, the entrance of the anterior ethmoid artery into the olfactory fossa. The region is more at risk on the right side, especially in right-handed surgeons, given tendency to drift medially during the ethmoid dissection. Aggressive resection of the vertical attachment of the middle turbinate to the skull base also risks injury to the cribriform plate. The posterior ethmoid roof is at risk in scenarios where the maxillary sinus is extensively aerated; this excessive pneumatization encroaches more medially and superiorly, resulting in inversely proportional decrease in total inferior to superior height of the posterior ethmoid. High entry into the basal lamella poses a significant risk of injury to the posterior ethmoid roof (Fig. 45.2). The size of the skull base defect can vary from millimeters to greater than 2 cm, especially in cases of use of powered instrumentation. Underlying dural and intraparenchymal brain injury may result from breach of the skull base boundary, especially in cases of significant anatomic disorientation and delay in recognition of this violation.

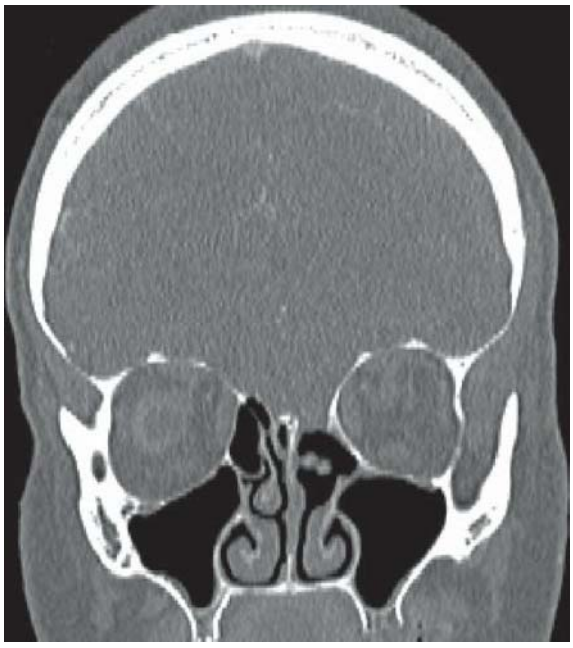


Figure 45.2 Reformatted coronal bone window CT scan illustrates bony defect in the left posterior ethmoid roof incurred during previous ESS. The patient had an asymmetric low-lying skull base that likely contributed to injury during the ethmoid dissection.

A variety of neurosurgical procedures can result in intraoperative CSF leaks. Historically, rhinologic involvement in this setting has been limited to addressing inadvertent postop leaks resulting from open transsphenoidal hypophysectomy or transcranial approaches to the anterior skull base (ASB) for neoplasm resection. Paraclinoid aneurysm clipping complicated by postop CSF rhinorrhea also represents another clinically challenging scenario given the narrow confines of the opticocarotid recess in the sphenoid sinus. In rare cases, a CSF leak from lateral skull base surgery may manifest as CSF rhinorrhea as it egresses via the eustachian tube. Management of the leak at the primary site represents the treatment of choice, though eustachian tube closure may be required in select cases.

The advent of advanced endoscopic techniques has greatly facilitated the surgical management of skull base neoplasms. Endoneurosurgical procedures, including transcribriform and transethmoid approaches to the anterior cranial fossa and transclival approaches to the posterior fossa, may result in large skull base defects with high-flow CSF leaks. This surgical paradigm involves close coordination between rhinology and neurosurgery for access to the skull base, combined tumor resection, and planned repair of the skull base defect with multilayered closure or vascular pedicled flap. Thus, the iatrogenic leaks in these cases are expected sequelae of the surgical procedure and addressed as an integral component of the surgery.

Spontaneous

Spontaneous CSF leaks represent an important clinical subset of leak patients whose prevalence may be increasing. No obvious definable etiology such as trauma, surgery, or neoplasm can be identified in this group. Emerging data have demonstrated that these represent a distinct clinical entity, being typically observed in middle-aged females with elevated body mass index. Common presenting symptoms include headaches, pulsatile tinnitus, and vertigo, along with CSF rhinorrhea. CT imaging may demonstrate a broadly attenuated skull base or arachnoid pit formation, while MR imaging may show partially or completely empty sella. This group also has the highest rate of encephalocele formation, being noted in 50% to 100% of cases. Many of these patients may have elevation of ICP or carry an underlying diagnosis of benign intracranial hypertension (BIH). The etiology of elevated ICP is not known but may be related to impaired CSF absorption at the arachnoid villi. Chronic elevation of ICP results in transmission of hydrostatic forces along the areas of least resistance such as the cribriform plate or lateral pterygoid recess of the sphenoid sinus causing erosion of the skull

base and ensuing herniation of meninges or brain and associated CSF rhinorrhea. Alternately, the forces may be exerted at the optic nerve sheath causing papilledema and visual loss (12,13).

Spontaneous CSF leaks represent the most challenging group for surgical repair and have been historically associated with the highest failure rate. This may in part be related to technical hurdles from a broadly, thinned skull base and associated encephalocele formation, along with underlying elevated ICP. The current surgical algorithm entails meticulous repair of the skull base defect and management of associated intracranial hypertension. Methods to accomplish the latter include administration of oral acetazolamide (ACTZ) to reduce the ICP. Ventriculoperitoneal (VP) shunting may be considered in severe cases.

Congenital

Congenital encephaloceles are herniation of meninges and/or brain through a skull base defect that maintain an intracranial connection. Though occipital lesions comprise 70% of these lesions, the otolaryngologist is most likely to encounter sincipital (20%) or basal (10%) encephaloceles. Sincipital encephaloceles are further subdivided into naso-frontal, nasoethmoidal, and naso-orbital lesions that exit anterior to the cribriform plate, typically presenting as a mass over the nose, glabella, or forehead. Basal encephaloceles present as an intranasal mass, with the defect being at the level of the cribriform plate or just posterior in the superior or lateral sphenoid. The mean age of presentation is 6 years, with common symptoms being nasal obstruction, CSF rhinorrhea, meningitis, or facial mass with hypertelorism.

Timely repair of the skull base defect is imperative to stop the CSF leak, to minimize risk of meningitis, to alleviate nasal obstruction, or to prevent further facial deformity. Traditional approaches have relied on combined extra- and intracranial repair by otolaryngology and neurosurgery. The advent of endoscopic techniques has facilitated minimally invasive resection of encephaloceles with layered skull base reconstruction and avoidance of external incisions with high success rate. Nonetheless, the technical challenges should not be understated given the narrow confines of the pediatric sinonasal anatomy and need for appropriate rigid scopes and instrumentation. In select cases, surgical management may need to be deferred till age of 2 to 3 years to allow for adequate facial growth to accommodate an endoscopic approach (14,15).

Tumors

Skull base neoplasms can result in CSF rhinorrhea in rare circumstances. Primary brain parenchymal or pituitary neoplasms can cause extensive bone erosion at the skull base with a resultant CSF leak. Conversely, aggressive sinonasal malignant neoplasms can invade the skull base and cause a CSF leak. Moreover, intracranial neoplasms may cause communicating or noncommunicating hydrocephalus, leading to CSF leakage. Management of the underlying neoplasm and elevated ICP are imperative in these scenarios. CSF leak repair, if clinically warranted, should only be undertaken after the underlying etiology is addressed.

PATIENT WORKUP

Patient History

The classic presentation of a CSF leak involves unilateral clear rhinorrhea that worsens with straining or bending over. Many patients with a spontaneous leak may recall a history of antecedent viral upper respiratory infection or significant sneezing or coughing as the inciting event. Patients may report a salty or metallic taste from posterior drainage of the CSF rhinorrhea. Headaches are a common symptom from sudden changes in the ICP from the CSF leakage. Careful history should ascertain for previous trauma and sinonasal or neurosurgical procedures. In select cases, sudden onset of meningitis may be the only presenting symptom of a skull base defect without associated CSF rhinorrhea. It is imperative for the otolaryngologist to evaluate for defects in the skull base as a potential etiology of unexplained meningitis. Equally importantly, any patient with an active CSF leak should be carefully counseled on the warning signs of meningitis until successful closure is performed.

Physical Examination

Complete head and neck examination is an integral component of the evaluation. Patient may be able to produce the clear rhinorrhea by leaning forward. The otologic evaluation may reveal a middle ear effusion suggestive of a possible temporal bone leak via the eustachian tube. An ophthalmologic examination may be necessary if papilledema from BIH is suspected. Rigid nasal endoscopy is crucial for accurate diagnosis of CSF rhinorrhea. Endoscopy may demonstrate a glistening pulsatile mass in the olfactory cleft (Fig. 45.3). Further, pooling of clear secretions in the nasal cavity may be noted that rapidly fills with suctioning.

Laboratory Testing

Historically, glucose strip testing has been employed as a rapid test to assay for CSF rhinorrhea. False positives are common given the reducing substances in nasal mucus. It represents a nonsensitive and nonspecific study and should not be relied upon in the contemporary diagnostic strategy for the CSF leaks. β2-Transferrin is a protein produced by the neuraminidase activity in the brain and is detectable almost exclusively in CSF. Low levels of β2-transferrin are found in the perilymph of the cochlea and aqueous and vitreous

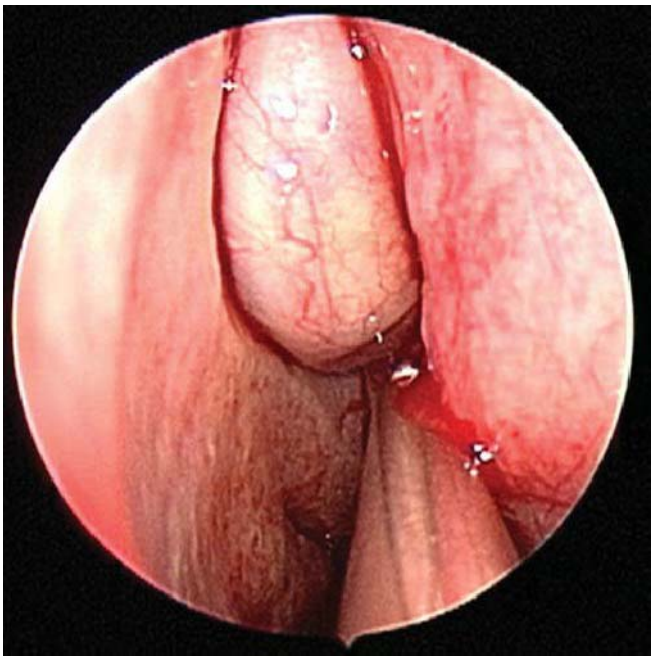


Figure 45.3 Endoscopic view on the left side with a 0-degree endoscope demonstrates an olfactory cleft encephalocele.

humor of the eye. It is a highly sensitive and specific noninvasive test that has been used successfully as a primary screening modality for suspected CSF leakage. Minimal volume of 0.5 mL is required for the assay, which may prove problematic in patients with slow or intermittent leaks. Further, the test is only performed at select laboratory facilities across the country, thus resulting in a delay of a few days to confirm diagnosis. The result should be interpreted with caution in patients with liver failure due to derangements in serum protein levels in this pathologic state. β-trace protein is synthesized primarily by the epithelial cells of the choroid plexus and is found in concentrations 35-fold higher in CSF than in plasma. It may represent a quantitative alternative to β2-transferrin for testing for CSF rhinorrhea. The test is available in Europe for commercial usage. It must be remembered that these biochemical tests can only prove the presence of CSF in the tested specimen, but are unable to directly demonstrate the CSF leakage or leak site (16).

Imaging Studies

Radiographic studies are an essential component of the diagnostic workup. The objectives of imaging for CSF rhinorrhea include to tentatively confirm the diagnosis, to precisely localize the defect site, and to evaluate for potential underlying etiologies. High-resolution CT imaging (1 mm or less) with triplanar coronal, axial, and sagittal views represents the initial study of choice to evaluate CSF rhinorrhea. Direct or reformatted coronal images are ideal for evaluation of the ethmoid roof, cribriform plate, and planum sphenoidale. Axial images are best for assessing posterior wall of the frontal sinus, posterior and lateral walls of the sphenoid sinus, and clivus. CT scanning facilitates close understanding of the underlying paranasal sinus anatomy, helps identify the skull base defect and any associated areas of bone disruption in iatrogenic or traumatic leaks, and serves as a roadmap for image-guided surgery. In cases of spontaneous leaks, CT imaging may demonstrate a soft tissue density in the olfactory cleft, ethmoid roof, or lateral pterygoid recess of the sphenoid sinus (Fig. 45.4A and B). Broad attenuation or arachnoid pits of the skull base may be seen from chronic ICP elevation. Careful review of the entire sinus CT scan is critical to identify multiple simultaneous defects. The sensitivity and specificity of CT scanning for CSF rhinorrhea has been demonstrated to be greater than 90% (17).

MR imaging can serve as an important adjunct in select cases of CSF rhinorrhea. It can facilitate differentiation of postobstructive secretions from herniated intracranial contents in an opacified cell adjacent to the skull base defect. Further, CSF can be distinguished from brain parenchyma in the meningoencephalocele sac on T2-weighted coronal images. Associated intracranial abnormalities, such as aberrant vessels or adjacent areas of encephalomalacia, can be appreciated prior to embarking on surgery, especially in cases of significant skull base trauma. MR imaging can also help establish presence of partially or completely empty sella in cases of spontaneous CSF leaks. Empty sella syndrome likely results from chronic ICP elevation with ensuing dural herniation through the sellar diaphragm and filling of the sella with CSF. This leads to perceived appearance of an empty sella, a finding that has been noted in 82% to 92% of cases of spontaneous CSF leaks (18).

The dilemma arises when the patient has a positive β2-transferrin and high-resolution CT is unable to identify the precise site of the leak. A variety of imaging techniques have been advocated for patients with intermittent or slow CSF leaks that remain elusive despite appropriate workup. CT cisternography has been utilized since 1970s to help isolate the site of sinonasal and temporal bone leaks. The procedure involves intrathecal injection of contrast material followed by high-resolution triplanar CT imaging, thus providing the ability to confirm the presence of active leak and to establish the exact location of the skull base defect. The study is especially useful for frontal or sphenoid leaks as these act as reservoirs of contrast material. The diagnostic capability is limited by its inability to identify intermittent leaks, with reported sensitivity for active and inactive leaks being 92% and 40%, respectively. MR cisternography involves T2-weighted fast spin-echo sequences with fat suppression and image reversal to define the CSF fistula. The technique is noninvasive that may be particularly helpful in patients with multiple skull base defects. Studies describing utility of MR cisternography have demonstrated sensitivity of 87% and accuracy ranging from 78% to 100% (17,19).

Radionuclide cisternogram, commonly known as the pledget study, involves endoscopic placement of multiple pledgets in the paranasal sinus confines followed by intrathecal injection of the radioactive tracer. Typically, these are

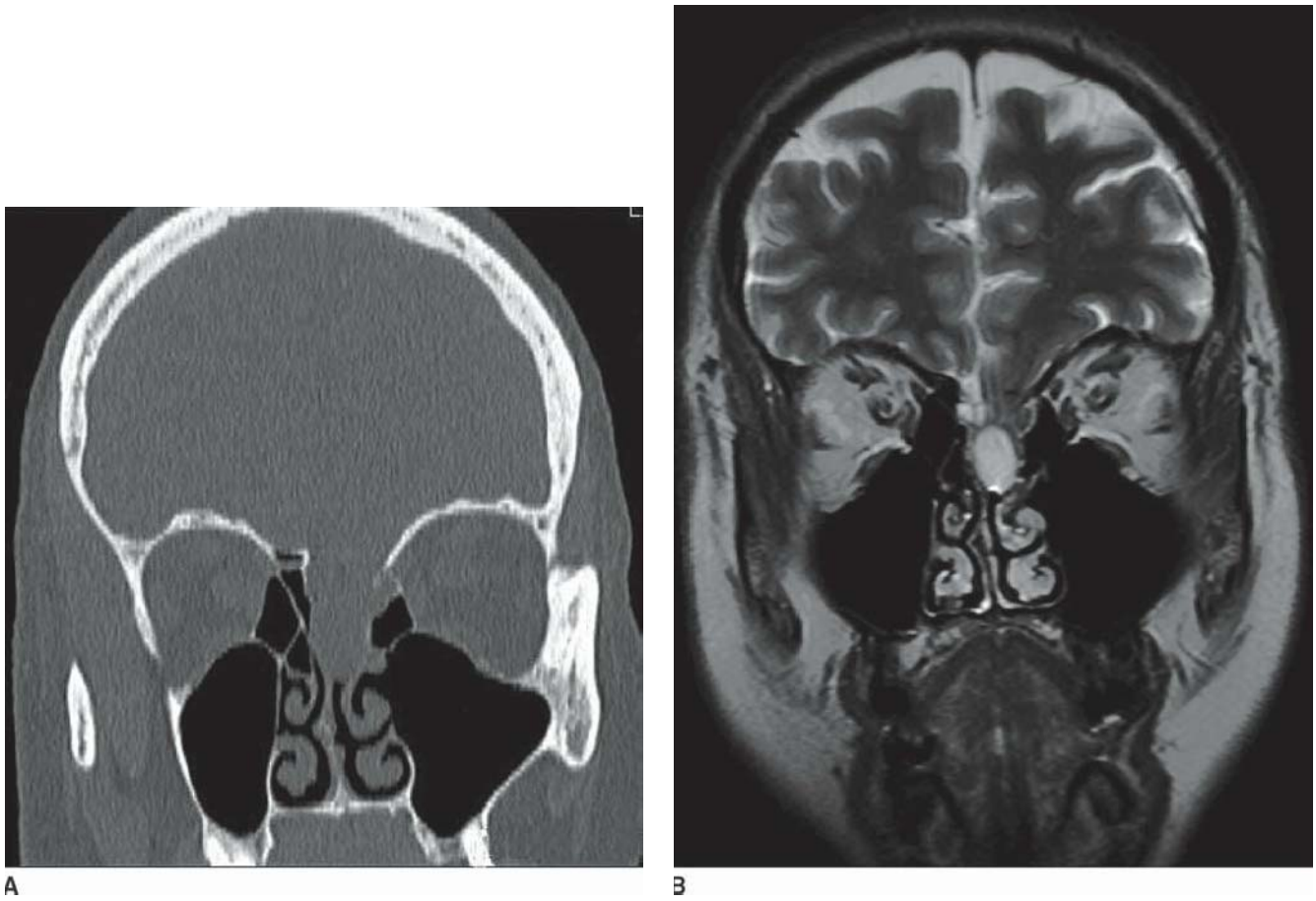


Figure 45.4 **A:** Corresponding reformatted coronal CT scan in patient from Fig. 45.3 demonstrates an extensive cribriform plate/ethmoid roof defect with resultant meningoencephalocele. **B:** Coronal T2-weighted MR shows that the mass contains both CSF and brain parenchyma.

placed in the olfactory cleft, middle meatus, and sphenoethmoid recess on both sides. The pledgets are removed 6 to 24 hours later and radiotracer activity is measured and compared to serum. A pledget:serum ratio of 1.5 to 3.0:1 is indicative of a leak. The primary advantage of this modality is in patients with very slow or intermittent leaks since the pledgets are left in place for many hours and can continuously collect CSF. The study is limited by its inherent inability to precisely localize the site of the leak; the reported sensitivity ranges from 62% to 76%. The breadth of laboratory and radiographic modalities available for diagnosis underscore the diagnostic dilemmas in accurately identifying CSF leaks. Since no gold standard study exists, the clinician should selectively order diagnostic laboratory and radiographic studies as dictated by careful history and physical examination.

PERIOPERATIVE ISSUES

Intrathecal Fluorescein

Fluorescein by intrathecal injection has been used to facilitate CSF leak identification and to ensure watertight closure. It may be particularly helpful in cases of multiple skull base defects or cases with significant alteration of skull base anatomy from accidental or iatrogenic trauma. Standard intrathecal injection entails use of 0.1 mL of 10% fluorescein mixed in 10 mL of patient's CSF, which is infused into the subarachnoid space through the LD over 10 to 15 minutes. An additional 5 mL of patient's CSF is utilized to flush the line. Intrathecal fluorescein (ITF) turns a bright green color when combined with CSF. It is generally visible endoscopically, though a blue light filter may be used to localize dilute fluorescein in select cases (Fig. 45.5). The sensitivity and specificity of ITF has been reported at 74% and 100%, respectively. The 26% false-negative rate underscores the potential diagnostic limitations of ITF; the surgeon should continue to look for the site of skull base defect based on preoperative imaging studies (20).

ITF is not approved by the Food and Drug Administration for intrathecal usage; thus, its utility in this setting represents an off-label usage. Informed consent is essential to ensure proper patient counseling in the preoperative period. Overall, the risk of adverse events with careful usage at lower doses is quite low at rate of 0.1%. Doses less than 100 mg are generally safe but can be associated with



Figure 45.5 Endoscopic view of left ethmoid cavity with 0-degree endoscope illustrates fluorescein-stained CSF from a spontaneous cribriform plate CSF leak.

headaches, nausea/vomiting, or dizziness in 2% to 10% of cases. Doses between 100 and 700 mg have resulted in neurologic deficits, grand mal seizures, pulmonary edema, and death (21). Pretreatment with steroids and diphenhydramine may be used to minimize the risk of untoward effects.

Lumbar Drain

Traditionally, LD placement has been considered an integral step in repair of CSF leaks. Possible advantages for usage include to inject the ITF, to obtain baseline ICP measurement in cases with suspected BIH variant, and to provide CSF drainage in the postoperative period. The CSF diversion may theoretically decrease risk of CSF leak by allowing for better apposition of the graft to the recipient site and attenuating sudden ICP changes that may result from bucking during extubation and vigorous coughing, sneezing, and movement in the postoperative period. These potential benefits must be carefully weighed against the risks posed by LDs. Associated risks include minor complications such as spinal headaches and paresthesias and major complications such as meningitis and pneumocephalus. Excessive CSF drainage has been linked to transtentorial herniation. With continued accrued experience, the practice of routine LDs in the perioperative period has evolved to selective use of lumbar drainage for special circumstances. Mounting evidence suggests that LD is not a prerequisite to achieving CSF leak repair; indeed, many skull base defects can be successfully reconstructed without use of LD (22). Specific situations that may require LD include high-pressure or high-flow leaks, problematic skull base reconstruction, or persistent postoperative CSF rhinorrhea.

LD may be placed while the patient is awake or after induction of general anesthesia. In the awake patient, the CSF pools in the lumbar cistern, thus facilitating easier placement of the LD. This may also be advantageous in the patient with chronic leak and relative CSF depletion. Alternately, LD placement may be deferred until anesthesia is achieved, especially in an anxious patient. Patients with large body habitus or previous spine surgery may require LD placement under fluoroscopy by interventional radiology. Postoperatively, the LD is drained at 5 to 10 mL/h with the patient in the recumbent position. The LD may be drained continuously, or may be drained as specified and then clamped for remainder of the hour. The typical duration of lumbar drainage should be 24 to 48 hours. The benefits of longer placement are unclear and may be associated with higher rates of infection. Ideally, patients should be monitored on a neurosurgical floor with nurses familiar with diligent care of LDs.

Antibiotics

Antibiotics have been historically utilized after traumatic CSF fistula to decrease risk of infectious intracranial complications. A recent Cochrane review evaluating use of antibiotics in patients with CSF rhinorrhea after skull base fractures failed to demonstrate any significant differences for reduction of frequency of meningitis, all-cause and meningitis-related mortality, and need for surgical repair of CSF leakage between antibiotic prophylaxis and control groups (23). Similarly, the putative benefits of long-term prophylactic antibiotics after CSF leak repair are unclear. Nonetheless, grafts are placed into and adjacent to the intracranial compartment through a contaminated sinonasal space. Perioperative antibiotics for 24 hours may be used to minimize risk of bacterial seeding of the intracranial space. Third-generation cephalosporins with good blood–brain barrier penetration, such as cefotaxime or ceftriaxone, may be used, with levofloxacin or vancomycin being reserved for penicillin allergic patients. In addition, all graft materials are soaked in a gentamicin solution to minimize risk of bacterial contamination.

SURGICAL MANAGEMENT

Rationale for Repair

Timely repair of CSF rhinorrhea and separation of intracranial from sinonasal contents is imperative to minimize risk of intracranial complications. Previous studies have demonstrated history of ascending meningitis in 19% to 36% of patients with an active CSF leak presenting for surgical management. The risk of developing meningitis has been estimated at 0.3 episodes per year.

Additional complications that may result from CSF rhinorrhea include pneumocephalus and cerebral or epidural abscess. Successful surgical repair decreases the risk of infectious intracranial complications to 0% to 0.9%, attesting to the timely efficacy of the endoscopic approaches (24).

Basic Surgical Principles

The surgical strategy should be tailored to each individual case based on the site and etiology of the leak. Certain key dictums must be followed to achieve successful repair of CSF rhinorrhea. Preoperative imaging review should guide the best endoscopic surgical route for repair. Potential surgical corridors that may be used include transcribriform, transethmoid, transsphenoid, transpterygoid, or combination thereof based on the site of the defect. The procedure is started with induction of general anesthesia. Standard surgical scrub is performed to reduce bacterial counts. Cotton pledgets soaked with oxymetazoline are placed in both nasal cavities to obtain maximal vasoconstriction. The sphenopalatine region and lateral nasal wall are injected with 1% lidocaine with 1:100,000 epinephrine. The paranasal sinuses are subsequently opened as dictated by the leak site. Adjacent paranasal sinuses should also be addressed to minimize risk of postoperative mucocele formation, since postoperative debridement adjacent to the reconstruction is deferred for 4 to 6 weeks.

Precise identification of the leak site is an absolute requisite to attaining good closure. This may be accomplished through use of preoperative CT imaging or intraoperative surgical navigation, along with intraoperative ITF in select cases. Systematic evaluation of all potential leak sites should continue, given risk of multiple leak sites in cases of trauma and spontaneous leaks. Once identified, careful cautery of the meningocele or meningoencephalocele is also critical prior to any reconstruction. Bipolar cautery is used for this objective; unipolar devices should be avoided as the depth of heat penetration cannot be controlled and may result in dural or brain parenchymal injury. The stalk and base of the encephalocele should only be resected after careful fulguration; aggressive manipulation of the base should be avoided. This may result in bleeding at the skull base interface; any vessel that retracts superiorly can potentially result in an intracranial bleed and stroke. Meticulous preparation of the graft recipient site is also an essential ingredient to success. All mucosa at the defect should be removed circumferentially for 2 to 4 mm. Gentle drilling of the bone adjacent to the defect may stimulate osteoneogenesis and further facilitate the closure. In most cases, multilayered reconstruction is required for optimal repair of the defect, though single-layer closure may suffice in select cases. Large dural high-flow defects, especially in the setting of endoscopic skull surgery, often require repair with pedicles flaps.

SITE-SPECIFIC REPAIR STRATEGY

Cribriform Plate/Ethmoid Roof

Both the cribriform plate and ethmoid roof are amenable to repair by a purely endoscopic approach. For ethmoid roof defects and larger cribriform plate defects, standard maxillary antrostomy and total ethmoidectomy is required for most cases. Frontal sinusotomy and sphenoidotomy may be required to enhance exposure to the anterior and posterior ethmoid roof, respectively. Further, these sinuses often need to be opened to minimize risk of scarring and mucocele formation. The one exception to this approach is small cribriform plate encephaloceles that resides strictly in the olfactory cleft. Often, the middle turbinate can be lateralized and the CSF leak can be addressed via transnasal approach to the olfactory cleft. The middle turbinate can be partially resected to increase exposure, if necessary. The reconstruction of these two areas differs given the variation in bony thickness. The bone at the ethmoid roof is much thicker, and a bone graft can often be placed in the epidural space. This facilitates the most robust reconstruction. On the other hand, the bone of the cribriform plate is quite thin and is frequently attenuated in spontaneous leaks. Attempts to place underlay grafts can further disrupt the bone and substantially increase the size of the skull base defect. Overlay grafts should suffice for these olfactory cleft meningoceles (25).

Sphenoid Sinus

Central sphenoid leaks can be managed via an endoscopic transnasal or transethmoid approach. A wide sphenoidotomy extending from the planum sphenoidale to the floor of the sphenoid and from the lateral sphenoid wall to the intersphenoid septum is essential to gaining wide exposure. Great care must be exercised during surgical maneuvers inside the sphenoid given close proximity of internal carotid artery (ICA) and optic nerve. Careful fulguration of the herniated dura and brain and circumferential removal of the mucosa around the defect remain key steps. Defects of the planum may be repaired with use of epidural bone grafts, along with other tissue arrays (Fig. 45.6A and B). In select cases, the nasoseptal flap may be used for skull base reconstruction of the central sphenoid. One surgical technique with limited clinical utility in the current surgical paradigm is fat obliteration of the sphenoid sinus. This approach entails removal of all sphenoid sinus mucosa to irreversibly obliterate the sphenoid sinus. Realistically, complete removal of mucosa is difficult and may pose risk to the ICA and optic nerve. Moreover, any residual mucosa may result in mucocele formation.

Lateral recess leaks pose a significant surgical challenge as they are not amenable to standard transnasal or transethmoid approaches. The transpterygoid approach affords access to the lateral sphenoid sinus. Wide maxillary

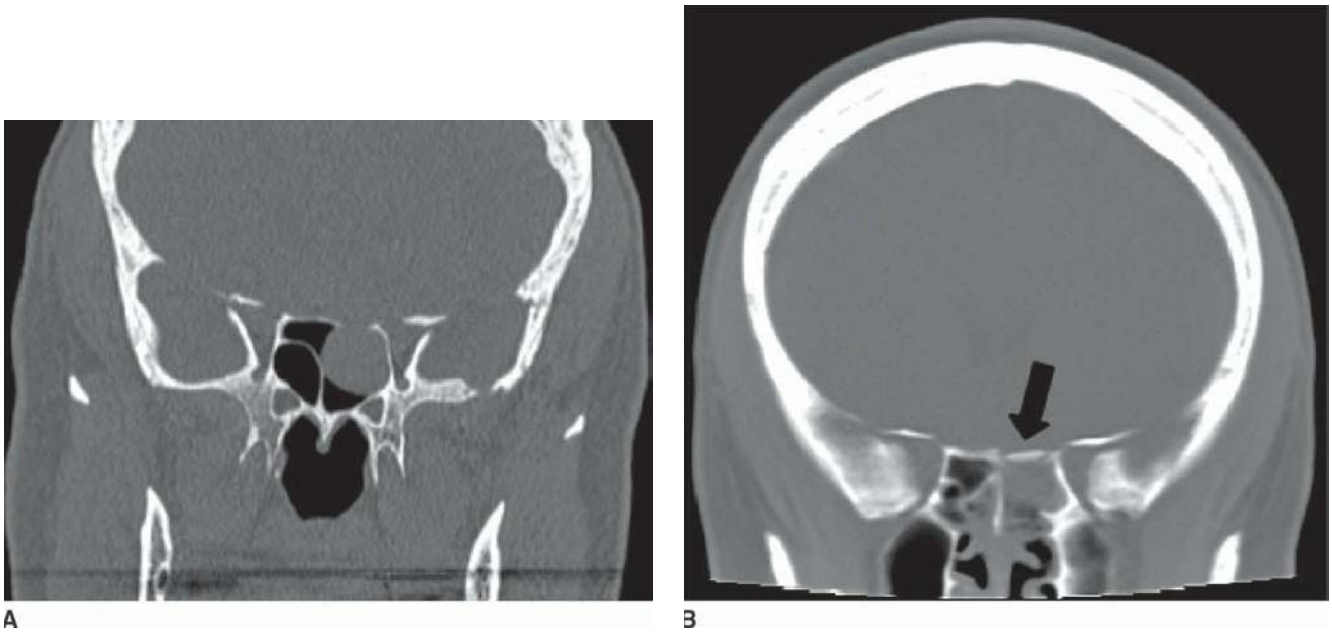


Figure 45.6 **A:** Reformatted coronal bone window CT shows a soft tissue mass in the left sphenoid sinus with a planum sphenoidale defect. **B:** Postoperative reformatted coronal bone window CT demonstrates septal bone graft (*arrow*) in the epidural space. The associated soft tissue density in the sphenoid sinus represents packing and mucus in the early postop period.

antrostomy, ethmoidectomy, and sphenoidotomy are performed to establish initial landmarks. The bone from the posterior maxillary sinus wall is removed to expose the pterygomaxillary fossa (PMF). Dissection in the PMF will expose the internal maxillary artery, which is either divided or reflected inferiorly. Great care must be taken to preserve the sphenopalatine ganglion, along with vidian, greater and lesser palatine, and infraorbital nerves. The pterygoid process that forms the anterior wall of the lateral recess is gently drilled to gain exposure. The skull base defect is then managed as per standard technique. Since spontaneous CSF rhinorrhea form majority of the leaks in this region, placement of a bone graft in the epidural space is preferred as a component of the definitive reconstruction (26).

Frontal Sinus

Frontal sinus CSF leaks represent a surgical challenge given the narrow anatomic confines of the frontal recess and proximity to critical structures, including the skull base and orbit. Traditionally, frontal sinus leaks have been managed by extracranial approaches such as osteoplastic flap with or without fat obliteration. The advances in endoscopic techniques, refinement of frontal instrumentation, and advent of image-guided surgery have afforded the ability to manage these leaks endoscopically. The two most common locations of frontal leaks include the frontal recess and posterior table of the frontal sinus. Frontal recess leaks can be repaired via an endoscopic frontal sinusotomy or Draf IIB approach if greater exposure is required. Posterior table leaks can be managed via an endoscopic modified Lothrop procedure providing broad exposure of the frontal sinuses orbit to orbit. Defects in an extreme superior or lateral frontal sinus location restrict the ability to address these endoscopically. An adjunct endoscopic frontal trephination or osteoplastic flap may be required to address these leaks. Great care must be taken to preserve uninvolved mucosa to minimize risk of frontal sinus stenosis and mucocele formation (27).

Anterior Skull Base

The CSF leaks are expected sequelae of minimally invasive endoscopic resection (MIER) of ASB neoplasms. Careful separation of the sinonasal and intracranial compartments and minimizing risk of potential cross-contamination are crucial steps in the success of MIER. A variety of surgical techniques have been employed to achieve skull base reconstruction with acceptable results. The surgical paradigm of multilayered reconstruction has also been applied to ASB reconstruction. After circumferential elevation of the dura, the initial two layers are placed in an underlay fashion in the epidural space. Autogenous tissues, such as temporalis fascia or fascia lata, or synthetic tissue arrays, such as acellular dermis or dural substitutes, can be used for this purpose. Additional layers of tissue may be placed in an overlay fashion, with the final layer being free mucosal graft from the floor of nose or septum (Fig. 45.7). Cartilage and bone grafts are avoided given risk of infection and possible extrusion in cases requiring postoperative radiation therapy. Alternately, single layer acellular dermis has been advocated for ASB reconstruction. Intuitively, a single layer

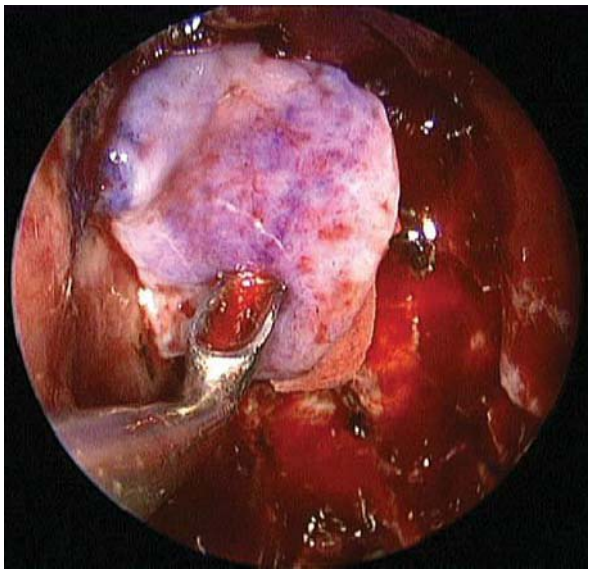


Figure 45.7 Endoscopic view of left ethmoid cavity with 30-degree endoscope illustrates mucosal graft as one component of multilayered reconstruction after minimally invasive resection of left ethmoid adenocarcinoma. The mucosal side is inked with a marking pen to facilitate orientation.

of tissue may increase the surgical challenge to achieve watertight closure. Moreover, this approach delays mucosalization by 6 months. Pedicled vascularized flaps represent a significant advance in reconstruction of the ASB. The nasoseptal flap provides robust vascularized tissue for ASB reconstruction, accelerating healing, and minimizing risk of postoperative leak, especially in cases of high-flow leaks (28,29).

Sella and Clivus

Intraoperative CSF leaks are encountered in pituitary adenoma surgery in 20% to 50% of cases, while postoperative leaks are seen in 1% to 10% of cases. A graduated approach is required for management of sellar leaks. For patients with no intraoperative leaks, no formal reconstruction is required. Alternately, a small amount of absorbable hemostatic gauze may be placed to fill the sellar defect. Patients with a small intraoperative leak without an obvious diaphragmatic defect can be managed with absorbable hemostatic gauze and abdominal fat within the sellar cavity followed by a free mucosal graft that can be harvested from the nasal septum, sphenoid sinus, or floor of nose. Patients with definite diaphragmatic or dural defect with high-flow sellar and clival leaks represent the most challenging group and pose the highest risk of postoperative persistent leak and meningitis. In these cases, the sellar cavity or clival defect should be packed with abdominal fat and absorbable hemostatic gauze followed by reconstruction of the sellar face or clivus with septal bone or cartilage or a resorbable microplate. A vascularized nasoseptal flap is subsequently placed over the entire reconstruction to facilitate healing (30,31).

RECONSTRUCTIVE TECHNIQUES

Multilayered Reconstruction

A variety of surgical techniques and graft materials have been employed over the years for management of CSF rhinorrhea. Meticulous surgical technique is more critical than the actual choice of reconstructive tissue for successful repair. Multilayered skull base reconstruction is preferred for most cases; one exception is small olfactory cleft meningoceles that only require a free mucosal graft as an overlay technique. The size of the skull base defect is determined by gentle probing to ascertain the full extent of the defect. Careful circumferential elevation of the dura should be performed in these cases. Frontal sinus seekers or otologic instruments can be used for this purpose. The initial layer consisting of collagen matrix, acellular dermis, temporalis fascia, or fascia lata is tucked along the edge of the exposed dura and brain as an underlay. A second layer of the same tissue array may be used to reinforce the first layer if deemed necessary. Tensor fascia lata as a bilayer button or abdominal fat graft as a bath-plug closure has also been described for this primary layer. An intervening graft that provides rigid support is important for cases of spontaneous leaks, especially if underlying elevated ICP is expected. Septal bone would be the graft of choice for this purpose; alternate options include cartilage (septal or conchal) or mastoid bone. The final tissue layer consists of a free mucosal graft from the nasal septum, floor of nose, or middle or inferior turbinate. The mucosal side should be inked to facilitate orientation at the skull base. Fibrin sealants or gelatin–thrombin matrix and absorbable packing, such as oxidized regenerated cellulose or absorbable gelatin sponges support the tissue grafts. The entire reconstruction is further supported by nonabsorbable polyvinyl alcohol sponges (32,33).

Pedicled Flaps

The nasoseptal flap based on the posterior septal artery, a terminal branch of the sphenopalatine artery, represents a significant advance in reconstruction for skull base surgery. It provides robust vascularized tissue, facilitating faster healing and tissue integration and decreasing risk of postoperative leaks to less than 5% in this setting. The flap can be harvested endoscopically and can avoid morbidity of a second donor site. One potential limitation is that the nasoseptal flap is not reliably available in cases of sinonasal and skull base malignancy as the septum is often infiltrated by the neoplasm. Thus, a backup plan should always be available if use of vascularized tissue is contemplated for reconstruction. Alternate flaps including transpterygoid temporoparietal fascia flap, endoscopic-assisted transglabellar pericranial flap, posterior pedicle inferior turbinate flap, and middle turbinate flap have been described for skull base reconstruction (34).

POSTOPERATIVE CARE

Traditionally, patients have been kept on strict bed rest for 3 to 5 days after CSF leak repair. However, the rationale for this approach is not born out in the literature; furthermore, a prolonged period of inactivity may increase the risk of pulmonary and venous thromboembolism complications. Typically, strict bed rest for 24 to 48 hours in the postoperative phase should suffice. If a LD is utilized, this is drained at 5 to 10 mL/h. This short period of inactivity will facilitate the healing process and avoid any sudden pressure changes or Valsalva maneuvers that may significantly elevate the ICP and compromise the reconstruction. The head-of-bed is elevated to 15 degree during this time period. This position will decrease the ICP at the ASB and the brain parenchyma may actually help maintain the position of the underlay grafts. Antibiotics are continued for 24 hours or until the LD is removed. A longer period of antibiotics are only required if the patients have permanent packing, given the theoretical risk of toxic shock syndrome. Stool softeners and antitussives are important adjuncts to minimize ICP spikes during this crucial period.

The LD is clamped at 24 to 48 hours. The patient is carefully observed for any signs of CSF leakage in the bed rest position. Patients may slowly be elevated to a sitting position and then to a standing position so long as there is no sign of CSF leak or postspinal headache. A similar approach is used even if no LD is utilized. Patients are generally discharged on postoperative day 2 on antibiotics (if nasal sponges in place), pain medication, stool softeners, and saline sprays. Patients are seen in the office 5 to 7 days after surgery. Any nasal tampons are removed at this time. Postoperative debridement is conservative at this juncture and is limited to suctioning of mucus or debris in the dependent sinuses to maintain patency. Debridement of the skull base reconstruction commences 4 to 6 weeks after surgery and continues until all healing has taken place. Patients are instructed to avoid any vigorous activity for 6 to 8 weeks. The activity restrictions are lifted based on the endoscopic examination rather than a rigid timeline (25).

LONG-TERM MANAGEMENT

Patients are followed long-term by serial endoscopy to ensure the success of the reconstruction and continued patency of the adjacent sinuses. The subgroup of spontaneous CSF leaks requires a postoperative management strategy to address elevated ICP, if present. Baseline elevation of ICP may be established in the early postoperative period by obtaining an ICP measurement with the LD clamped. However, it is unclear if this will accurately reflect ICP over the ensuing weeks to months. The reliability of this single measurement is further challenged given significant positional and diurnal variations of this data point. Continuous CSF pressure monitoring has been advocated as a more reliable technique to ascertain ICP in this patient population (35). Alternately, baseline ICP measurement can be obtained 6 to 8 weeks after surgery. This in turn can guide any additional measures to target the ICP into the normal range and minimize risk of recurrent leak in the same or different location.

Management of spontaneous leak patients should account for both elevated ICP (less than 15 cm H_2O) and patient symptomatology, that is, headaches, pulsatile tinnitus, imbalance, and visual disturbances, prior to instituting medical measures. ACTZ is a carbonic anhydrase inhibitor that has the ability to decrease CSF production. It has been demonstrated to decrease ICP by mean of 10 cm H_2O in spontaneous leak patients. The exact dosage for this indication is not clear but could range from 250 mg two to four times a day. An important side effect of ACTZ is development of hyperchloremic metabolic acidosis with hypokalemia. Thus, careful electrolyte monitoring is imperative during chronic ACTZ therapy, along with replacement of potassium and bicarbonate to maintain normal electrolyte values. VP shunting may be considered in patients who develop recurrent CSF leaks or continue to display persistent ICP elevation and BIH symptoms despite ACTZ therapy. Given the invasive and irreversible nature of VP shunting, this should be considered a last resort measure (12,36).

OUTCOMES

The data accrued in the literature from multiple studies attest to the efficacy of the transnasal endoscopic approach for management of CSF rhinorrhea. The success rate after initial attempt ranges from 90% to 95%, with success rate increasing to 95% to 100% after second attempt for releaks (37,38). This is accomplished with extremely low risk of serious intracranial complications, such as meningitis (less than 1%). Spontaneous leaks represent the most challenging subgroup; however, recent work has demonstrated that a comprehensive management approach directed against the leak and the underlying pathophysiology with ACTZ or VP shunting in selected cases can lead to a low failure rate (12). A variety of graft techniques have been employed for skull base reconstruction; data are unable to definitively demonstrate superiority of one tissue array over another. A repair strategy employing multilayered reconstruction is more important, irrespective of the choice of graft materials. Vascularized pedicled flaps represent a significant advance in endoscopic skull base surgery and should be incorporated in the reconstructive strategy for high-flow large skull base defects, when technically feasible. In general, a rigid cookbook approach is unlikely to replicate this high success rate; an individualized approach carefully considering the underlying etiology and site of leak are critical to optimize outcomes.

HIGHLIGHTS

- The most common etiologies of CSF rhinorrhea include accidental trauma, surgical trauma, spontaneous, congenital, and tumors.
- The risk of iatrogenic CSF leaks from ESS has decreased to 0% to 3% in clinical series, with the two most common locations being the LLCP and posterior ethmoid roof as it transitions to the sphenoid sinus.
- Spontaneous CSF leaks represent an emerging clinical entity that is likely related to underlying elevation of ICP, typically being observed in middle-aged females with elevated body-mass index.
- β2-Transferrin is a protein detectable almost exclusively in CSF, perilymph of the cochlea, and aqueous and vitreous humor of the eye. It is a highly sensitive and specific noninvasive test for suspected CSF leakage.
- High-resolution triplanar CT imaging (1 mm or less) represents the initial study of choice to precisely localize the skull base defect for CSF rhinorrhea.
- Key surgical dictums for successful CSF leak repair include precise identification of the leak site, careful cautery of the herniated intracranial contents, meticulous preparation of the graft recipient site, and multilayer reconstruction with variety of tissue arrays.
- Endoscopic management of CSF rhinorrhea has demonstrated success rate of 90% to 95% after initial attempt and 95% to 100% after second attempt for releaks, with low risk of serious intracranial complications, such as meningitis (less than 1%).

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Frontal Sinus Surgery

46

Yuresh S. Naidoo *Peter-John Wormald*

Endoscopic sinus surgery (ESS) has been accepted as the treatment of choice for chronic sinusitis refractory to medical treatment. However, surgery of the frontal sinus is perhaps the most technically demanding of all ESS. The complex and varied anatomy, acute nasofrontal angle, and proximity to critical structures such as the olfactory fossa, skull base, and orbit contribute to the surgical difficulty. These narrow confines, and a penchant for postoperative scarring, make surgical treatment of chronic frontal sinusitis challenging.

The literature and evolution of endoscopic frontal sinus surgery supports a graduated stepwise approach to tackling disease in the frontal sinus (1–4). A wide spectrum of defined endonasal surgical procedures of the frontal sinus has been developed. These are based on the drainage or sinusotomy classification of Draf (1) (Table 46.1).

Our philosophy is an all-or-nothing approach to frontal sinus surgery once maximum medical treatment has failed. Limited surgery in the frontal recess places raw surfaces in close proximity to each other, which increases the likelihood of scarring and failure. Draf IIA sinusotomies are performed for primary surgery on the frontal sinus. Failed frontal sinus surgery is treated with a Draf III sinusotomy (otherwise known as endoscopic modified Lothrop procedure [EMLP] or frontal drillout procedure). At present, a primary EMLP is not performed for chronic rhinosinusitis.

SURGICAL ANATOMY

The key to successful frontal sinus surgery is a fundamental understanding of its anatomy.

Development of the frontal sinus begins in the fourth fetal month when the entire nasofrontal area is represented by the frontal recess. It is the last paranasal sinus to develop. At birth, the sinus has usually not formed. At around 2 years of age, the most anterior ethmoidal sinus invaginates into the frontal bone and continues its vertical growth trajectory at an average annual rate of 1.5 mm until the 15th year. Final growth is completed before 20.

The sinus is compartmentalized by the intrasinus septa, which divides the sinus into halves. The frontal sinus has the most complex and variable drainage of any paranasal sinus. The frontal recess itself can be considered to be bordered by the frontal beak anteriorly, the anterior face of the bulla ethmoidalis posteriorly, the middle turbinate medially, and the lamina papyracea laterally (Fig. 46.1).
These limits are altered by the variable pneumatization of anterior ethmoidal cells. Along the frontal beak, the agger nasi cell and other frontoethmoidal cells protrude into the frontal recess and sinus to alter the drainage pathway. Along the skull base, suprabullar cells may protrude anteriorly compressing the drainage pathway. When a suprabullar cell pneumatizes along the skull base into the frontal sinus, it is called a frontal bulla cell. Frontal bulla cells can considerably narrow the frontal sinus drainage pathway.

The types and variability of cells that can be found in the frontal recess and frontal sinus, which can markedly alter the frontal sinus drainage pathway, were first described by Kuhn (5) in a landmark paper. He described four basic cells: the agger nasi cell, the frontoethmoidal cell(s), the intersinus septal cell(s), and the cell(s) originating from the bulla ethmoidalis/suprabullar region.

This classification was modified by Wormald (6), who more clearly defined the frontoethmoidal cell and redefined type 3 and 4 cells (Table 46.2).

The three-dimensional (3D) reconstruction of the frontal recess anatomy using the building block model, with each block representing a cell within the frontal recess, is an excellent aid to the surgeon in understanding the anatomy of the frontal sinus. It allows the surgeon to carefully

TABLE 46.1 DRAF CLASSIFICATION OF ENDONASAL FRONTAL SINUS PROCEDURES

Type	Extent of Surgery	Indication
I	Anterior ethmoidectomy with drainage of the frontal recess by removal of obstructing disease inferior to the frontal ostium. The frontal ostium itself and any cells protruding into it are not touched	• History, endoscopy, and CT findings suggest chronic frontal sinusitis is due to sinus outflow tract obstruction at the level of the frontal recess
IIA	Removal of all ethmoidal cells protruding into the frontal sinus thereby creating an opening between the middle turbinate medially and the lamina papyracea laterally	• Complicated frontal sinusitis or failed Draf I • Recommended in frontal sinuses with a large A–P diameter (anticipated minimum diameter of frontal neo-ostium 5 mm or more), hypoplastic internal nasal spine (small frontal beak), and a broad ethmoid
IIB	Removal of the frontal sinus floor between the nasal septum medially and the lamina papyracea laterally	• Complicated frontal sinusitis in frontal sinuses with a small A–P diameter, hyperplastic internal nasal spine (i.e., large frontal beak), or narrow ethmoid
III	Bilateral Draf IIB with removal of the upper part of the nasal septum and intersinus septum	• As for Draf IIB recommended over type II sinusotomy for cases with severe polyposis

From Weber R, Draf W, Kratzsch B, et al. Modern concepts of frontal sinus surgery. *Laryngoscope* 2001;111:137–146.

plan the surgical approach and to identify each cell to be dissected as well as to understand the drainage pathway of the frontal sinus allowing the dissecting instruments to be placed along the drainage pathway facilitating a safe dissection. This should allow a stepwise cell removal with complete exposure of the frontal ostium.

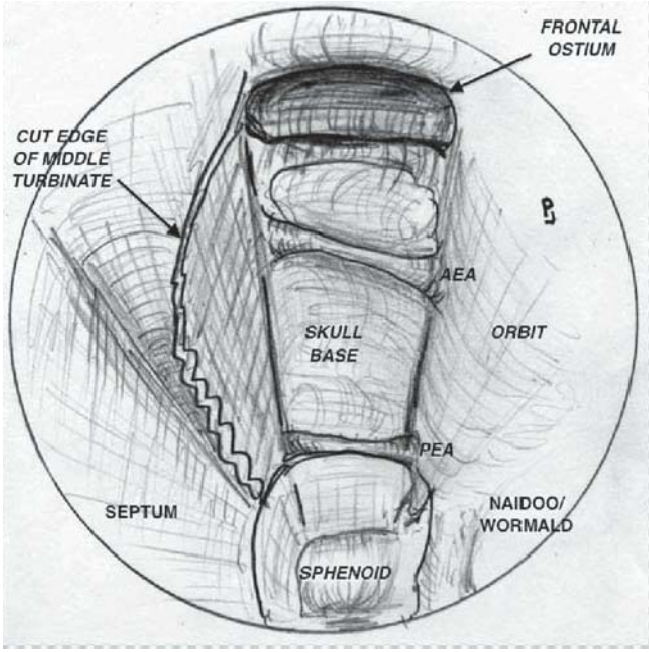


Figure 46.1 Boundaries of frontal recess. The frontal ostium is bounded by the lamina papyracea laterally, the middle turbinate medially, the skull base posteriorly, and the frontal beak anteriorly. All of the cells impinging on this ostium must be removed to maximize the frontal ostium. AEA, anterior ethmoidal artery; PEA, posterior ethmoidal artery.

The first step in the reconstruction is to identify on the coronal computed tomography (CT) scan, the first cell anterior to and directly above the insertion of the middle turbinate. In most cases, this is the agger nasi cell (Fig. 46.3A). This is confirmed on the parasagittal scan (Fig. 46.3B). A building block is placed for the agger cell. The cell above the agger nasi cell is then identified and confirmed by cross reference with the parasagittal scan. This is a T1 cell and a block is placed to represent this. A cell is noted above this cell and on the parasagittal scan this cell is seen to extend above the frontal beak. This is a T3 cell and a block is placed to represent this cell.

Similarly, blocks are placed for the ethmoid bulla and suprabullar cell, which are seen on the coronal and parasagittal scans (Fig. 46.3B).

The final aspect of the reconstruction is to identify how the frontal sinus drains in relation to these cells. This is done by following the frontal sinus from superiorly to inferiorly on sequential axial scans. In this way, the frontal sinus itself can be distinguished from cells that protrude into the sinus. An asterisk (*) marks the frontal sinus on the sequential scans (Fig. 46.3C). This shows an anterior and medial drainage pathway. The completed building block model is shown in Figure 46.3D.

OPERATIVE TECHNIQUE

Mucosal sparing and maximizing the size of the frontal sinus tract are the crucial elements to successful surgery. Where maximum medical therapy including systemic steroids has failed to resolve mucosal thickening in the frontal sinus or recess, our institution's philosophy is to make the frontal sinus outflow tract as wide as possible by removing *all* cells that impinge on this drainage pathway

TABLE 46.2 WORMALD CLASSIFICATION OF FRONTAL RECESS AND FRONTAL SINUS CELLS

Cell	Description
Agger nasi	Cell that is either anterior to the origin of the middle turbinate or sits directly above the most anterior insertion of the middle turbinate into the lateral nasal wall (see Fig. 46.2a - Small agger and Fig. 46.2b - large agger cell)
Frontal ethmoidal	Anterior ethmoidal cell that needs to be in close proximity or touching the frontal process of the maxilla
Type 1	Single cell above agger nasi, not extending above the frontal beak (see Fig. 46.2c)
Type 2	Tier of frontal ethmoidal cells above agger nasi, not extending above the frontal beak (see Fig. 46.2d)
Type 3	Frontal ethmoidal cell pneumatizing cephalad into the frontal sinus but extending less than 50% of the vertical height of the frontal sinus (see Fig. 46.2e)
Type 4	Frontal ethmoidal cell that extends more than 50% of the vertical height of the frontal sinus (see Fig. 46.2f)
Frontal bulla	Suprabullar cell that pneumatizes along the skull base into the frontal sinus along its posterior wall (see Fig. 46.2g)
Suprabullar	Cells above the ethmoid bulla that do not extend into the frontal sinus (see Fig. 46.2h)
Intersinus septal	A medially based cell related to the frontal sinus septum which opens into the frontal recess (see Fig. 46.2i)

Adapted from the Kuhn classification.

EXAMPLES OF FRONTO-ETHMOIDAL CELLS

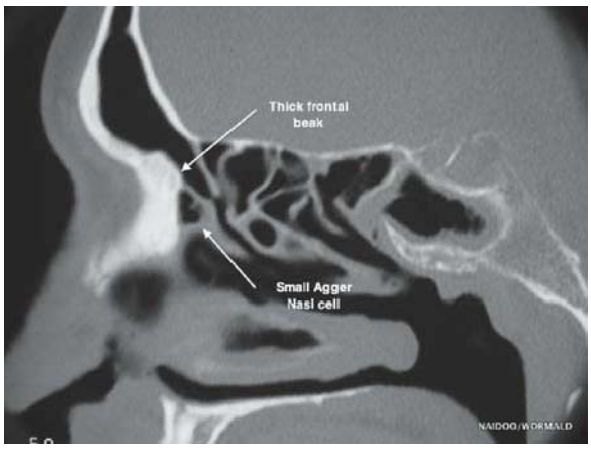


Figure 46.2a Small agger cell: A small agger cell is usually associated with a prominent frontal beak, which narrows the A–P dimension of the frontal ostium

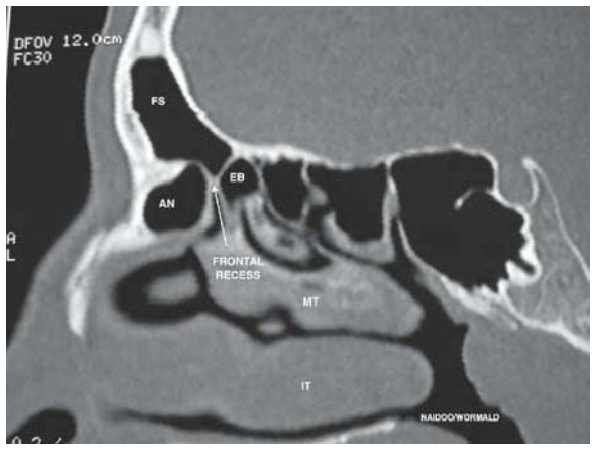


Figure 46.2b Large agger cell: A large agger cell tends to push the frontal drainage pathway more posteriorly. In general, it is associated with a less prominent frontal beak, making the A–P diameter of the frontal ostium larger. AN, agger nasi; EB, ethmoid bulla; FS, frontal sinus; MT, middle turbinate; IT, inferior turbinate



Figure 46.2c T1 cell. One cell above the agger nasi cell. This cell does not protrude superior to the frontal beak

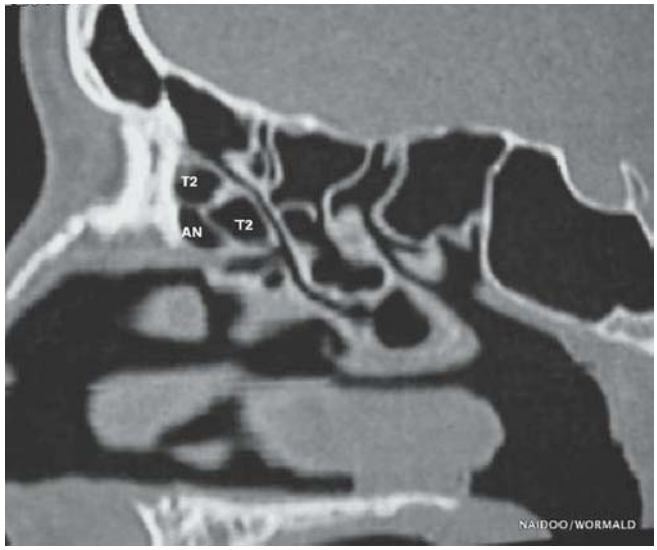


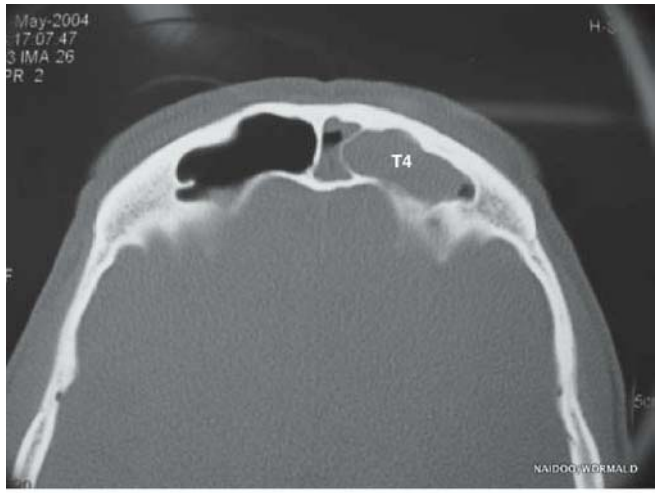
Figure 46.2d T2 cell. A tier of cells above the agger nasi cell, none of which extend superior to the frontal beak



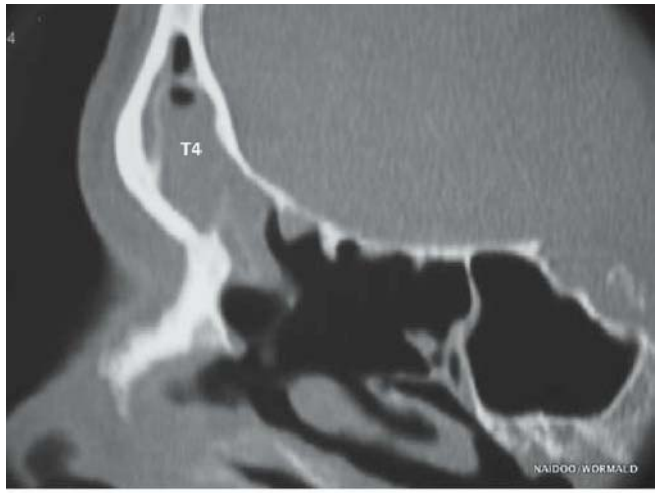
Figure 46.2e T3 cell. A frontoethmoidal cell that extends above the frontal beak. It is limited to less than 50% of the vertical height of the frontal sinus



A



B



C

Figure 46.2f T4 cell. **A–C:** Coronal, axial, and parasagittal CT scans of a T4 cell. It is a frontoethmoidal cell that extends greater than 50% of the vertical height of the frontal sinus

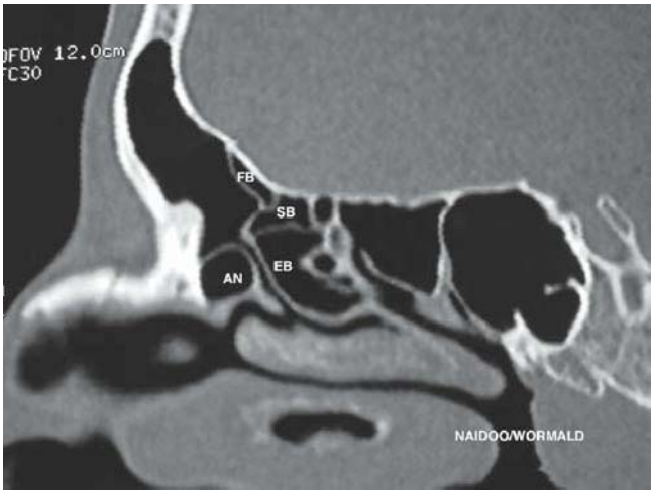
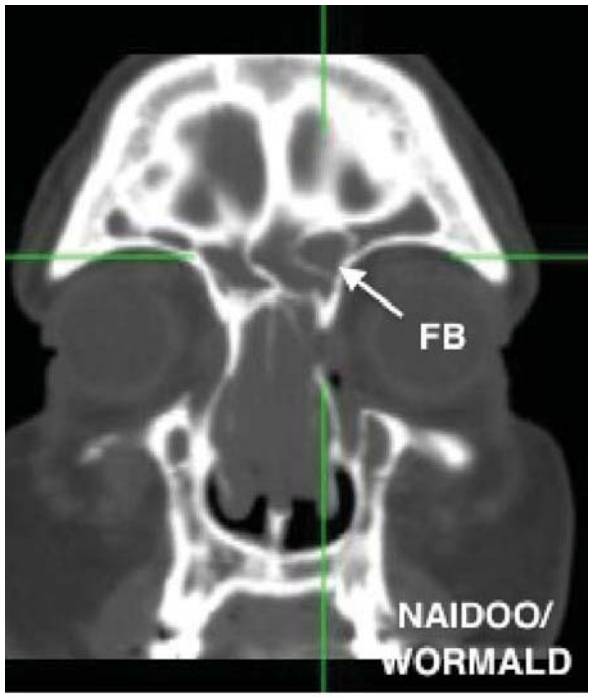
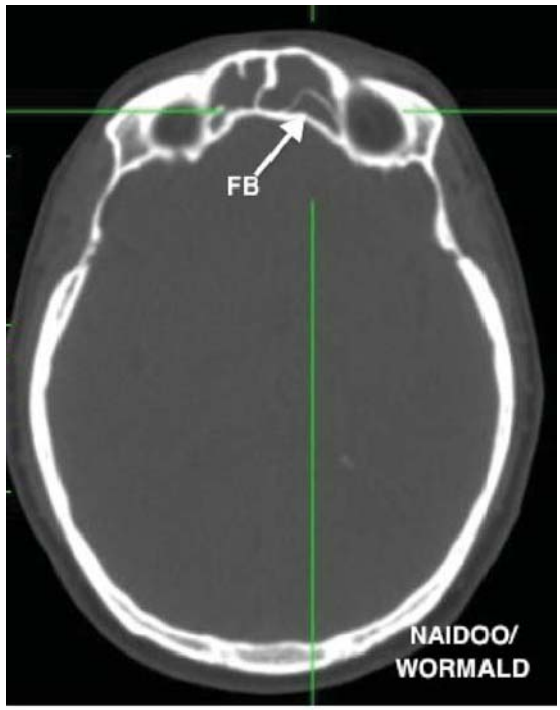


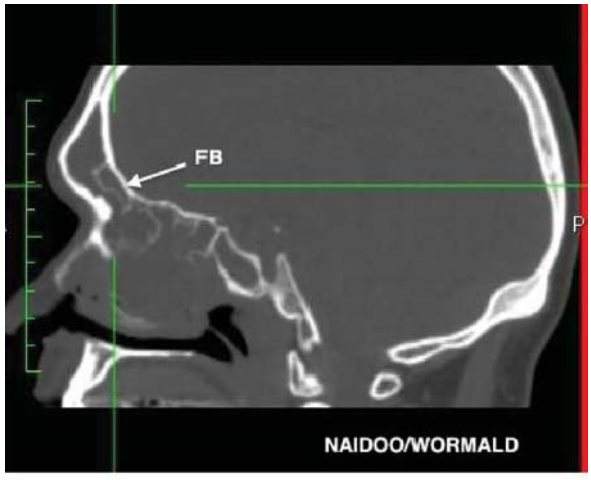
Figure 46.2g Suprabullar cell. A cell above the ethmoid bulla that pneumatizes along the skull base but does not enter into the frontal sinus. In this example, there is both a suprabullar (SB) cell and a frontal bulla (FB) cell. AN, agger nasi



A



B



C

Figure 46.2h **A–C:** Coronal, axial, and parasagittal scans showing a frontal bulla (FB) cell. It is a suprabullar cell that pneumatizes along the skull base into the frontal sinus along its posterior wall. Finally, the intersinus septum itself might pneumatize in the midline and push the frontal recess laterally

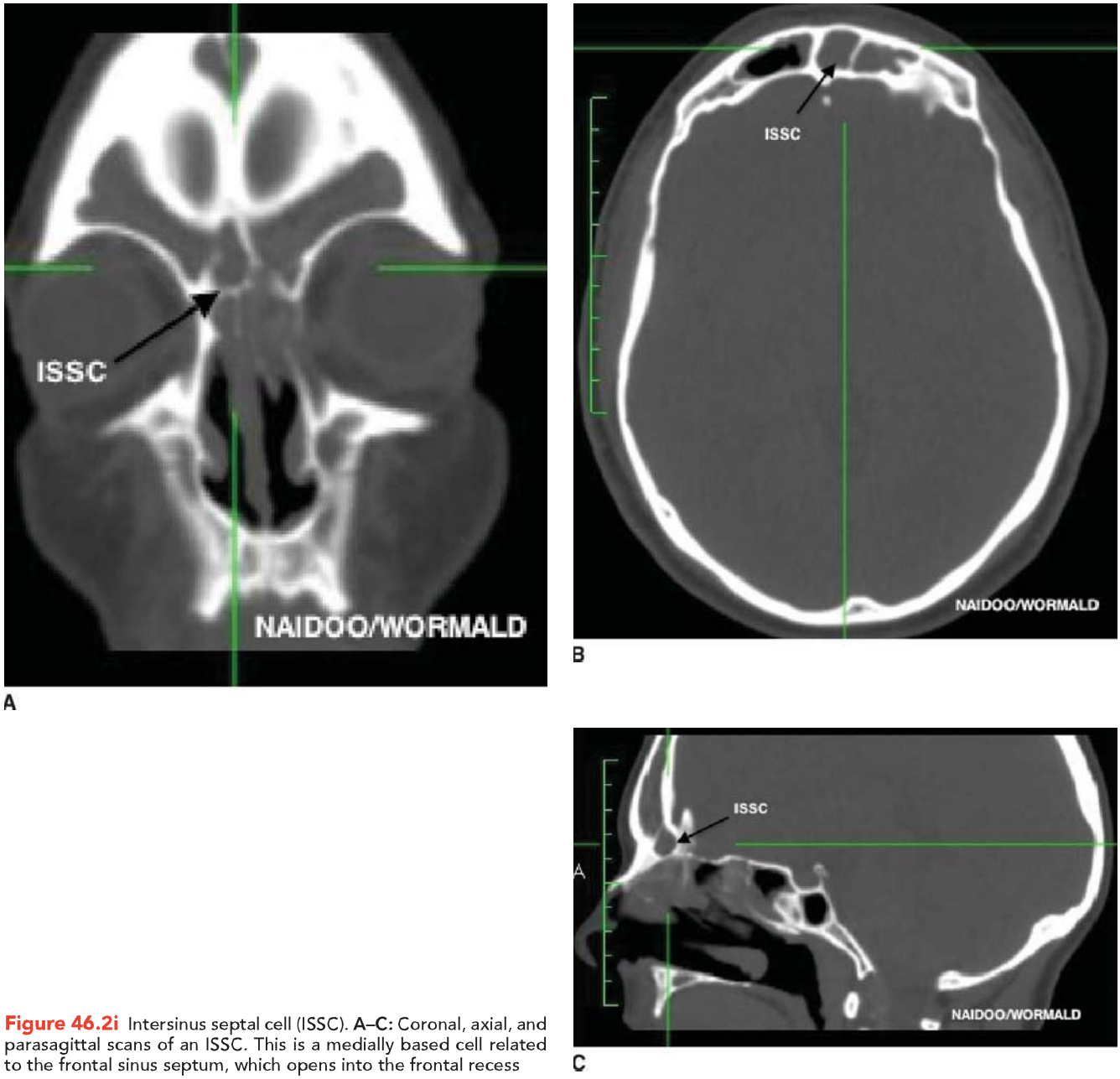


Figure 46.2i Intersinus septal cell (ISSC). **A–C:** Coronal, axial, and parasagittal scans of an ISSC. This is a medially based cell related to the frontal sinus septum, which opens into the frontal recess

(Draf IIA approach). The cells in the frontal recess are in close approximation and partial clearance predisposes the formation of adhesions with obstruction of the drainage pathway. Frontal sinus surgery, therefore, is an all-or-nothing consideration. The frontal sinus is either left alone or *all* cells are removed so that the frontal ostium is completely visualized.

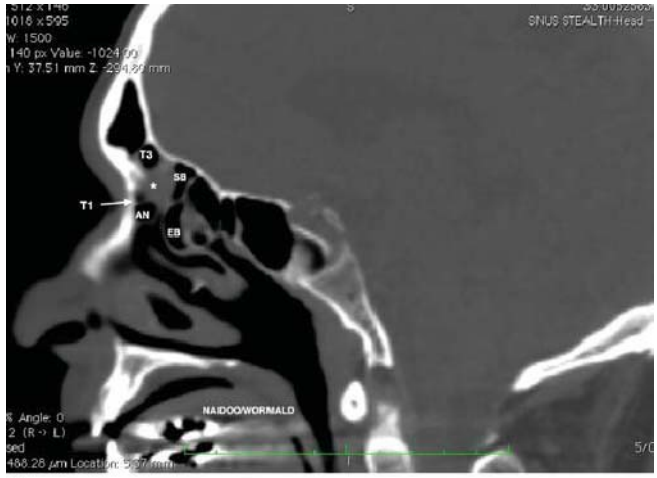
Should this fail, an EMLP is the procedure of choice (a.k.a. Draf III/frontal drillout). The Draf IIB approach for chronic sinusitis is only performed in patients with isolated frontal sinusitis with little disease in the other sinuses. In our experience, Draf IIB has a high failure rate when performed for pansinus disease as the wide exposure of bone in the frontal ostium results in extensive scarring and closure of the neo-ostium. For example, a small medially positioned frontal osteoma might be readily addressed by a unilateral Draf IIB procedure. The key difference here is that the mucosa and underlying bone is unlikely to be chronically inflamed, as it is in cases of chronic sinusitis. This reduces the chance of healing by secondary intention with an intense, predominantly fibroblastic reaction.

Indications for Frontal Sinus Surgery in Chronic Rhinosinusitis

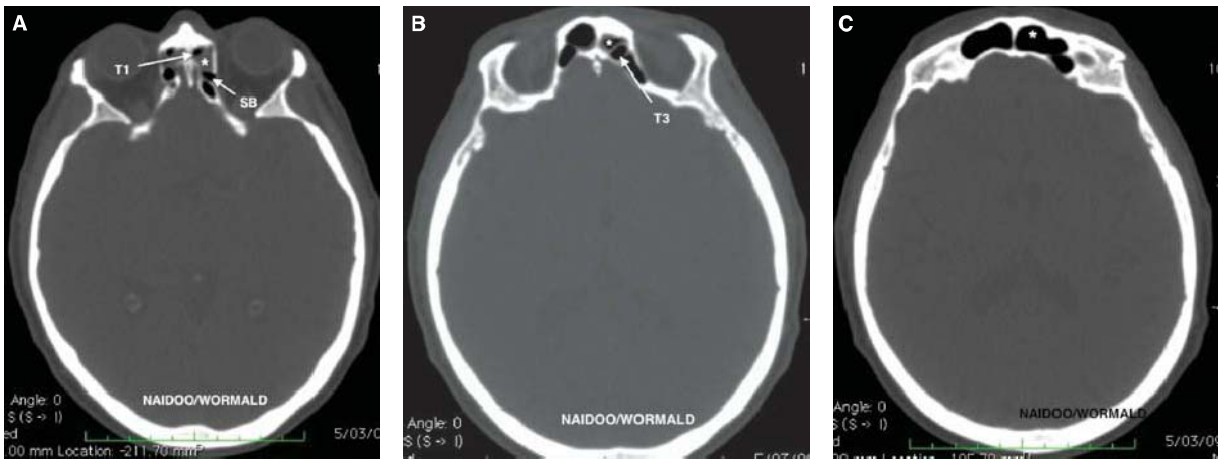
Frontal sinus surgery is indicated in chronic rhinosinusitis (CRS) when there is clinical and radiologic evidence of disease in the frontal recess and sinus that is nonresponsive to medical therapy. Patients in our department, only undergo surgery if they have previously failed at least a 2-month



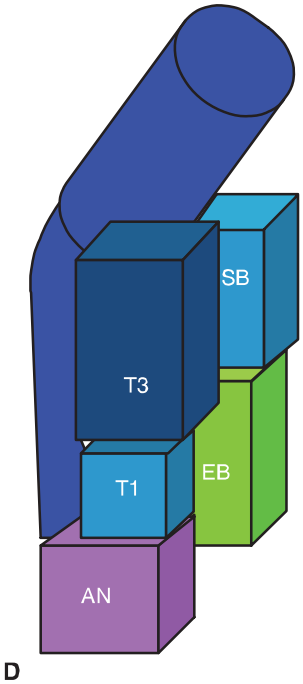
A



B



C



D

Figure 46.3 Example of the 3D reconstruction. **A**: Coronal CT. **B**: Parasaggital CT. **C**: Axial CT. **A–C:** Dimension reconstruction of LEFT frontal sinus drainage pathway. Sequential axial CT scans from superior to inferior. *Asterisk* marks the frontal sinus drainage pathway. **D:** Building block model. AN, agger nasi cell; EB, ethmoid bulla; SB, suprabullar cell; *asterisk* marks the frontal sinus drainage pathway.

course of maximal medical treatment that includes culture-directed antibiotics, saline douches, topical nasal steroids, and oral steroids.

Frontal sinusotomy is only performed if there is objective evidence of persistent posttreatment mucosal thickening in the frontal recess or frontal sinus on paranasal CT scans, and endoscopic evidence of ongoing disease such as polyposis, mucosal edema, or mucopurulence.

Our philosophy is that the frontal sinus should be treated no differently to any of the other sinuses. Frontal pain or headaches should not be thought of as the only surgical indication for endoscopic frontal sinusotomy. Mucosal disease in the frontal sinus without symptoms of headache can still contribute to the other symptoms of CRS such as nasal obstruction, anosmia, postnasal drip, and rhinorrhea. The philosophy that frontal sinus disease should not be treated without specific frontal sinus pain being present has no scientific basis in the literature and is not supported by our experience.

Preoperative Planning and Assessment

Surgery is planned preoperatively using a CT scan of the paranasal sinuses performed in three orthogonal planes. Each cell is confirmed by reference to the coronal, sagittal, and paranasal planes and the building block model created.

The scan is then assessed routinely for surgical danger points:

- Location and course of the anterior and posterior ethmoidal arteries
- Height and more importantly symmetry of the lateral lamella of the cribriform plate (Keros classification)
- Angle and potential breaches of the skull base
- Dehiscence of the lamina papyracea
- Location and potential dehiscence of carotid artery and optic nerve

The nose is prepared topically with 2 mL of 10% cocaine, 2 mL of 1:1,000 adrenaline, and 2 mL of saline soaked onto neuro patties. The septum and lateral nasal wall is injected with 2 mL of 2% lignocaine and 1:80,000 adrenaline. Total intravenous anesthesia is used preferably, with the aim of having the mean arterial pressure no higher than 60 mm Hg and pulse rate of approximately 50.

Complications of Frontal Sinus Surgery

Complications in frontal sinus surgery are due to the technically demanding nature of the surgery and the proximity of the frontal sinus to the lamina papyracea, anterior ethmoidal artery (AEA), cribriform plate, and skull base. The most common complications are orbital entry (with potential damage to the eye, ocular muscles, optic nerve), hemorrhage (from AEA either from the nose or into the eye with proptosis), and cerebospinal fluid (CSF) leak from inadvertent intracranial entry. Without a thorough knowledge of the anatomy of the frontal recess, these structures are likely to be placed at risk with potentially catastrophic results. Iatrogenic injury with scarring of the frontal recess and/or incomplete removal of all cells in the frontal recess can also lead to persistence or worsening of symptoms. Frontal sinus surgery is technically the most demanding aspect of ESS and is best undertaken by experienced sinus surgeons.

Axillary Flap

The axillary flap technique allows use of a 0-degree endoscope to approach the frontal sinus (6,7). By improving (reducing) the angle of attack and the distance to the frontal ostium, cells pneumatizing into the frontal sinus are more easily removed with standard endoscopes and instruments. A similar technique without preservation of mucosa was described by Pletcher et al. (8) for accessing the frontal recess.

Surgery begins with removal of the middle third of uncinate process. The maxillary ostium is identified and then opened as indicated by the extent of disease involving this sinus. The maxillary ostium allows identification of the medial orbital wall and floor of the orbit and should be the first step in all sinus surgery.

An 8-mm incision superior to the axilla of the middle turbinate is extended anteriorly for 8 mm. The scalpel is turned vertically and the incision is continued inferiorly to the level of the axilla. The inferior limb is taken back to the root of the middle turbinate. A suction Freer elevator is used to raise the flap, which is tucked medial to the middle turbinate. A forward-biting Hajek-Koeffler punch is used to remove bone at the junction of the anterior attachment of the middle turbinate and lateral nasal wall. The Hajek punch is oriented in a vertical direction, parallel to the middle turbinate, so as to avoid destabilizing this structure. Typically one or two "bites" with the rongeur are sufficient to remove the anterior face of the agger nasi cells allowing for direct visualization into the frontal recess. A frontal sinus probe or malleable suction curette is placed behind the posterior wall of the agger nasi cell into the previously identified drainage pathway. If the drainage pathway is posterior, cells are curetted from a posterior to anterior direction (away from the skull base) and if it is medial then curettage is medial to lateral (away from the lateral lamella of the cribriform plate) to enlarge the frontal sinus drainage pathway. Curetted fragments of bone and soft tissue are removed with a microdebrider or an up-biting Blakesley or giraffe sinus forceps.

With the anterior face, posterior wall and roof (cap) of the agger nasi cell removed, the frontal sinus drainage pathway should be identified as per the 3D reconstruction. The pathway is probed using the building block model as a map. The curette or probe is gently slid up the pathway and once in position, the wall of the obstructing cell is fractured and removed. This process is repeated until all the cells in the frontal recess and protruding through the frontal ostium are removed. At the end of the dissection,

the frontal ostium should be clearly visible, and no cells should remain in the frontal drainage pathway or ostium. The surgical limits, therefore, is the frontal "beak" anteriorly, the skull base posteriorly, middle turbinate medially, and lamina papyracea laterally.

Surgery then proceeds to the bulla ethmoidalis with its complete removal. Care should be taken not to damage the AEA. The AEA is generally found behind the anterior face of the bulla ethmoidalis unless a suprabullar cell or recess exists. The AEA must be identified radiologically prior to surgery and incorporated into the building block model if necessary.

MINI-TREPHINATION

Frontal sinus mini-trephination is a particularly helpful technique when the drainage pathway is not seen. A cannula placed in the frontal sinus allows the instillation of fluorescein-stained saline. The stained fluid can then be followed in the frontal recess, allowing a malleable probe to be passed into the frontal sinus, facilitating careful clearance of the frontal recess.

Technique of Placing Mini-Trephines

Safe placement of the mini-trephines requires assessment of the CT scans to assess the superior extent and pneumatization of the frontal sinuses. Placement of the mini-trephine too high can result in intracranial penetration by the drill. The CT is also assessed for dehiscences of the posterior table of the frontal sinus, which might allow fluorescein-stained saline to enter the intracranial cavity.

If the CT confirms the presence of a sufficiently pneumatized frontal sinus, the skin landmark is 1 cm lateral to the midpoint of an imaginary line between the medial end of the eyebrows. To camouflage the skin incision, the incision is best made in a vertical frown line or in the medial hairs of the eyebrow. The skin over the frontal bone is mobile and the mini-trephine guide is easily placed into the correct position onto the frontal bone by moving the overlying skin.

It is important to place the mini-trephine guide carefully through the skin without "cookie-biting" an ellipse of skin, and directly onto bone with the teeth of the guide firmly engaged so that it does not move when drilling. Cooling the drill meticulously will reduce the chance of burning the skin and bone, which can leave an unsightly circular scar and local osteitis.

The trephine burr is designed to penetrate not more than 11 mm beyond the guide. Properly placed, it should not be able to penetrate the posterior table of the frontal sinus. Occasionally, it might not be able to penetrate the anterior table. This is dealt with by moving the guide together with the overlying skin inferomedially to an area of the thinner bone of the anterior table.

Once the drill enters the frontal sinus, the guide is held in place and a wire stylet is introduced. The guide is removed and the frontal cannula introduced over the wire stylet and gently rotated into the skin. A syringe partially filled with fluorescein-stained saline is attached to the cannula and aspiration is attempted. The aspiration of pus, mucus, or air admixed with blood is expected. Clear fluid should alert the surgeon to intracranial penetration. If the frontal sinus is completely blocked, nothing will be aspirated and a vacuum will be created within the syringe. As long as clear fluid has not been aspirated, the frontal sinus can be flushed gently with the fluorescein-stained saline and the frontal recess is observed for its emergence. This area can then be probed to identify the frontal ostium and clear the frontal recess.

IMAGE-GUIDED SURGERY

Image-guided surgery uses CT or Magnetic Resonance Imaging (MRI) (or both CT and MRI) data presented to the surgeon in three planes: coronal, axial, and parasagittal. By placing the cross-hair on a particular cell, this cell can be identified in each plane. This facilitates the 3D building block reconstruction. It also allows intraoperative confirmation of critical areas such as the skull base, orbit, optic nerve, carotid, and AEA. This is particularly relevant in revision cases where many, if not all, landmarks have been altered. It is also useful in patients with extensive polyps and pansinusitis where erosion of the cellular lamina makes clear differentiation of cells difficult. It is used routinely for all Draf III/EMLP/drillout procedures, for paranasal sinus malignancies, and for difficult revision sinus cases in our department.

Draf III/Modified Lothrop/Frontal Drillout Procedure

The efficacy of the EMLP, otherwise known as a Draf III or Frontal Drillout Procedure, is now well established. It is an effective intranasal approach to the treatment of frontal sinus disorders. The operation aims to reestablish normal or near-normal frontal sinus function. Anderson et al. recently reviewed EMLP outcomes. They noted frontal ostium patency rates of greater than 95% with a significant improvement in symptoms noted in 82%. The overall failure rate was 13.9%. Only 1.2% of patients reported a worsening of symptoms. In addition, this review confirmed the safety of this procedure with a serious complication rate of less than 1% (9).

Draf III/EMLP has proved effective in the treatment of following (10):

- Failed prior ESS
- Frontal sinus mucocele
- Fractures of the frontoethmoid complex
- Repair of CSF leaks and meningoencephaloceles
- Failed osteoplastic flap frontal sinus obliteration
- Resection of sinonasal neoplasms

Technique

All Draf III/EMLPs are performed in our department with image guidance. The placement of frontal mini-trephines provides additional help by delineating the posterior limit of the dissection intraoperatively, and facilitating irrigation of the neo-ostium postoperatively. Identification of the posterior limit is crucial, as dissection anterior (but not medial) to this puts the skull base at minimal risk.

Surgery begins by revision ESS to address disease in maxillary, ethmoid, and sphenoid sinuses. The frontal ostium is identified and confirmed with the aid of image guidance and fluorescein flushes.

The mucosa above the middle turbinate up to the roof of the nose is removed with a microdebrider. The mucosa of the septum anterior the middle turbinate is then removed bilaterally, and the intervening cartilage excised to create a superior septal window (Fig. 46.4).

The limits of this window are dictated by the access required to perform the drillout. Superiorly, the septum is removed to the roof of the nasal cavity (which in this region corresponds to the floor of the frontal sinus and frontal beak). Inferiorly the window is lowered sufficiently to allow a straight 3.2-mm bur to pass across the septal window to enter under the axilla of the middle turbinate of the contralateral side. Similarly, the anterior limit of the window must allow the 3.2-mm bur to be passed from the ipsilateral nostril, across the window, to the contralateral frontal process of the maxilla, which is where drilling is initiated. Posteriorly, the septum is removed to the anterior border of the middle turbinate. Usually, the window measures 3 cm by 2 cm, but the key issue here is one of access to all the aforementioned areas.

Drilling starts laterally on the frontal process of the maxilla. Optimum access is achieved by passing instruments (0-degree nasendoscope and 3.2-mm cutting bur) across the septal window. The bone of the frontal process is removed until a small area of skin is exposed to define the lateral limit of the resection (Fig. 46.5).

The bur is swept from the ostium anteriorly and laterally widening the ostium until the frontal sinus is entered. Once the frontal sinus has been clearly defined, drilling proceeds anteriorly and medially removing bone of the floor of the sinus and frontal beak, until the septum is reached. (At this point a Draf IIB procedure has been completed) (Fig. 46.6).

It is important to not proceed medially until the frontal sinus is clearly identified, as the skull base might be placed at risk further posteriorly (Fig. 46.7).

The opposite side is then addressed in a similar manner such that a bilateral Draf IIB has been performed. The intersinus septum is then removed. The neo-ostium is now crescent shaped and further bone removal is required in the anteroposterior (A–P) plane to maximize its size, and convert this to an oval-shaped cavity (Fig. 46.8).

The posterior limit of the dissection is the bone over the forward projection of the skull base. This bony projection forms the frontal "T" formed by the superior attachment of the middle turbinates to septum and skull base (Fig. 46.9).

The amount of bone that can be removed here is determined by the level of the first olfactory neuron. This is identified by carefully reflecting the mucosa of the olfactory cleft with an olive tipped curved sucker until the first olfactory neuron is seen. This is then confirmed by image guidance. Note that the image guidance is used to confirm our clinical landmarks. Clinical correlation is vital as the reference frame for the image guidance can shift during the

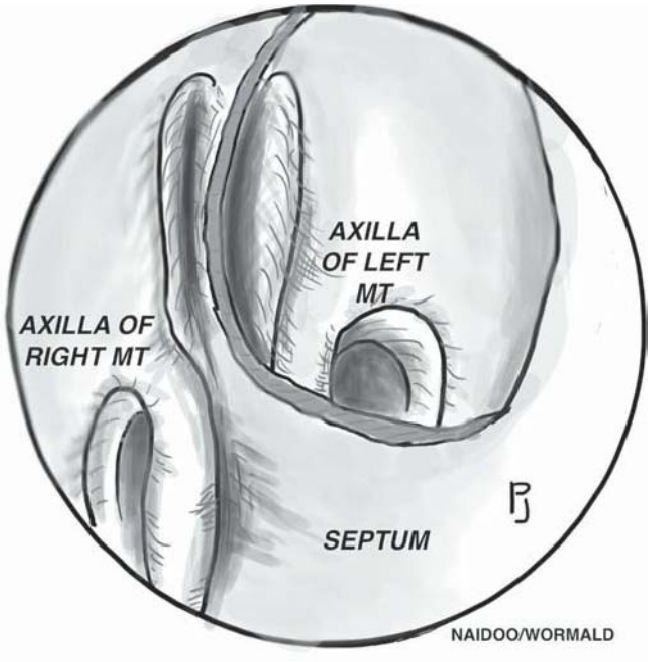


Figure 46.4 Septal window. The superior septal window allows access for the bur to pass across the nasal septum. Its boundaries are determined by the access required to the frontal recess and frontal process of the maxilla.

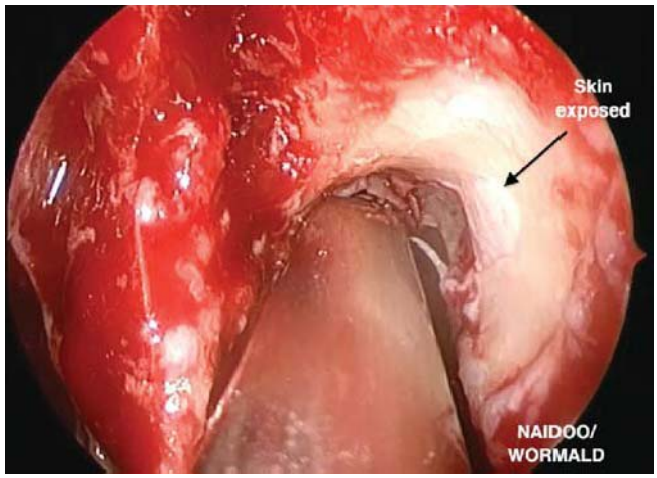


Figure 46.5 Skin exposed laterally. To maximize the lateral dimensions of the neo-ostium and to create space for the bur, the bone should be removed over the frontal process of the maxilla until a small amount of skin is exposed.

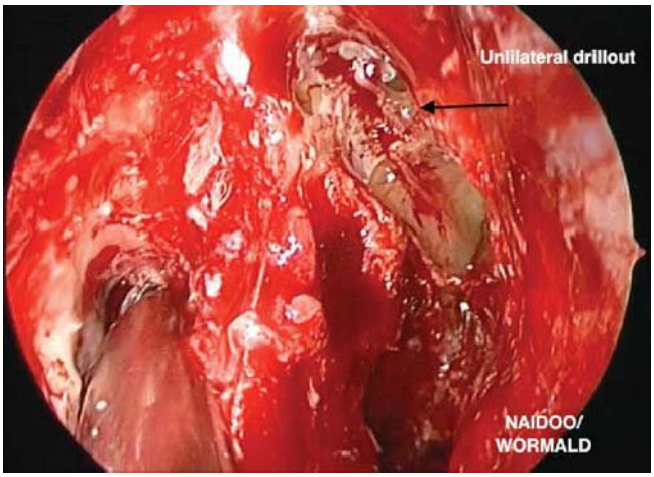


Figure 46.6 Draf IIB. A unilateral drillout has been performed. The frontal ostium has been widened from the orbit laterally to the septum medially.

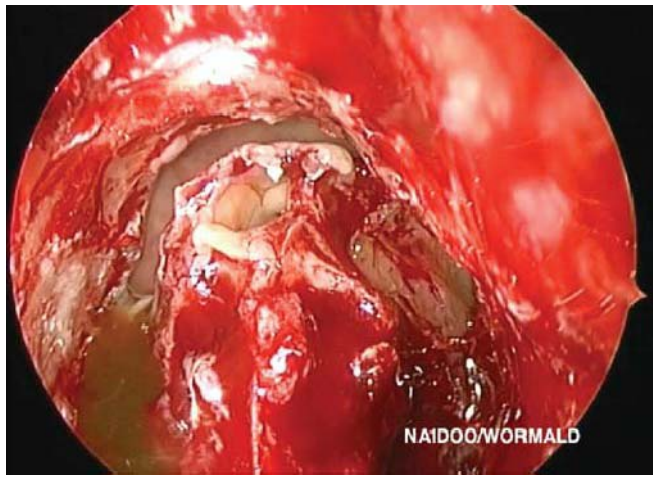


Figure 46.8 Crescent-shaped ostium. A bilateral Draf IIB has been performed. However, the frontal neo-ostium is still quite small and prone to stenosis.

procedure. The bone of the "T" is then removed to within 1 mm of the first olfactory neuron.

The bur is now changed to an angled bur and for the first time, a 30-degree telescope is used to tackle the anterior aspect of the frontal neo-ostium. This thick bone of the frontal beak is removed until there is no lip of bone separating the frontal sinus from the nasal cavity. The transition from frontal sinus to nasal cavity should be smooth.

At the end of the procedure, an oval-shaped neo-ostium is created. The ultimate dimensions are determined by the patient's anatomy and average ~approximately 18 mm from frontal beak to first olfactory neuron and 20 to 24 mm from skin to skin laterally. It should always be made as large as possible. The *major* risk factor for restenosis has been shown to be the initial size of the neo-ostium (11) (Fig. 46.10).

Hemostasis is achieved by bipolar cautery, and particular care is taken at the posterior edge of the septal window and the mucosa overlying the forward projection of the skull base where septal branches of the AEA can cause postoperative bleeding.

POSTOPERATIVE CARE

Careful postoperative management is crucial. The postoperative regimen we use is:

- Oral antibiotics for 10 days for frontal sinusotomy and 3 weeks for EMLP. Intraoperative cultures are checked and the antibiotic regimen changed to culture-directed antibiotics if required.



Figure 46.7 Axial CT scan at olfactory fossa. This scan illustrates the dangers of passing the bur medially before you enter the true frontal sinus. If the bur is not in the frontal sinus, movement of the bur medially will place the skull base at risk.

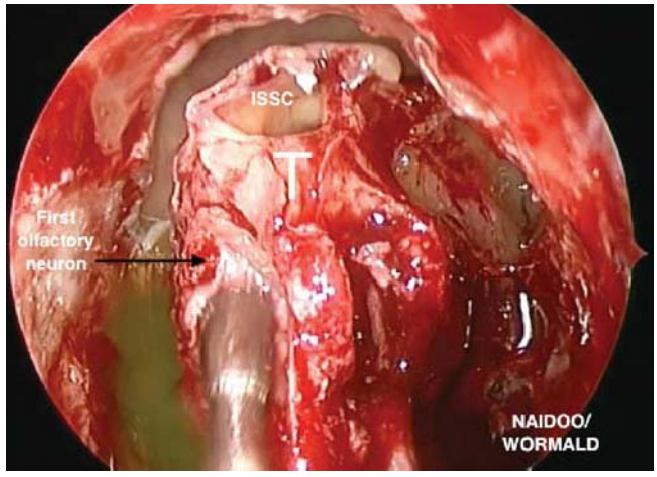


Figure 46.9 Defining the frontal T and first olfactory neuron. A curved sucker is used to carefully reflect the mucosa in the olfactory cleft until the first olfactory neuron is seen. The bone overlying the frontal "T" must be removed to about 1 mm of this neuron.

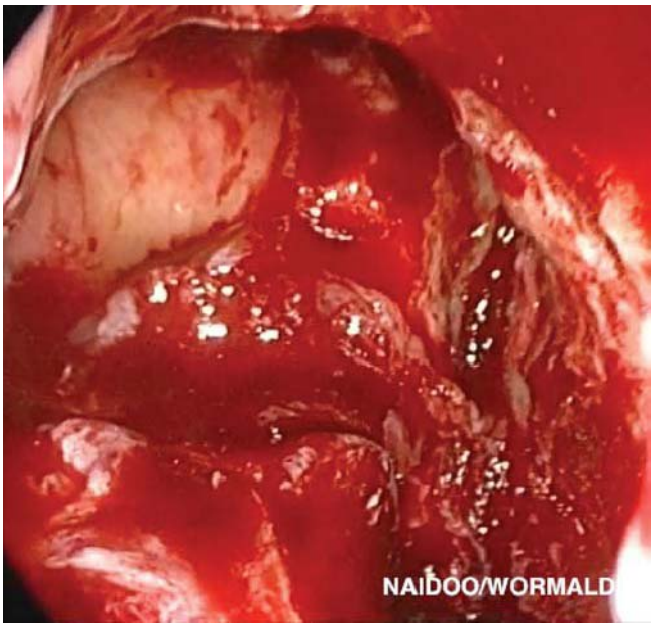


Figure 46.10 Final oval shape of neo-ostium. A large neo-ostium has been created. Its final dimensions are dictated by the underlying patient anatomy. The limits are always the skin laterally and anteriorly, and first olfactory neuron posteriorly.

- Saline irrigation four to six times daily.
- Oral steroids for 3 weeks on a tapering schedule for sinonasal polyposis.
- Where mini-trephines are placed for frontal sinusotomies, 5 mL of saline flushes every 2 hours via each cannula are started immediately after surgery. With every second flush, 0.5 to 1 mL of prednisolone solution is instilled. The trephines are left in place for up to 3 days.
- For EMLP, 5 mL of steroid and antibiotic *cream* are injected via the cannula just prior to removal. This coats the cavity and decreases the amount of crusting. (Note, ointment should not be used as it is lipid based and causes a granulomatous reaction in the sinus mucosa—*myospherulosis*.)
- The patient is reviewed at 10 to 14 days postoperatively, where the sinuses are examined endoscopically and crusts removed and adhesions divided. A thin-curved suction is passed into the frontal sinus and the sinus cleaned while minimizing mucosal trauma. If significant crusting or adhesion formation is noted, an early revisit is scheduled. If all appears to be healing well, the patient is reviewed 4 to 6 weeks later.

CONTROVERSIES IN FRONTAL SINUS SURGERY

The extent of frontal sinus surgery in CRS is controversial. Techniques such as Balloon Sinuplasty (Acclarent) offer a minimally invasive approach to the sinuses but is not, as yet, supported by the literature. The extent of frontal recess dissection varies from surgeon to surgeon across the world with some surgeons only performing endoscopic frontal sinusotomy when patients have symptoms of frontal headache or congestion. Our philosophy is that the frontal sinus should be treated no differently to any of the other sinuses. Mucosal disease in the frontal sinus without symptoms of headache can still contribute to the other symptoms of CRS such as nasal obstruction, anosmia, postnasal drip, and rhinorrhea.

The evidence base for frontal sinus dissection is limited but growing. In our experience, careful and complete clearance of the frontal sinus using the 3D building block model and the axillary flap technique produces excellent long-term results.

Our department is currently looking at the evidence for the extent of surgery in CRS. In particular, the extent of frontal sinus surgery required for high-risk CRS patients such as Samter triad is being investigated. These patients have a higher rate of failure from standard endoscopic frontal sinusotomy and appear to do better with more extensive surgery such as the EMLP (unpublished data). Data collected in the department suggest that these patients might be best served with a primary EMLP.

HIGHLIGHTS

- Understanding the complex anatomy of the frontal recess is key to safe and complete dissection.
- Frontal sinus surgery should be an all-or-nothing consideration. The narrow confines of the frontal recess predispose this area to adhesion formation if only partial clearance is performed.
- The use of a 0-degree endoscope reduces the angle of attack and distance to the frontal ostium. The axillary flap technique facilitates the use of a standard 0-degree endoscope and standard ESS equipment to dissect in the frontal recess. Replacement of the flap after dissection limits adhesion formation.
- The 3D building block model of the frontal recess aids surgical dissection. Cells are removed in a stepwise fashion to completely clear the frontal recess.
- Mini-trephination of the frontal sinus is a useful adjunct to frontal sinus surgery. It can be used for:
  - Intermittent flushing of the frontal sinus with fluorescein-stained saline to safely identify the natural drainage pathway of the frontal sinus
  - Postoperative irrigation of the frontal ostium to prevent adhesion formation and stenosis
- The EMLP is an extended frontal sinus approach, which creates a single frontal sinus draining into the nose via a superior septectomy. Its safety and efficacy in treating recalcitrant frontal sinusitis is now well established.
- Optimum results with the Draf III/EMLP are achieved by creating the largest possible neo-ostium and meticulous postoperative care.

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III

General Otolaryngology

David E. Eibling *Shawn D. Newlands*

Anatomy and Physiology of the Salivary Glands

47

Rohan R. Walvekar *Bridget C. Loehn* *Meghan N. Wilson*

The major salivary glands of the head and neck consist of the parotid glands, submandibular glands, and sublingual glands. There are also hundreds to thousands of minor salivary glands located throughout the upper aerodigestive tract concentrated mainly in the buccal, labial, palatal, and lingual regions. The main function of the salivary glands is the production of saliva for lubrication and protection, buffering action and clearance of food, maintenance of tooth integrity, antibacterial activity, taste, and digestion. It is important for a head and neck surgeon to understand the anatomy, embryology, function, and imaging of salivary glands to assist in the diagnosis and surgical management of benign and malignant disease of the salivary gland.

EMBRYOLOGY

The salivary glands share an overall common embryogenesis in that they all develop from outpouchings of oral ectoderm into the surrounding mesenchyme and they have a similar anatomic structure (Fig. 47.1). The major salivary glands develop during the sixth to eighth weeks of embryonic life. The parotid anlagen are the first to develop, followed by the submandibular glands, and then the sublingual glands. The primordia originate at the site of the eventual ductal orifice and the gland develops into an elaborate tubuloacinar system. The parotid gland is unique in that as its epithelial buds are growing and branching, they extend between the divisions of the facial nerve, eventually surrounding the nerve. This phenomenon has clinical and surgical relevance, explaining why neoplastic processes may often extend both superficial and deep to the facial nerve rather than honoring traditional definitions of superficial and deep parotid lobes. During development, all three of the major salivary glands become encapsulated. Although the parotid gland is the first to develop, it is the last to become encapsulated in loose connective tissue. This becomes important in the adult parotid anatomy as the lymphatic system develops prior to the encapsulation of the parotid but after the encapsulation of the submandibular and sublingual glands. Therefore at the completion of embryogenesis, the parotid gland has lymph nodes and lymphatic channels within the capsule whereas the submandibular and sublingual glands do not. This fact has driven recent studies that examined the feasibility of submandibular gland preservation in patients with oral cancer, demonstrating a lack of direct metastasis to the submandibular glands in neck dissection specimens (1,2). The minor salivary glands develop from oral ectoderm and nasopharyngeal endoderm in the 12th week of intrauterine life.

Parotid Gland Anatomy

The parotid gland is the largest of the three major salivary glands with an average weight of 25 g. The parotid gland is an irregular, wedge-shaped, unilobular gland found overlying the mandibular ramus and anterior inferior to the external ear (Fig. 47.2). It is located within the parotid space. This space is bound superiorly by the zygomatic arch, posteriorly by the external auditory canal, inferiorly by the styloid process, styloid muscles, internal carotid artery and jugular vein, medially by the lateral parapharyngeal space and laterally by the dermis of the skin. Anteriorly, the parotid gland extends superficial to the masseter muscle. This space not only contains the parotid gland but also the parotid lymphatics, blood vessels, and nerve supply. A small tail of parotid extends posteroinferior toward the mastoid process and overlies the sternocleidomastoid. Histologically, the parotid gland contains purely serous secreting acinar cells. The serous secreting cells are mainly spherical in shape and secrete a protein-rich fluid.

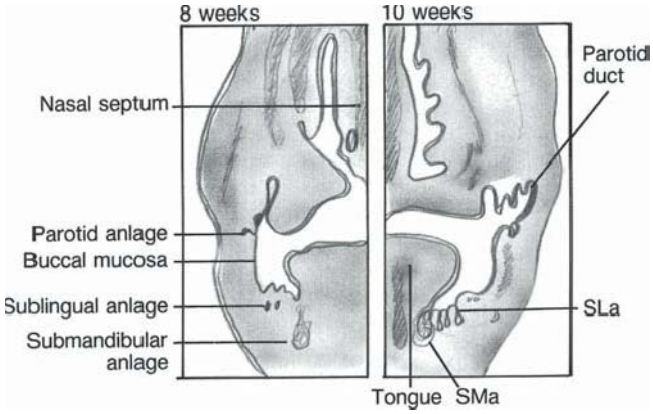


Figure 47.1 Development of the major salivary glands in 8- and 10-week embryos (axial section). SMa, submandibular anlage; SLa, sublingual anlage. (From Meyerhoff WL, Rice DH. Salivary gland anatomy and physiology. In: Paparella MM, Shumrick DA, Meyerhoff WL, eds. *Otolaryngology-head and neck surgery*, 3rd ed. Philadelphia, PA: WB Saunders, 1992, with permission.)

The parotid gland is encapsulated in its own dense connective tissue, which is continuous with the superficial layer of the deep cervical fascia. The parotid fascia consists of a superficial and deep layer. The superficial layer extends from the sternocleidomastoid and masseter muscles to the zygoma. This fascia sends septae into the glandular tissue. These septations make it difficult to separate the parotid gland from its investing fascia. The deep layer extends from the fascia of the posterior belly of the digastric muscle and forms the stylomandibular membrane, which separates the parotid and submandibular glands (Fig. 47.3). Occasionally the parotid tissue can herniate through the stylomandibular ligament and present as a parapharyngeal space mass.

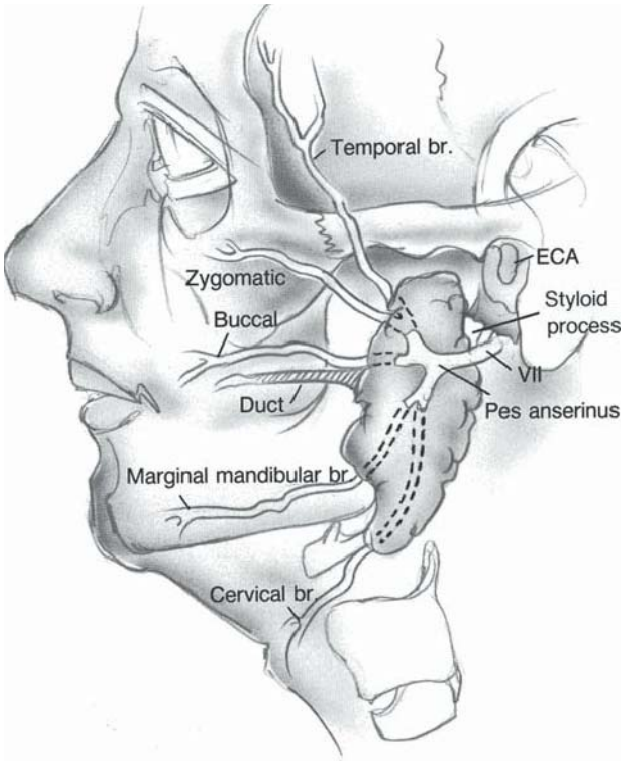


Figure 47.2 The parotid gland and the facial nerve. Note that the nerve exits the stylomastoid foramen lateral to the styloid process. Also note the relationship of the nerve branches to the surrounding structures.

The main parotid duct (Stensen duct) arises from the anterior border of the gland and runs parallel to the zygomatic arch. It is located approximately 1.5 cm below the zygomatic arch. The duct travels superficial to the masseter muscle, then turns 90 degrees and pierces the buccinator muscle to enter the oral cavity at the level of the second maxillary molar. The buccal branch of the facial nerve normally travels along with the parotid duct (Fig. 47.4). The parotid duct is approximately 4 to 6 cm in length. The diameter of the duct is approximately 0.5 to 1.4 mm and the narrowest portion is located at the ostium (3). The parotid duct tends to be more readily amenable to dilation and access. However, its course around the masseter can be difficult to navigate from the perspective of performing endoscopic procedures like salivary endoscopy. This curve has also been termed the "masseteric bend" in sialendoscopy literature (4).

Accessory parotid gland tissue is present in 21% of the population. It is salivary tissue adjacent to Stensen duct that is separate from the main body of the parotid gland (5). The duct of this accessory tissue empties directly into the parotid (Stensen) duct. Its histology is comprised of mucinous acinar glands in addition to the serous acinar gland that dominate in the parotid gland. The accessory parotid gland can be present and may be asymptomatic (Fig. 47.5) or be a site for neoplastic transformation similar to other major salivary glands (6).

The arterial blood supply to the parotid gland is from the external carotid artery. The external carotid artery terminates into two branches (maxillary and superficial temporal artery) in the deep aspect of the parotid gland behind the neck of the mandible. The transverse facial artery, a branch of the superficial temporal artery, supplies the parotid gland, Stensen duct, and the masseter muscle. This artery travels anteriorly between the zygomatic arch and Stensen duct accompanied by the transverse facial vein.

The venous drainage is located in the middle section of the parotid gland, deep to the facial nerve. The venous drainage is provided by the retromandibular (posterior facial) vein. The retromandibular vein, formed by the joining of the superficial temporal vein and the maxillary vein, exits the parotid gland lateral to the carotid artery and joins the postauricular vein to form the external jugular vein, which eventually drains into the internal jugular vein.

The superficial compartment of the parotid gland contains the neural structures including the facial nerve (cranial nerve VII), the great auricular nerve, and the auriculotemporal nerve.

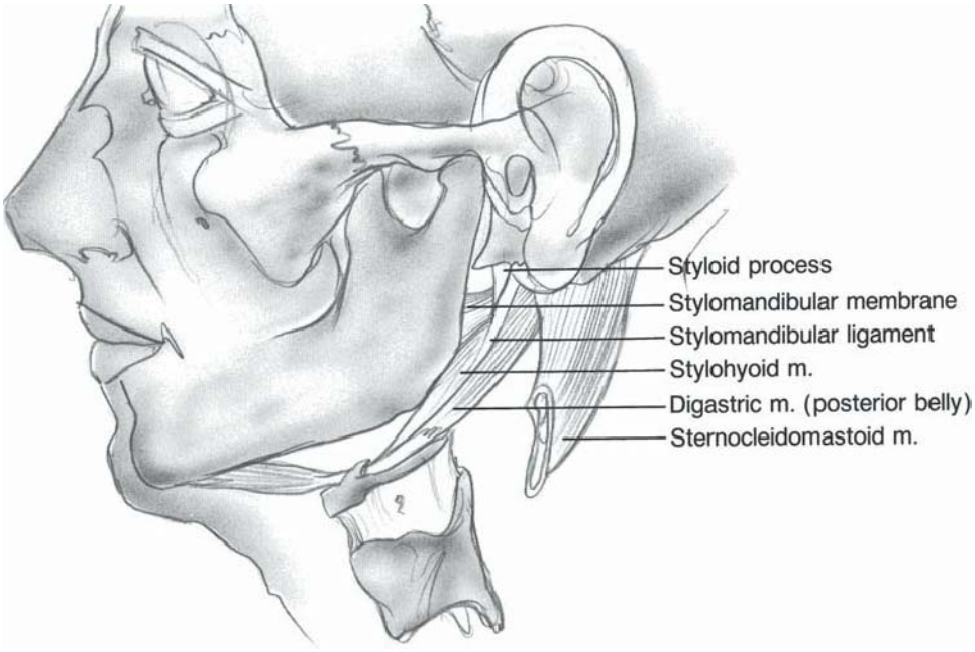


Figure 47.3 Stylomandibular membrane (deep layer of parotid fascia). Herniations of parotid tissue through this membrane can result in a parapharyngeal mass.

The *facial nerve*, as previously stated, is intimately associated with the parotid gland. It divides the gland into two surgical zones (superficial and deep lobes). The facial nerve exits the skull base through the stylomastoid foramen. It immediately gives off three motor branches: the nerve to the stylohyoid muscle, the nerve to the postauricular muscle, and the nerve to the posterior belly of the digastric muscle. Once these branches are given off, the nerve turns laterally to enter the posterior aspect of the parotid gland. Approximately 8.56 to 10.20 mm from the stylomastoid foramen, the facial nerve divides at the *pes anserinus* into the superiorly directed temporofacial and inferiorly directed cervicofacial branches (7). The nerve finally terminates into five branches: temporal, zygomatic, buccal, marginal mandibular, and cervical branches. The number of branches immediately after the *pes anserinus* and the number of terminal branches are variable dependent on the individual patient. The main trunk bifurcates into two branches at the pes anserinus in 86.7% and into three branches in 13.3%. The branching

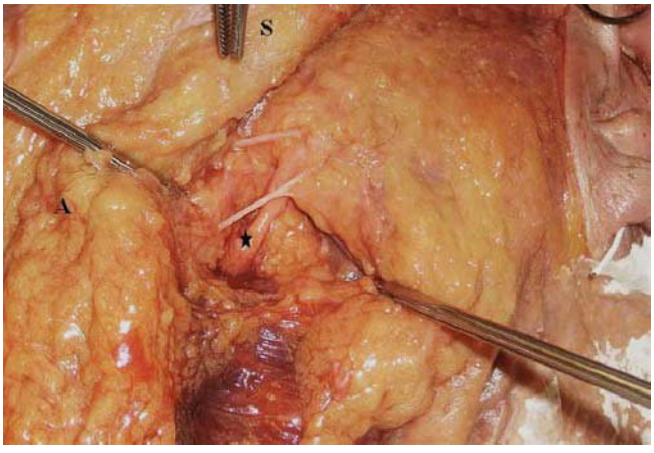


Figure 47.4 Cadaveric dissection showing the relationship of the buccal division of the facial nerve to the Stenson duct (the *black star* denotes the Stenson duct).

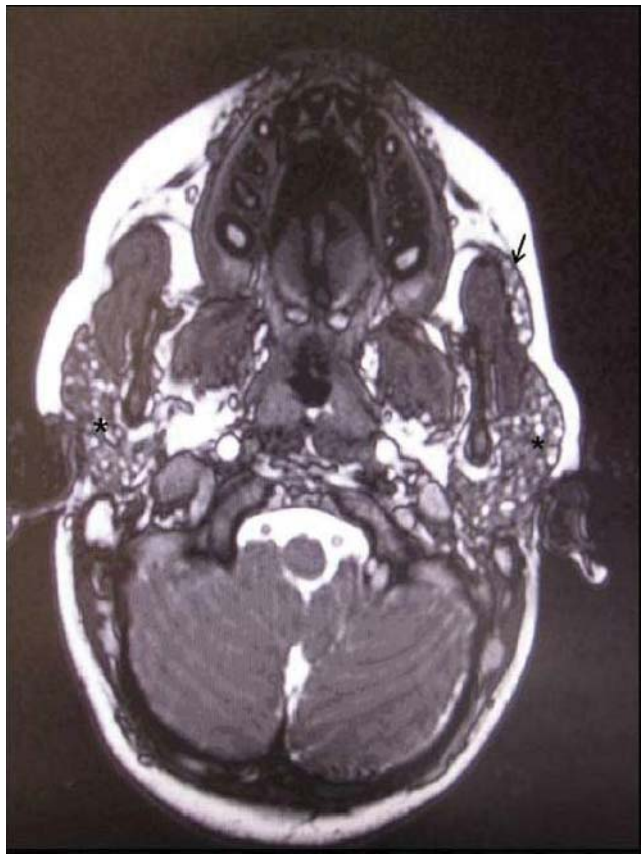


Figure 47.5 Axial MRI scan showing accessory left parotid lobe. (*Black arrow* points to left accessory parotid lobe; *asterisk* denote right and left parotid glands.)

pattern of the facial nerve is variable, and communicating or internerve branches are frequently present. Numerous variation patterns have been published. The buccal branch is the most variable and communicates with the zygomatic branch in 62% of cases and the marginal mandibular nerve in nearly 35% (8).

During parotidectomy, the localization of the facial nerve is critical. When the normal parotid anatomy is distorted as with a tumor, there are several constant relationships that will aid in finding the facial nerve. The tragal pointer is a projection of conchal cartilage that points toward the main trunk of the facial nerve. The facial nerve lies less than 1 cm medial and inferior to the tragal pointer (5). The nerve can also be found approximately 6 to 8 mm deep to the tympanomastoid suture line at the stylomastoid foramen. The styloid process is another constant landmark and the facial nerve lies on the posterolateral aspect of the styloid process near its base. The facial nerve is also located superior, posterior and deep to the cephalic portion of the posterior belly of the digastric muscle. After the nerve is identified at the stylomastoid foramen, anterograde dissection is required to continue surgical extirpation of the parotid glands. The surgical exposure of the nerve at this stage can be restricted and consequently care must be taken to avoid traction injury to the nerve at this juncture. Once the main divisions of the nerve are exposed, the plane of surgical dissection becomes more obtuse along the direction of the branches of the nerve (Fig. 47.6). Retrograde dissection of the buccal branch and temporal branch can be used to localize the main trunk. The buccal branch usually runs parallel to the parotid duct. The temporal branch can be roughly located along a line extending from the attachment of the ear lobule anterosuperior to a point 1.5 cm above the lateral aspect of the eyebrow (9). If the facial nerve cannot be identified using the above landmarks, a mastoidectomy may be performed and the facial nerve may be located in the mastoid (vertical) segment and thus may be traced to the stylomastoid foramen.

The *great auricular nerve* (C2, 3), a branch of the cervical plexus passes around the posterior border of the sternocleidomastoid muscle, ascends diagonally across

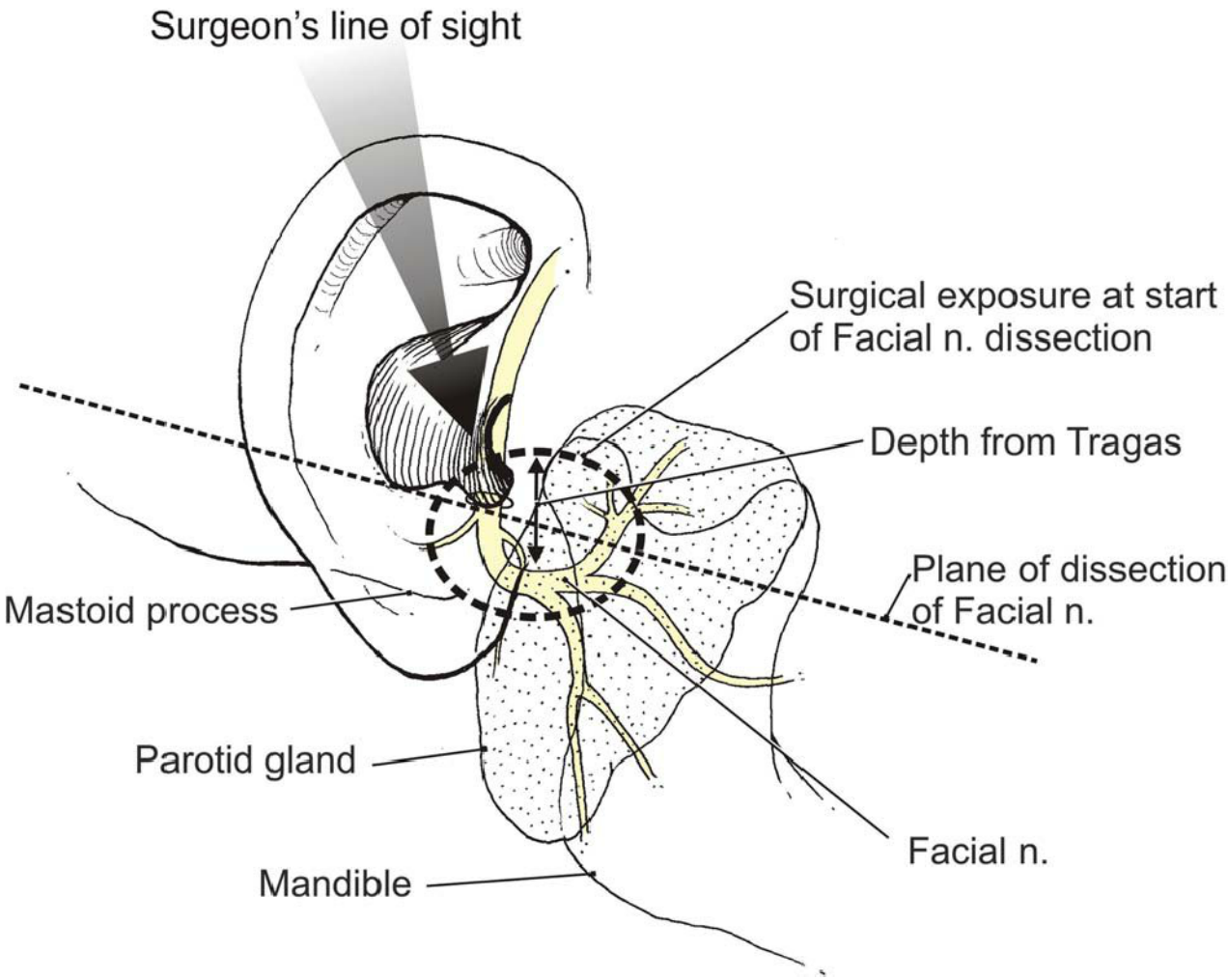


Figure 47.6 Illustrations depicting the depth of nerve at its point of entry into the parotid gland and surgical planes of dissection as compared to surgeon's line of sight.

the sternocleidomastoid muscle onto the parotid gland. It supplies sensation to the skin over the parotid gland, the posterior aspect if the auricle, and an area of skin from the angle of the mandible to the mastoid process. The nerve divides into an anterior and posterior division. This nerve is often damaged or intentionally sacrificed during parotidectomy causing numbness over the earlobe and skin over the parotid gland. Meticulous intraglandular dissection of the nerve can allow the nerve to be preserved if the location of the tumor permits such a dissection (10). Alternatively, in the author's experience, in most cases the posterior division of the nerve can be preserved avoiding complete anesthesia over the distribution of the nerve.

The ***auriculotemporal nerve*** is a branch of the mandibular division of the trigeminal nerve (V3). This nerve exits the skull base via foramen ovale, turns and runs anterior to the external auditory canal, and parallels the superficial temporal vessels. Its functions include supplying sensation to the scalp and carrying postganglionic parasympathetic fibers from the otic ganglion to the parotid gland. The auriculotemporal nerve and the facial nerve are intimately associated as communications between the auriculotemporal nerve and the facial nerve were observed in 93.3% of patients in one study (8).

The salivary glands receive their secretomotor innervation from the parasympathetic and sympathetic nervous systems. The parotid gland receives its parasympathetic stimulation by the glossopharyngeal nerve. The preganglionic parasympathetic fibers originate in the inferior salivatory nucleus, join the glossopharyngeal nerve, course through the lesser superficial petrosal nerve, and then travel through the foramen ovale to synapse in the otic ganglion. The postganglionic fibers then join the auriculotemporal nerve and thus are projected to the parotid tissue. The sympathetic stimulation is by the superior cervical ganglion. Sympathetic fibers begin in the thoracic spinal cord and synapse in the superior cervical ganglion. The postganglionic fibers form a plexus and travel on the external carotid artery to the parotid gland.

The parotid gland's unique lymphatic system is secondary to the fact that development of the capsule around the parotid gland occurs after the development of lymphatic system. Consequently, lymphatic structures are found within the parotid gland. There are periparotid as well as intraparotid lymph nodes; the periparotid lymph nodes are the most numerous and are found between the capsule and parotid gland while the intraparotid lymph nodes are located deep within the parotid gland. Both the periparotid and intraparotid lymph nodes drain the forehead, lateral temporal, frontal, and periorbital regions to include the scalp, pinna, external auditory canal, parotid gland, and lacrimal gland (11). Intraparotid nodes also drain the posterior nasopharynx, and soft palate. These two systems then drain into the superficial and deep cervical lymph nodes. Of clinical relevance, due to its lymphatic anatomy and patterns of drainage, a superficial parotidectomy if often considered in the clinical staging or management of cutaneous malignancies located in these anatomic subsites.

Submandibular Gland Anatomy

The paired submandibular glands are the second largest salivary glands and are located inferior to the floor of mouth. Each submandibular gland weighs approximately 15 g. Each submandibular gland is located within the submandibular triangle of the neck, which is bound by the mandible, posterior belly of the digastric muscle, and anterior belly of the digastric muscle (Fig. 47.7). Each submandibular gland forms a "C" shape around the posterior margin of the mylohyoid muscle, which divides the gland into a superficial and deep lobe (Fig. 47.8). The superficial lobe is above the mylohyoid muscle in the lateral sublingual

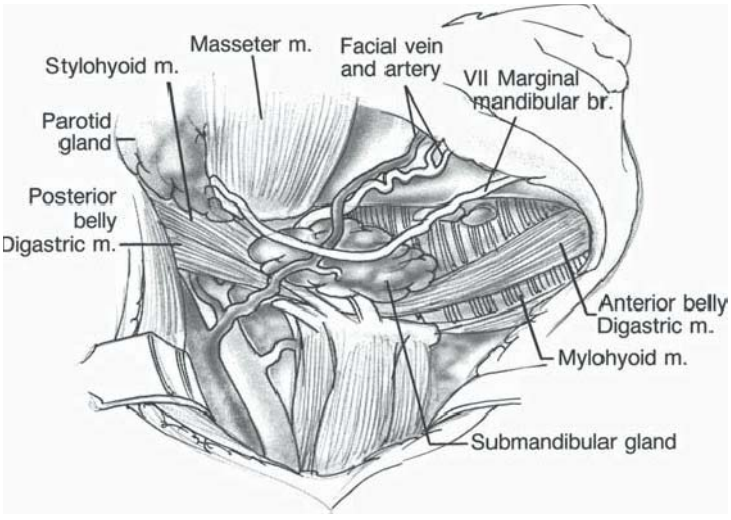


Figure 47.7 The submandibular triangle. Note the relationship of the marginal mandibular nerve to the mandible and facial vessels.

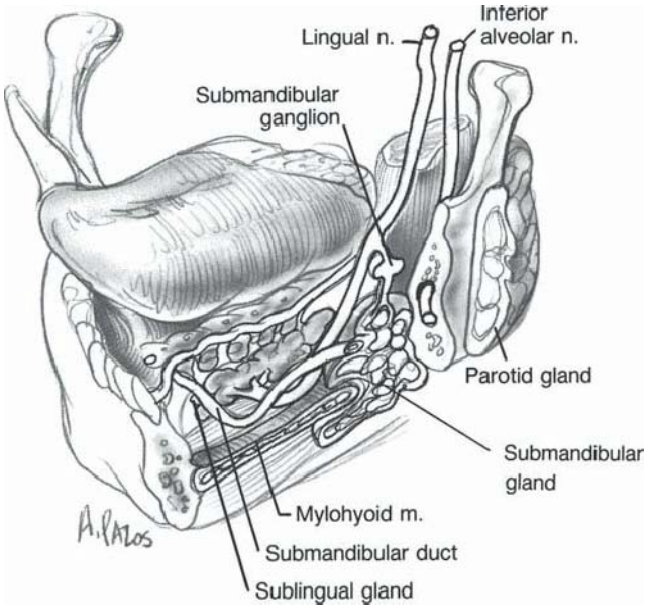


Figure 47.8 The superficial and deep lobes of submandibular gland are separated by the mylohyoid muscle. The sublingual gland has multiple ducts that open along the plica of the floor of the mouth.

space while deep lobe constitutes the majority of the gland and is located inferior to the mylohyoid. The capsule around the gland is derived from the superficial layer of the deep cervical fascia, as in the case of the parotid gland. Histologically, the submandibular gland contains both serous and mucous cells with serous cells predominating.

The submandibular duct (Wharton duct) is approximately 5 cm in length with a mean diameter between 0.5 and 1.5 mm (3). It begins on the medial aspect of the submandibular gland and passes superior to the hypoglossal nerve and inferior to the lingual nerve. It travels forward between the mylohyoid and hyoglossus muscles then onto the genioglossus muscle and opens into the oral cavity lateral to the lingual frenulum. The narrowest portion of the duct is at the ostium in the floor of the mouth near the papilla (3). From the perspective of the newer endoscopic salivary ductal procedures or sialendoscopy, the submandibular duct papilla is more difficult to access. The salivary duct may have multiple openings on the papilla or the opening may be located either at the apex of the papilla or on either side of it. Consequently, identification of the location of the papilla is often the rate-limiting step for sialendoscopy procedures. Once identified and dilated, the submandibular duct provides a more direct path for navigation of the endoscopes than the parotid duct.

The arterial blood supply to the submandibular gland is from the external carotid artery via the facial artery, which branches off of the external carotid artery in the carotid triangle above the lingual artery. It travels obliquely beneath the digastric and stylohyoid muscle and arches to enter a groove on the posterior surface of the submandibular gland. The artery then runs superior and anterior. Once it reaches the superior aspect of the gland, it curves superiorly over the body of the mandible at the anteroinferior angle of the masseter muscle to supply the face. The venous drainage is by the anterior facial vein. The anterior facial vein travels superficial to the submandibular gland. This vein lies deep to the marginal mandibular nerve. The Hayes-Martin maneuver is often used during submandibular gland excision to protect the marginal mandibular nerve by ligating the anterior facial vein 2 to 3 cm inferior to the mandible and elevating the vein superiorly off the gland thus protecting the marginal mandibular nerve in the elevated fascia (12).

The sympathetic innervation to the submandibular gland is through the superior cervical ganglion with postganglionic fibers that travel along the lingual artery to the gland. The parasympathetic innervation begins in the superior salivatory nucleus in the pons. The fibers join the facial nerve via the nervous intermedius within the cerebellar pontine angle or internal auditory canal and then exit the facial nerve along the chorda tympani. The chorda tympani exits the skull base via the petrotympanic fissure and then joins the lingual branch of the mandibular division of the trigeminal nerve in the infratemporal fossa. The preganglionic fibers synapse in the submandibular ganglion then reach the gland directly from the submandibular ganglion.

In contrast to the parotid gland, the capsule of the submandibular gland is developed prior to the formation of the lymphatic system; therefore, there are no intraglandular lymph nodes. The submandibular gland drains to the deep cervical and jugular chain lymph nodes.

Sublingual Gland Anatomy

The sublingual gland is the smallest of the three major salivary glands. The sublingual gland is an almond-shaped gland located anterior to the submandibular gland just below the floor of mouth mucosa in the sublingual space. The sublingual space is a potential space between the mylohyoid muscle and the geniohyoid and genioglossus muscles. It is medial to the mandible. This space also contains the lingual artery and nerve, hypoglossal nerve, glossopharyngeal nerve, and Wharton duct. In contrast to the parotid and submandibular glands, there is no capsule surrounding the gland. Histologically, the sublingual gland is composed of primarily mucous secreting cells.

Unlike the parotid and submandibular gland, the sublingual gland often has no associated major duct but rather drains via 8 to 20 small ducts (ducts of Rivinus) into the oral cavity. These ducts exit the superior aspect of the gland and drain along the sublingual fold. Occasionally, some of the ducts join together to form one major sublingual duct (Bartholin duct), which joins the submandibular duct.

The arterial blood supply to the sublingual gland is via the submental branch of the facial artery and the sublingual

branch of the lingual artery, both branches of the external carotid artery. The venous drainage is via the corresponding veins. The lymphatic drainage of the sublingual gland is to the submandibular lymph nodes.

The sublingual gland's sympathetic innervation is through the superior cervical ganglion with postganglionic fibers traveling along the lingual artery. The parasympathetic innervation is the same as with the submandibular gland, with preganglionic fibers traveling via the chorda tympani to join the lingual nerve and synapse in the submandibular ganglion. The postganglionic fibers then innervate the sublingual gland via branches of the lingual nerve.

Minor Salivary Gland Anatomy

There are approximately 600 to 1,000 minor salivary glands located mainly in the buccal, labial, palatal, and lingual regions. There can also be minor salivary gland tissue on the superior pole of the tonsil (Weber gland), tonsillar pillars, base of tongue (von Ebner gland), paranasal sinuses, larynx, trachea, and bronchi. Histologically, the minor salivary glands are composed of serous, mucous, or mixed cells. In contrast to the parotid and submandibular gland, each salivary unit has its own duct as opposed to a branching network of drainage.

The arterial blood supply, venous drainage, and lymphatic drainage correspond to the region the minor salivary gland is located. The majority of the minor salivary glands receive parasympathetic innervation from postganglionic fibers from the submandibular ganglion. However, the minor salivary glands of the palate receive parasympathetic innervation from the palatine nerves, supplied by the sphenopalatine ganglion.

PHYSIOLOGY OF THE SALIVARY GLAND

Microstructure of Salivary Glands

The basic secretory unit of the salivary gland consists of the acinus, myoepithelial cells, and ductal system. The acinar cells determine the type of secretion produced. The acini are divided into three types: serous cells (spherical and protein secreting), mucous cells (tubular and mucin secreting), or mixed cells (13). The acini are responsible for producing the primary secretion. The primary secretion has an electrolyte composition and osmolality similar to that of plasma. The serous cells produce secretory granules with amylase, whereas mucous cell granules contain mucin (13,14). As previously stated, the parotid gland contains purely serous cells (forming a thin watery saliva); the submandibular gland contains mixed cells but mainly serous cells; the sublingual gland contains mostly mucous cells (forming a thick, viscous mucin-rich saliva); and minor salivary glands have either serous, mucous, or mixed cells. Myoepithelial cells surround the acinar and proximal duct cells. They are contractile cells instrumental in moving secretory products toward the excretory duct (13,14).

As the saliva moves distally, the ductal system alters the composition of the saliva creating the ductal secretion. The first sets of ducts are the intercalated ducts, which lead from the acini and possess a carbonic anhydrase activity. In serous secreting and mixed glands, they secrete bicarbonate and absorb chloride from the acinar product (13). The next ductal cells are the striated duct cells, which are involved in the reabsorption of sodium from the primary secretion and the secretion of potassium and bicarbonate into the secretion. More sodium is resorbed than potassium is secreted causing the secretion to become more hypotonic (13,14). The excretory ducts are the final ducts in the secretory unit and connect to the oral cavity. These cells continue the process of sodium resorption and potassium secretion (14).

Basal cells of the intercalated duct and excretory duct cells are capable of giving rise to fully differentiated ductal epithelial cells. This is a significant feature with respect to the bicellular theory of tumorigenesis, which states that all tumors either arise from intercalated duct stem cells (pleomorphic adenoma, Warthin tumor, oncocytoma, acinic cell carcinoma, and adenoid cystic carcinoma) or excretory duct stem cells (squamous cell carcinoma and mucoepidermoid carcinoma). The bicellular theory has been somewhat abandoned in favor of multicellular theory of tumorigenesis, which states that salivary gland tumors arise from the differentiated cells of the salivary unit (15).

The final result of the secretory unit system is the production of a hypotonic solution, the degree of which is determined by the transport time. The hypotonicity of saliva allows the taste buds to perceive different tastes without being masked by normal plasma sodium levels (14). In general saliva is composed of 99.5% water in addition to proteins, glycoproteins, and electrolytes. The normal pH of saliva is 6 to 7 (14).

Salivary Gland Function

The function of saliva can be organized into five categories: lubrication and protection, buffering action and clearance, maintaining tooth integrity, antibacterial activity, and taste and digestion (14). The saliva produced from the salivary glands creates a seromucous coating. This coating helps to lubricate and protect the oral tissues and act as a barrier to irritants. Irritants include proteolytic and hydrolytic enzymes in plaque, carcinogens from tobacco use and exogenous chemicals, and extreme dryness from mouth breathing (16). The best lubricating component of saliva is the mucin. Its properties include low solubility, high viscosity, high elasticity, and strong adhesiveness, which allow the saliva to act as a good lubricant and biofilm barrier (17).

The second function is that saliva produces a buffering action. This can occur because saliva contains bicarbonate,

phosphate, urea and amphoteric proteins and enzymes. The bicarbonate is the most important component of the buffering system. It diffuses into dental plaque and caries, and neutralizes the acids. All of the substances together act to buffer ingested chemical and maintain an oral pH of 6 to 7 during stimulated high flow rates (14).

The maintenance of tooth integrity is the third function, in that it facilitates the demineralization and remineralization process. The demineralization process occurs when acids diffuse through the plaque to the actual tooth and dissolve the mineral in the tooth. These minerals then diffuse out of the tooth structure and into the saliva. Remineralization is the process of replacing lost minerals by the supersaturation with calcium and phosphate, which are found in saliva. Fluoride helps the remineralization process by forming a fluorapatite-like coating causing the tooth structure to be more resistant to dental caries (14).

Saliva contains immunologic and nonimmunologic agents for the protection of teeth and mucosal surfaces. The immunologic agents are secretory IgA, IgG, and IgM. The nonimmunologic agents include selected proteins, mucin, peptides, and enzymes. Secretory IgA is produced by plasma cells in connective tissues and then travel to the major and minor salivary glands where they are excreted through the duct with saliva. IgA is an antibody against bacterial antigens; it neutralizes viruses and promotes the aggregation of bacteria to prevent the attachment of bacteria to host tissue. The nonimmunologic agents are all products of acinar cells; they help protect the dentition from physical, chemical, and microbial insults. Lactoferrin is a nonimmunologic agent produced by the intercalated cells, which binds ferric iron in the saliva. Ferric iron is a nutritional source for bacteria. The lactoferrin essentially depletes the iron content in the saliva, thus starving the bacteria. Lysozymes are produced in the basal cells of striated ducts in the parotid gland, destroy and inhibit bacterial growth by causing cell lysis. Other proteins such as glycoproteins, statherins, agglutinins, histidine-rich proteins work to cause bacterial aggregation or clumping. The aggregation process prevents the ability of the bacteria, fungus, and viruses from attaching and colonizing the oral cavity tissues (14).

The final function of saliva is to enhance taste and begin digestion. As previously stated, saliva is a hypotonic solution in its final state, which enhances the tasting capacity of salty foods and nutrients. The hypotonic saliva contains proteins and gustin, which bind to zinc and enhance taste. Saliva also plays a role in the beginning stages of digestion as it contains amylase, which is produced in the parotid gland and assists in the breakdown of starch (14).

Secretion of Saliva

The secretion of saliva is controlled by a salivary center in the medulla; however, there are many specific stimuli that trigger the secretion including: physical (the act of chewing), gustatory (sweet is the least stimulating and acid is the most stimulating), and olfactory (poor stimulus). Other factors that can affect the secretion of saliva include medications (sedatives, antipsychotics, antidepressants, and diuretics), systemic conditions (autoimmune diseases, granulomatous diseases, cystic fibrosis, diabetes, eating disorders), or any condition affecting the salivary gland itself (16).

Salivary glands are innervated by both parasympathetic and sympathetic nerve fibers. Both systems use different neurotransmitters to produce the desired effect. The parasympathetic nervous system uses acetylcholine as its neurotransmitter. While acetylcholine can bind to a nicotinic or a muscarinic receptor, it is the muscarinic receptor that is involved in salivary gland stimulation. When the parasympathetic stimulation is predominant, the result is predominantly watery saliva. The sympathetic nervous system uses norepinephrine as its neurotransmitter and with all synapses being adrenergic. When the sympathetic stimulation is predominant, the result is a scant viscous saliva with increased concentrations of protein, organic solutes, and inorganic solutes (14).

A common complication after parotidectomy is gustatory sweating (Frey syndrome). In the normal patient the auriculotemporal branch of the trigeminal nerve carries sympathetic fibers to the sweat glands of the scalp and parasympathetics to the parotid gland. Frey syndrome occurs from aberrant reinnervation of the cholinergic sympathetic sweat glands with postganglionic parasympathetic fibers that have been exposed following parotidectomy. While the phenomenon of Frey syndrome is common (up to 80%) based on potassium iodide testing of postoperative patients, the degree that patients are actually symptomatic is quite variable (18). Clinically significant Frey syndrome is confirmed based on a patient history of problematic sweating while eating. Treatment consists of application of an anticholinergic topical ointment such as scopolamine, injection of botulinum toxin (18), or surgical transection of nerve fibers with or without placement of intervening grafts or adipose tissue.

Salivary Flow Rates

Salivary flow rates vary per individual and may also vary if stimulated or not stimulated by the autonomic nervous system. The normal flow for unstimulated saliva is anything above 0.1 mL/min and the minimum flow for stimulated saliva is 0.2 mL/min (14). The maximum stimulated flow rate is 7 mL/min (17). Stimulated saliva contributes approximately 80% to 90% of the average daily saliva production (17).

The average daily flow of saliva varies between 1.0 and 1.5 L. The different salivary glands each contribute a portion of the unstimulated saliva: 20% from the parotid gland, 65% from the submandibular gland, 8% from

the sublingual gland, and less than 10% from the minor salivary glands. When the glands are stimulated to produce saliva, the parotid gland contributes more than 50% of the total salivary secretions (14).

Hypersalivation, or ptyalism, can be secondary to either overproduction of saliva or oversecretion, which surpasses swallowing. This can be treated with botulinum toxin injections into the salivary glands (18), bilateral parotid duct rerouting with or without bilateral submandibular gland excision, or bilateral tympanic neurectomies. Salivary gland hypofunction is defined as salivary flow less than 0.1 mL/min or a 50% reduction below basal rates (14). This most commonly affects the elderly and is usually secondary to medication use or systemic disease.

IMAGING

Salivary gland imaging has evolved over the past years from plain films and sialograms to now an almost complete shift to computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound. CT scan is the modality of choice for patients with suspected acute or subacute inflammatory disease based on the history and physical, sialoliths, or salivary gland masses (Fig. 47.9). MRI is also a useful imaging tool in the work-up of a salivary gland mass. It is used to determine perineural, meningeal, or skull base invasion. Sialography is still useful and is reserved for the evaluation of chronic sialadenitis unrelated to sialolithiasis (19).

Ultrasound is a highly sensitive means to evaluate the major salivary glands. As a result of the technologic advances in ultrasound and the superficial nature of the salivary glands, the majority of the major salivary glands are accessible by ultrasound. On ultrasound all salivary glands are homogenous echogenic organs (20). While ultrasound is a useful tool in salivary gland evaluation, it is limited in its assessment of the deep lobe of the parotid gland due to shadowing by the mandible and the minor salivary glands due to their location in the floor of the mouth; therefore any abnormalities in these regions should be assessed with CT or MRI (21). Salivary gland imaging is discussed further in Chapter 48.



Figure 47.9 Axial CT scan showing a large sialolith in hilum of the left submandibular gland.

SIALENDOSCOPY

Sialendoscopy is a relatively new procedure that allows for the endoscopic intraluminal visualization of major salivary glands and offers a mechanism to diagnose and treat both inflammatory and obstructive pathology related to the ductal system. The most common indications for sialendoscopy include sialolithiasis (52%) followed by salivary gland swelling (6%). The overall success rate for endoscopic stone removal is 74% (22). The size of the stones removed ranged from 0.2 to 1.2 cm (23). Major complications are rare with sialendoscopy. Injury to the facial nerve has not been reported during sialendoscopy (22). Sialendoscopy is further discussed in Chapter 48.

HIGHLIGHTS

- Main function of the salivary glands is the production of saliva for lubrication and protection, buffering action and clearance of food, maintenance of tooth integrity, antibacterial activity, taste and digestion.
- Embryologically, all derived from outpouchings or oral ectoderm into the surrounding mesenchyme.
- Histologically, the parotid gland contains purely serous secreting acinar cells, the submandibular gland contains both serous and mucous secreting cells with predominately serous cells, and the sublingual gland is composed of primarily mucous secreting cells.
- The parotid duct enters the oral cavity at the level of the second maxillary molar.
- The facial nerve divides the parotid gland into superficial and deep lobes and terminates into five branches.
- The parotid gland receives parasympathetic innervation from the glossopharyngeal nerve via the auriculotemporal nerve and sympathetic innervation from the superior cervical ganglion.
- The submandibular duct enters the oral cavity in the floor of mouth lateral to the lingual frenulum.
- The submandibular gland and sublingual glands receive parasympathetic innervation from the superior salivatory nucleus and facial nerve via the lingual nerve and sympathetic innervation from the superior cervical ganglion.
- The basic secretory unit of the salivary gland consists of the acinus, myoepithelial cells, and ductal system.
- In general, saliva is composed of 99.5% water, in addition to proteins, glycoproteins, and electrolytes. The normal pH of saliva is 6 to 7.
- The average daily flow of saliva varies between 1.0 and 1.5 L.
- Salivary gland imaging has evolved from plain films and sialograms to now an almost complete shift to CT, MRI, and ultrasound.
- Sialendoscopy is a relatively new procedure that allows for the endoscopic intraluminal visualization of major salivary glands and offers a mechanism to diagnose and treat both inflammatory and obstructive pathology related to the ductal system.

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48 Nonneoplastic Diseases of the Salivary Glands

Rohan R. Walvekar *Matthew A. Bowen*

Nonneoplastic disorders of the salivary gland encompass a wide range of disease processes that can affect the salivary glandular and the ductal system. These can be acute or chronic in their presentation and can also be broadly classified into inflammatory and noninflammatory disorders. Nonneoplastic disease processes affect both the major and minor salivary glands; however, they occur more commonly in the major salivary glands. Classification of the disease process is of importance. Treatment can be targeted toward a more generalized disease process affecting the entire gland (e.g., antibiotics in acute suppurative sialadenitis) or a locally directed treatment aimed at improving salivary flow and function (e.g., stone removal for an obstructed salivary gland). A history and physical examination allows differentiation of lesions or disease processes into their appropriate classification. Additional laboratory studies, special tests, imaging studies, and rarely a pathologic analysis via a diagnostic biopsy may be required to make a specific diagnosis. Extensive testing is rarely necessary to classify nonneoplastic disorders of the salivary gland. This chapter provides an overview of a variety of common nonneoplastic disease processes and also introduces the emerging field of sialendoscopy and its impact on the management of nonneoplastic salivary gland diseases (SGDs).

ACUTE INFLAMMATORY LESIONS

Acute Suppurative Sialadenitis

Acute sialadenitis is a bacterial infection of the salivary glands. High bacterial loads in the oral cavity provide opportunity for infection of the salivary glands. Normal salivary flow is protective against retrograde colonization and overgrowth of bacteria in the salivary ducts and parenchyma. Saliva has antimicrobial properties due to the presence of lysosomes, IgA antibodies, and sialic acid. These proteins are more concentrated in the submandibular, sublingual, and minor salivary glands as compared to the less viscous saliva in the parotid gland. Acute sialadenitis was first reported in 1828. It gained increased attention when President Garfield died from acute parotitis following abdominal surgery in 1881. The current incidence of acute sialadenitis has been reported at 0.02% of hospital admissions (1), with the parotid gland being most commonly affected. Thirty to forty percent of these episodes can occur in the postoperative patient. The disease occurs with the highest incidence after gastrointestinal procedures between postoperative day 3 and 7.

Salivary stasis, reduced flow, and obstruction can be precipitating events for acute sialadenitis. Dry mouth is seen with increasing age affecting up to 30% of patients over the age of 65 years. This could be attributed to a disease process but can also be subsequent to prescribed medications. Eighty percent of prescribed medications cause some degree of xerostomia and more than 400 medications can cause some degree of salivary gland dysfunction. Consequently, it is not surprising acute sialadenitis most frequently occurs in sixth or seventh decade of life. However, all age groups can be affected. A decrease in saliva production can be caused by multiple medical conditions and drug therapies, increasing the risk for acute suppurative sialadenitis. Examples include diuretic therapy for hypertension, osmotic diuresis from diabetes mellitus, and postsurgical fluid shift, especially after gastrointestinal procedures. Debilitated individuals who rely on caregivers for hydration and oral hygiene are also at risk for acute suppurative sialadenitis (Table 48.1). Antisialogogue medications and physical obstruction of salivary flow due to sialolithiasis or salivary duct stricture result in salivary stasis and can cause acute sialadenitis.

TABLE 48.1 SYSTEMIC AND EXOGENOUS SOURCES OF SALIVARY DYSFUNCTION

Alzheimer Disease	Scleroderma
Cystic fibrosis	SS
Diabetes	Dehydration
HIV/AIDS	Radiation therapy
Systemic lupus erythematosus	Various medications
Parkinson disease	Chemotherapy
Rheumatoid arthritis	
Sarcoidosis	

The classical presentation of acute suppurative sialadenitis is the sudden onset of diffuse enlargement of the involved gland with associated induration and tenderness (Fig. 48.1). A detailed history may reveal underlying risk factors or etiology. The gland should be palpated when possible. Bimanual palpation is more effective for the submandibular gland. Palpation may often reveal obstructing salivary stones. Palpation and massage of the gland may result in the expression of purulent exudate from the papilla of the involved gland. The unaffected glands should be palpated while the papillae are visualized to observe for expression and consistency of normal saliva. The purulent exudate should be cultured for aerobic and anaerobic bacteria, and a specimen for Gram staining.

Historically, *Staphylococcus aureus* has been attributed as the causative microbe in up to 90% of cases of suppurative sialadenitis. Other aerobic organisms implicated include *Streptococcus pneumoniae*, *Escherichia coli*, and *Haemophilus influenzae*. More recent microbiology studies have revealed that while *S. aureus* remains the most common bacteria; anaerobic, gram-negative, and polymicrobial infections are not uncommon (2,3). The most common anaerobic organisms are *Bacteroides melaninogenicus* and *Streptococcus micros*. In one study, anaerobic bacteria were isolated in 64% of cases, and β-lactamase-producing organisms were isolated from 51% of cases (3). Histologic examination shows glandular destruction with abscess formation. Ductal wall erosion is seen with associated penetration of glandular parenchyma.



Figure 48.1 Acute suppurative parotitis affecting the left parotid gland.

Initial treatment consists of antibiotics, warm compresses, gland massage, and sialogogues. Aerobic and anaerobic cultures are obtained to direct antimicrobial therapy. Empiric treatment with penicillinase-resistant antistaphylococcal antibiotic should be initiated while awaiting cultures. Efforts should be made to correct causative risk factors or comorbidities, such as uncontrolled diabetes, which can compromise treatment response. Oral or parenteral hydration should be given as appropriate. Computed tomography (CT) or ultrasound imaging is useful if an abscess or regional spread of infection is suspected. Sialography is contraindicated. Similarly, sialendoscopy, a relatively new diagnostic and therapeutic technique, is also contraindicated in this setting (4). Imaging can detect obstruction due to sialolithiasis or salivary strictures that can be addressed once the active infection has subsided.

In the event of abscess formation, incision and drainage is indicated and can be performed using a modified Blair incision to expose the parotid capsule. A hemostat can then be used to spread in the direction of the facial nerve fibers to enter the abscess cavity. Management of the abscess cavity follows standard recommendations that include packing or placement of a drain based on each individual case scenario. CT-guided or ultrasonography-guided needle aspiration may also be an option that can obviate open surgery. Treatment initiation usually results in rapid improvement within 24 to 48 hours. If the patient does not respond to therapy, antibiotic resistance, immune status, and abscess formation should be considered. Mortality rates up to 20% have been reported in the literature.

Mumps

The most common acute viral infection of the salivary glands is mumps. Prior to the release of the mumps vaccine in 1967, the incidence of mumps in the United States was as high as 300,000 cases per year and the most common cause of parotid swelling. This dramatically decreased to 266 reported cases in 2001 (5). Subsequently, the demographics of mumps shifted from being a disease of childhood to most commonly affecting young adults. Several outbreaks in the United States and other vaccinated countries have been reported in recent years (6–8). Prodromal symptoms include fever, malaise, myalgia, and anorexia.

The onset of parotitis usually occurs within 24 hours but may follow up to a week later. Parotitis is generally bilateral, but may be unilateral. Other salivary glands, such as the submandibular gland and sublingual gland, are less frequently involved and are almost never solely involved. Other manifestations include orchitis, aseptic meningitis, pancreatitis, and myocarditis. Sensorineural hearing loss is a rare complication. Diagnosis is made by confirmation of antibodies to the mumps S and V antigens. Diagnosis can also be made by isolating the virus from the cerebrospinal fluid (CSF) during the first 3 days of clinical symptoms for patients presenting with aseptic meningitis. Virus is also present in the saliva for approximately 1 week starting 2 to 3 days before onset of parotitis. Viral cultures of urine will also be possible for the first 2 weeks of illness (9–11). PCR or viral cultures can also be used to detect the virus. Therapy is symptom based. Chronic obstructive sialadenitis may develop many years after the acute episode of mumps.

Other Viral Diseases

Other viruses have been implicated in acute viral parotitis, including cytomegalovirus, Coxsackie A and B, cytopathic human orphan virus, echoviruses, influenza A, and lymphocytic choriomeningitis virus (12). Treatment of all viral infection is symptomatic. Added antibacterial therapy is indicated in the presence of superimposed infections.

HIV

Several salivary gland manifestations may occur in patients with human immunodeficiency virus (HIV). Diffuse gradual enlargement of the salivary glands may be seen and has been termed HIV-associated SGD (HIV-SGD). HIV-SGD may be encountered at any time in the HIV disease process, and may be the presenting symptom. The parotid gland is most commonly affected. Xerostomia can be present, mimicking Sjögren syndrome (SS). Other salivary gland manifestations of HIV include Kaposi sarcoma and lymphoma. While non–HIV-related lymphoepithelial (LE) cysts also occur, a significantly increased incidence of parotid LE cysts has occurred since the emergence of HIV. LE cysts histopathologically resemble branchial cleft cysts with an epithelial-lined cyst within a lymphoid stroma. Dave et al. (13) propose a classification system for lymphocytic parotid gland enlargement in HIV-positive pediatric patients: (a) parotid gland lymphadenopathy, (b) benign LE lesion, and (c) benign LE cysts. Treatment consists of observation and antiretroviral therapy. Needle aspiration can offer temporary symptomatic relief for large cysts, but recurrence is expected. For severe symptomatic cases, or for cosmetic reasons, sclerotherapy is a reasonable option (13). Sclerotherapy agents used include alcohol (14), doxycycline (15), and sodium morrhuate (16). Surgery or radiation therapy should be reserved for resistant cases (13).

GRANULOMATOUS INFECTIONS OF THE SALIVARY GLANDS

Tuberculosis of the Salivary Glands

Although cervicofacial involvement is the most common extrapulmonary manifestation of *Mycobacterium tuberculosis* infection (17), salivary gland involvement by far is rare. Older children and adults are most commonly affected. Parotid involvement is most common with primary *M. tuberculosis* infection, while in disseminated pulmonary infections, the submandibular gland is more commonly involved. Most cases of primary tuberculosis of the salivary gland are believed to arise from a focus of infection in the tonsil or teeth. The presentation is that of an enlarging firm parotid mass that is identical to a neoplasm on imaging (18). Clinical presentation may mimic acute inflammatory sialadenitis and diagnosis requires positive acid-fast salivary stain and purified protein derivative (PPD) test. However, PPD test is unreliable because of increasing incidence of nontuberculous mycobacterial (NTM) infections that give a negative PPD test. Fine needle aspiration can reveal caseous necrosis in some cases. PCR of fine needle aspirate is highly sensitive (18), but may not be easily obtained. After the diagnosis is made, treatment is the same as for any tuberculosis infection. In resistant cases, excision may be necessary and will be curative.

NTM are more common than *M. tuberculosis* in cervicofacial mycobacterial infections. Salivary gland involvement is still rare relative to involvement of cervical lymph nodes. *Mycobacterium kansasii*, *Mycobacterium scrofulaceum*, and *Mycobacterium avium* are the most commonly encountered NTM. These organisms are common in soil, water, and food, and are carried by domestic and wild animals. NTM infection is most commonly encountered in children younger than 5 years old. The typical presentation is tender induration in the region of the salivary gland that fails antibiotic therapy. The overlying skin develops thinning and adherence to the infected gland, with a characteristic violaceous hue. Abscess formation is common. Fine needle aspiration biopsy carries a risk of fistula formation, but is useful for microscopic evaluation for acid-fast bacilli in the aspirate. Culturing NTM takes weeks and is frequently negative, but useful if positive. Antibiotic treatment with clarithromycin or other antibiotics can be attempted, but often results in several weeks to months of treatment, during which the patient remains symptomatic and fistulization or repeated abscess formation must be managed. Therefore, complete gland excision of the affected gland is advocated as the definitive treatment (i.e., parotidectomy with facial nerve preservation).

Cat-Scratch Disease

Cat-scratch disease is caused by the gram-negative bacillus *Bartonella henselae*. A local infection at the scratch site is followed 1 to 2 weeks later by lymphadenopathy in the

draining lymph nodes. Parotid or submandibular lymph nodes may be involved. Lymph node enlargement progresses over 1 to 2 weeks and can persist for 2 to 3 months. Abscess formation may occur. Observation is usually sufficient with reassurance that the lymphadenopathy will spontaneously resolve. If the patient is highly symptomatic, antibiotics can be prescribed. Rifampin, erythromycin, gentamycin, azithromycin, and ciprofloxacin are all therapeutic options (19). Actinomycosis may also involve the salivary glands. Long-term penicillin therapy is combined with incision and drainage and excision of necrotic tissue for symptom control.

Sarcoidosis

Sarcoidosis is a granulomatous disorder with many systemic manifestations encompassing every organ system. Parotid gland involvement has been reported in 6% to 30% of patients with sarcoidosis (20–22). One notable presentation is that of uveoparotid fever (Heerfordt syndrome), which is characterized by uveitis, parotid enlargement, and facial paralysis, and has been reported to affect 0.3% of patients with sarcoidosis (23). Parotid swelling can last months to years and eventually resolves spontaneously. Submandibular, sublingual as well as minor salivary gland involvement may also occur. Biopsy of the minor salivary glands may establish diagnosis. Corticosteroids are effective, especially in the acute phase and for the management of facial paralysis. Uveitis can lead to glaucoma.

Sjögren's Syndrome

Sjögren's Syndrome (SS) is an autoimmune disorder with symptoms including xerostomia, dry eyes, and salivary gland enlargement (Fig. 48.2). SS is common and underdiagnosed. In the United States, approximately 1 million people have an established diagnosis, with an estimated 2 to 4 million people being affected. The male:female ratio is 9:1. SS affects people of all ages, but is typically diagnosed between the fourth and sixth decades. Primary SS affects the exocrine glands alone. In secondary SS, there is a coincidence of another autoimmune disorder, such as rheumatoid arthritis or systemic lupus erythematosus. The pathophysiology is poorly understood, but leads to B and T cell–mediated damage to exocrine glands. Non–organ-specific autoantibodies are present in approximately 60% of cases (24). These include rheumatoid factor (RF), antinuclear antibodies, and antibodies to the small RNA–protein complexes Ro/SS-A and La/SS-B. The histopathologic hallmark of SS is focal dense lymphocytic infiltration with little or no surrounding edema or fibrosis. CD4+ T cells predominate, with B cells accounting for approximately 20% of cells. Infiltration begins by surrounding glandular ducts and expanding to replace acinar epithelial cells. Acinar loss leads to decreased glandular function (25). A wide range of systemic and other organ-specific manifestations are possible. Fatigue and arthritis are common. Interstitial pneumonitis, rash or dry skin, achlorhydria, hepatosplenomegaly, genital dryness, myositis, and pancreatitis may be encountered. SS patients have been found to have a 44 times higher relative risk of developing lymphoma, which may present early or late in the disease. Predictors of lymphoma development include persistent enlargement of the parotid glands, splenomegaly, lymphadenopathy, palpable purpura, leg ulcers, low C4 level, mixed monoclonal cryoglobulinemia, and cross-reactive idiotypes of monoclonal RFs (26). Although the most prominent ocular symptom of the disease is dry eye, this is not a frequent presenting symptom. On the contrary, dry mouth (xerostomia) is a more common presenting complaint (27). Dry mouth is a debilitating feature of the disease and affects overall quality of life of these patients. Examination often denotes a dry oral mucosa with minimal expression of saliva when the parotid or submandibular glands are massaged. Placement of a tongue blade in the oral cavity causes it to adhere to the buccal mucosa confirming xerostomia.



Figure 48.2 SS in patient with acquired immunodeficiency syndrome-related complex.

Diagnostic criteria have been established (European-American Consensus Group Modification of the European Community Criteria for Sjögren's Syndrome) based on the presence of four of the following six criteria: symptoms of dry eye, signs of dry eye (abnormal results of Schirmer test), symptoms of dry mouth, signs of abnormal salivary glandular function, minor salivary gland biopsy focus score of greater than 1, and presence of SS-A or SS-B antibodies (28). Sensitivity and specificity range from 85.1% to 93.5% and 93.3% to 94.0%, respectively. Imaging such as CT or magnetic resonance (MRI) of the parotid gland can demonstrate speckled calcification that is often encountered in patients with SS having parotid involvement (Fig. 48.3).

Treatment for SS involves symptomatic treatment for xerostomia and prevention of ocular or dental damage. Salivary production can be improved by stimulation of



Figure 48.3 CT of a patient with SS showing stippled calcification.

existing salivary flow. This can be done by use of sugarless or sour candies, fruit slices such as peaches or nectarines. Citrus flavored sugarless tablets ("Salivasure," Scandinavian Health and Beauty Products, Perkasie, PA) are available. Malic acid in the tablets and maltose lozenges also stimulate salivary sections and reduce symptoms of oral dryness (29). Pilocarpine, a muscarinic–cholinergic agonist acting predominantly on M3 receptors, is a systemic sialogogue that may be prescribed and does provide symptom relief. However, side effects including sweating, flushing, and increased urination are common and can be dose-limiting. Cevimeline is a derivative of acetylcholine with a higher affinity for M1 and M3 receptors on the salivary glands (30,31) and has been shown to be of benefit in a double-blinded placebo controlled randomized study that studied the drug randomly in 197 patients with primary and secondary SS (32).

Oral secretions can be replaced by encouraging the patient to take frequent sips of water. Artificial saliva preparations that contain methyl cellulose provide more viscosity and lubrication than water. Fluoride treatments can be used to reduce dental caries. In addition, patients should be counseled to take meticulous care of dentition with frequent (at least once every 6 months) visits to the dentist for cleaning and plaque control (33). Novel therapeutic options such as sialendoscopy with irrigation of the salivary ductal system with or without instillation of steroids has also been shown to demonstrate benefit in terms of improvement of salivary gland discomfort, reduced incidence of salivary gland swelling, and improved salivation (34). The authors' personal experience in this area suggests a potential in the future for a combined therapeutic options that would involve salivary endoscopy with irrigation with or without steroid injections in conjunction with medical therapy to optimize and individualize treatment protocols.

Chronic Sialadenitis

Chronic sialadenitis is characterized by recurrent inflammation and pain in the major salivary glands. Precipitating events include the triad of stasis, obstruction, and reduced salivary flow rate. Sialolithiasis, salivary duct stricture, external duct compression, systemic disease (e.g., SS), or states (e.g., dehydration) may be causative. As seen with acute suppurative sialadenitis, the parotid gland is more commonly involved. Repeated glandular infection results in permanent damage to the salivary gland characterized by sialectasia, ductal ectasia, and progressive acinar destruction combined with a lymphocytic infiltrate. Symptoms are often exacerbated by eating. The structural changes with chronic repeated infections result in reduced function. Xerostomia develops in up to 80% of patients as the salivary glands become progressively damaged. Chronic inflammation damages the gland, with findings of ductal ectasia, acinar destruction, and a lymphocytic infiltrate of the parenchyma.

Patients with chronic sialadenitis present with a history of recurrent painful swelling of the affected salivary gland(s) that is often aggravated by eating. Physical examination confirms asymmetric, firm, and occasionally tender glands. The glands can also be atrophic and hard in consistency that can be either diffuse or discrete. In the latter case, imaging and needle biopsy may be required to rule out a coincidental neoplasm. Examination of the oral cavity must be performed to assess xerostomia, quality and consistency of the saliva, patency of the duct opening at the papilla, and to perform bimanual palpation of the glands. Examination may often reveal a calculus that may be palpable in the floor of the mouth or over the masseter muscle. Ultrasonography is a valuable adjunct to physical examination and can help detect salivary stones that are not palpable clinically, as well as neoplastic process and strictures.

Gland massage during exam typically reveals decreased salivary output. The consistency of saliva may also vary and can be more tenacious as compared to a normal water-like consistency of saliva. Changes in saliva occur as a result of the chronic inflammatory process. During acute episodes, sodium and chloride values approach those in the serum; glucose is elevated while phosphate levels decrease. Levels of plasma derived IgA, IgG, IgM, albumin, and transferrin are increased, as well as myeloperoxidase, lactoferrin, and lysozyme, which are derived from inflammatory infiltrate or the acini. The pattern of immunoglobulins in the saliva shifts from IgA-predominance (normal for saliva) to IgG-predominance. After the acute episodes have resolved, the increased levels of sodium and proteins in the saliva remain in patients with chronic sialadenitis. However, these levels normalize in patients with noninflammatory enlargements.

The diagnostic workup should include imaging with a CT with and without intravenous contrast to evaluate for calculi or neoplasms within the gland. Sialography may be useful to detect ductal abnormalities such as ectasia or strictures. More recently, several authors have described specialized MRI protocols to view the salivary gland ducts, termed MRI sialography, which may prove useful as the technique is developed (35–37). Workup for SS or indolent mycobacterial infections should be considered.

After excluding treatable causes, initial treatment for chronic sialadenitis includes sialogogues, hydration, massage, and antibiotics during acute exacerbations. When conservative management is insufficient, several procedures have potential to decrease symptomatic burden. However, results are inconsistent, which can lead to frustration for the patient and physician. Treatment options include papillary dilation (with or without sialodochoplasty), steroid injection into the duct, dilation of ductal strictures, ductal ligation to promote gland atrophy, gland irradiation, and surgical gland extirpation. Sialendoscopy has been gaining increasing attention as a diagnostic and therapeutic tool, which may spare gland removal (38).

Chronic recurrent parotitis from several causes can eventually lead to the development of benign LE lesion. This lesion belongs in the spectrum of diseases characterized by a lymphoplasmacytic infiltrate combined with acinar atrophy and ductal metaplasia. Lymphoid follicles surround epithelial nest giving rise to the development of the so-called epimyoepithelial island. The LE lesion generally affects one gland, most commonly the parotid gland and there is a female preponderance (60% to 80%) (Fig. 48.4). This first presents as an asymptomatic enlargement unless there is an associated infection. In the absence of symptoms or complications, no treatment is necessary. Intermittent infections should be managed like episodes of acute sialadenitis. Recurrent or chronic infections with drainage and pain as well as cosmetic deformity may necessitate surgical removal.



Figure 48.4 Sialogram of patient with benign LE lesion.

Juvenile Recurrent Parotitis

Sialadenitis can also result in progression to juvenile recurrent parotitis (JRP) or recurrent parotitis of childhood that have similar consequences in terms of salivary gland damage. JRP is a well-recognized salivary gland disorder and is the second most common salivary disease in children. The clinical presentation of JRP involves recurrent, nonobstructive, nonsuppurative swelling of either one or both of the parotid glands (39). The condition usually affects children from infancy to age 12 years. Most children will stop having further episodes after puberty, but in some cases this phenomenon can continue into adulthood. In either case, acute flare ups require intense treatment with antibiotics, analgesic, and hospital admissions. In the authors' personal experience, the unpredictability of the condition and need for repeated treatment and hospital admission creates a huge burden on the family and also impacts quality of life of the patients.

JRP is idiopathic. Many possible theories have been proposed to explain this condition including a congenital malformation of the Stenson duct, genetic aberrations, viral or bacterial infections, allergic, and autoimmune origins (39,40). Diagnosis of JRP is based on the clinical presentation and exclusion of other potential etiologies (Fig. 48.5). The treatment for JRP is similar to acute suppurative sialadenitis (41). Superficial parotidectomy is contraindicated since the disease in most cases is self-remitting. Due to its inflammatory nature, surgery carries a higher risk of facial paralysis. Some minor procedures have been investigated for treatment of JRP such as duct ligation or tympanic neurectomy without promising results (42). In 1986, Galili and Marmary (43) reported improvement of JRP with the use of sialography. These traditional treatment options have found to have limited effectiveness or carry



Figure 48.5 MRI sialography showing multiple dilatations bilateral parotid glandular system in patient with JRP (A, anterior; R, right; L, left; *asterisk* denote parotid glands).

a high morbidity associated with them. Interventional sialendoscopy with duct dilation, irrigation of the glandular system, instillation of steroid and stent placement, if necessary, have been shown to have therapeutic benefit and provides long-term symptom relief (39,44,45).

Sialolithiasis

Salivary stones are composed of various ratios of organic and inorganic substances. The inorganic substances are mainly calcium carbonate and calcium phosphate. The organic components include glycoproteins, mucopolysaccharides, and cellular debris. The formation of the sialolith is thought to occur around an inorganic nidus (38). Salivary calculi most commonly present in the submandibular gland (80%), followed by the parotid gland (20%) and sublingual gland (1%). Minor salivary calculi are uncommon, with a predilection for the upper lip and buccal mucosa (46). In 75% of calculi involving the major glands, only a single calculus is found. Multiple gland involvement occurs in approximately 3%, and there is a slight male preponderance, with most occurring in middle age. Calculi commonly occur in patients with chronic sialadenitis but are otherwise only infrequently associated with other diseases. Gout is the only systemic disease known to cause salivary gland calculi. Despite their similar chemical makeup, 90% of parotid calculi are radiolucent with standard facial x-rays (Fig. 48.6). Sialography is essentially 100% effective in making the diagnosis as essentially all are detectable with CT. Stones less than 2 mm in size may be missed by imaging (Fig. 48.7). Ultrasonography is an excellent tool for imaging of salivary stones (Fig. 48.8). It is useful both for diagnosis and for guidance intraoperatively. Ultrasonography for SGD is not widely used in the United States whereas in Europe, it is widely utilized. It is relatively inexpensive, repeatable, dynamic, versatile as it can be used to guide surgery, and accurate in trained hands; it also provides real-time images. MRI is not an optimal tool to detect calculi. However, MRI sialography is a new modification of MRI that allows delineation of the ductal system and consequently stones with high definition. Virtual MRI endoscopy is another innovation that allows three-dimensional reconstructions to provide a virtual endoscopic image of the salivary ductal system (37).

A theoretical prerequisite for calculus formation is the presence of a nidus of material allowing the precipitation of salts, almost certainly coupled with salivary stasis.



Figure 48.7 CT showing parotid calculus.

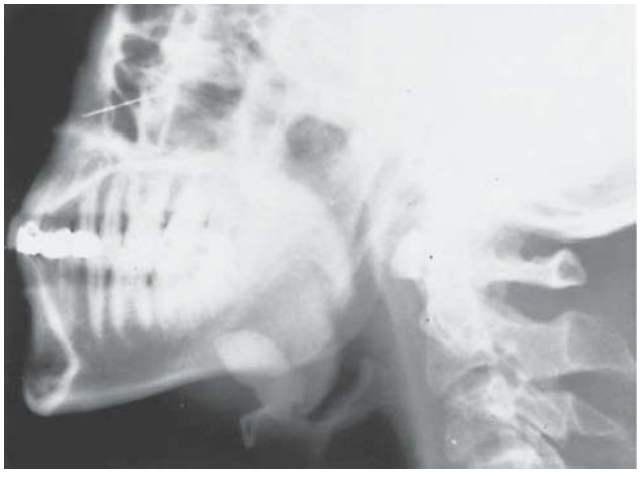


Figure 48.6 Plain radiograph showing large submandibular calculus.



Figure 48.8 Ultrasonography pictures showing a large submandibular salivary stone appearing as a hyperechoic casting a hypoechoic shadow. (*Black arrow* points to salivary stone.)

The submandibular duct is believed to be more susceptible to calculus formation because its saliva is more alkaline and has a higher concentration of calcium and phosphate and higher mucus content. Furthermore, the duct is longer and has an antigravity flow. Submandibular calculi usually arise within the duct, whereas those in the parotid are at the hilum or within the parenchyma.

Most patients present with a history of recurrent swelling and pain in the involved glands, often associated with eating. Calculi can present as acute suppurative sialadenitis. However, there are many patients with stones that do not result in significant infection for many years and are detected incidentally on imaging or physical examination. Consequently, acute suppurative sialadenitis with repeated episodes of obstruction and swelling is not a requirement for diagnosis. The calculus may be palpable in the involved duct, and the gland may be diffusely enlarged and mildly tender. Massage of the gland demonstrates decreased flow of cloudy or mucopurulent saliva. Complications of sialolithiasis include acute suppurative sialadenitis, ductal ectasia, and stricture.

Treatment depends on the location, size, and shape of the calculus. Traditional options include conservative therapy with sialogogues, gland massage, and hydration to facilitate spontaneous passage of the calculus. This is usually successful for extremely small stones, that is, 2 mm or less. Transoral stone removal or salivary gland excision is usually required for patients with recurrent symptoms. Newer treatment options include extracorporeal or intraductal shockwave lithotripsy, interventional sialendoscopy (discussed in the next section), or combined hybrid techniques using endoscopic/transoral or endoscopic/external approaches for removal of submandibular and parotid stones, respectively.

Sialendoscopy

Sialendoscopy involves the passage of miniature endoscopes into the salivary ducts. Saline is irrigated through the tip of the endoscope to distend the ductal walls and promote visualization. Sialendoscopy allows diagnosis of salivary gland pathology and treatment of sialolithiasis, ductal pathology, and inflammatory SGDs. The endoscopic anatomy of the salivary glands was described by Katz in 1990, including the genu of Stenson duct at the masseter (47). Various endoscopes have been used, ranging in size from 0.8 to 1.6 mm (Fig. 48.9) (48). Sialendoscopes typically have at least one port for irrigation, with larger endoscopes incorporating a second channel for instrumentation. Interventional capabilities utilizing sialendoscopes include endoscopic stone removal with forceps and wire baskets, laser fragmentation of stones, balloon dilation for stenosis, and instillation of medication for therapy (4,38,49,50). Current indications for sialendoscopy can be stratified into mechanical and nonmechanical interventions. Mechanical indications include those performed



Figure 48.9 Erlangen 1.6 mm "all-in-one" interventional sialendoscope with a distant camera head and light source attachment. Two ports: water drops on the hub of the scope indicating the irrigation port. The middle port is the 0.8 mm interventional channel.

with the goal of relieving an obstruction to salivary flow such as endoscopic management of salivary stones and strictures (Fig. 48.10). In addition, sialendoscopy can be both diagnostic and therapeutic for inflammatory disorders such as radioiodine-induced sialadenitis, JRP, and autoimmune-related sialadenitis. For these disease processes, irrigation of the duct with or without instillation of medication seems to help improve symptoms in 50% to 100% of cases with single interventions (39,49,51–53). The procedure is minimally invasive, low-risk, repeatable, and can often be performed in the office setting or as an outpatient procedure. Consequently, sialendoscopy provides a minimally invasive option for the management of nonneoplastic

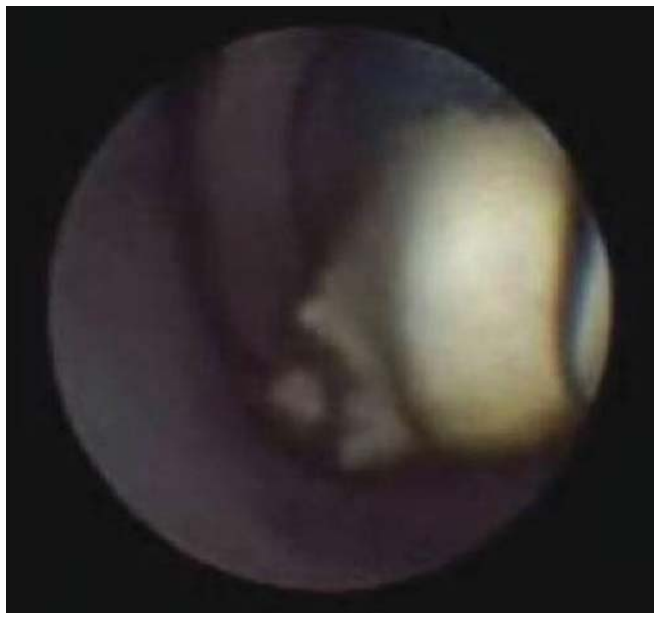


Figure 48.10 Figure illustrating endoscopic stone removal with wire basket.

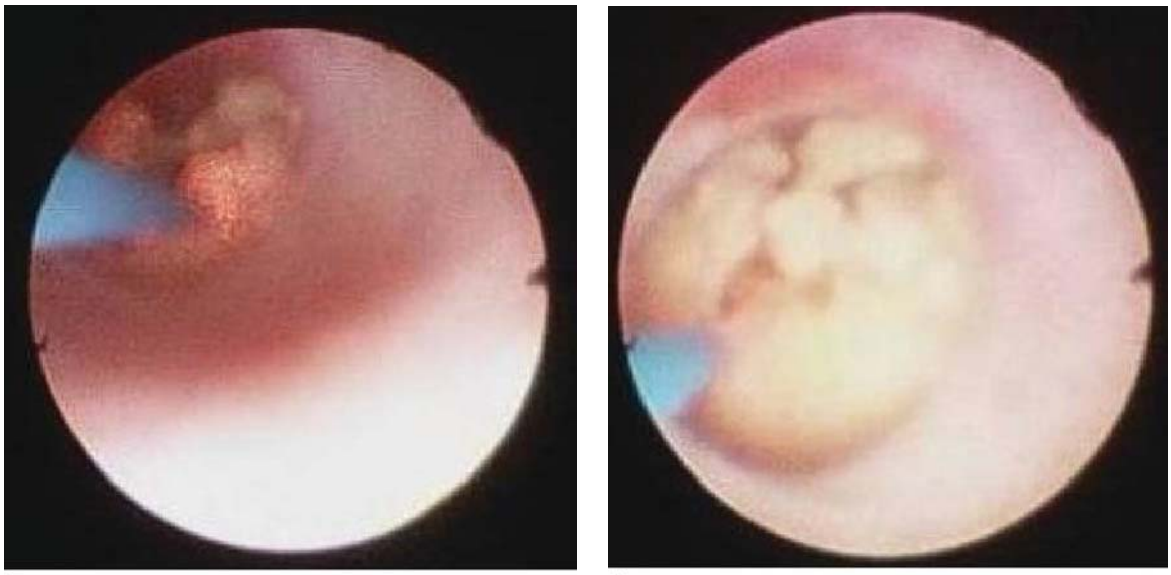


Figure 48.11 Laser fulguration of large hilar submandibular stone with holmium laser **(A)**. Submandibular stone being broken into smaller fragments amenable to removal **(B)**.

diseases of the salivary glands with the possibility of gland preservation.

One of the major impacts sialendoscopy has made on the therapy of SRDS is in the management of salivary stones. Marchal (38) has provided an algorithm for the management of salivary stones. Stones less than 4 mm for the submandibular gland and 3 mm for the parotid gland can often be managed with complete endoscopic removal. For larger stones up to 5 or 6 mm, laser lithotripsy and endoscopic stone removal can be performed (Fig. 48.11). For larger stones, hybrid techniques that involve a transoral incision or an external approach with the use of sialendoscopy to guide dissection site permit stone removal with gland preservation (54,55). Walvekar et al. (56) recently described a novel approach utilizing the da Vinci robotic system for management of large hilar-glandular submandibular stones using a combined approach technique. Ultrasonography can also be a useful adjunct to sialendoscopy to permit preoperative and intraoperative stone identification and removal (57).

Cystic Lesions

Most true cysts of salivary tissue occur in the parotid gland, where they account for 2% to 5% of all parotid lesions. Cysts may be acquired or congenital. A type of congenital cyst is the dermoid cyst, which consists of keratinizing squamous epithelium with associated skin appendages, and is treated by complete removal with preservation of the facial nerve. A congenital ductal cyst, generally manifested in infancy, requires sialography for diagnosis but no therapy unless repeated infections occur (58). First branchial cleft cysts account for less than 1% of all branchial cleft anomalies. They often present within the parotid gland and are classified as type 1 and 2 cysts. Type 1 cysts are duplications of the external auditory canal and are derived from ectoderm. Type 2 is an ectodermal and mesodermal lesion arising from the first and second arches (surrounding the first branchial cleft) (59). Regardless of the type and location of the cyst, the tract of the cyst is intimately associated with the facial nerve. Furthermore, frequent prior infections may obscure the true nature of the lesion, with many patients having repeated incision and drainage before the correct diagnosis is made. Excision during a quiescent period with preservation of the facial nerve is curative. Facial nerve anatomy may be anomalous in these cases; consequently, intraoperative facial nerve monitoring is useful.

Acquired cysts may be associated with neoplasms, benign LE lesions, trauma, parotitis, calculi, duct obstruction, mucus extravasation, and HIV infection (60). The neoplasms most frequently associated with cysts are pleomorphic adenoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, and Warthin tumor. Nonneoplastic cysts that are asymptomatic do not need to be treated, while those that become repeatedly infected should be excised.

Mucoceles (mucous extravasation phenomenon) and mucous retention cysts almost invariably involve the minor salivary glands, most commonly on the lips, buccal mucosa, and ventral portion of the tongue. Mucous cysts are true cysts with epithelia lining and result from duct obstruction. Mucoceles, however, do not possess an epithelial lining and are not true cysts but represent mucus extravasation into the surrounding soft tissues. If required, treatment of both is by marsupialization or excision.

The ranula is an extravasation mucocele that arises from the sublingual gland, either from a ruptured main salivary duct or from ruptured acini following obstruction (61). It presents as a cystic swelling in the floor mouth superficial to the mylohyoid muscle. A more advanced presentation of ranula is the plunging ranula that is an extension of the oral ranula into the neck along the deep lobe of the submandibular gland between the mylohyoid and hyoglossus muscles or through congenital dehiscence in the mylohyoid muscle (62,63). The therapeutic options for oral and plunging ranulas are aimed at either surgical excision of the lesion or attempts at inducing fibrosis and scarring that would eliminate the formation of the ranula (61,62,64). These interventions can range from simple incision, marsupialization with or without packing, excision of the ranula with or without the sublingual gland, laser vaporization, and the use of sclerosing agent OK-432 (61,63). Excision of the ranula with the associated sublingual gland is associated with the best outcomes with lowest recurrence rates (61,62,64,65). Usually, this can be accomplished via a transoral route. Transoral resection can be achieved with routine surgical techniques. A transoral robot-assisted approach has been described for the management of simultaneous bilateral floor of mouth ranula (66).

RADIATION INJURY

It has been estimated that radiation therapy for head and neck cancer causes radiation-induced xerostomia in 30,000 to 50,000 individuals in the United States annually (67). Xerostomia occurs when the salivary glands are exposed to radiation doses above 20 to 30 Gy (68). When radiated, heavy metal ions present in the granules of serous cells catalyze lipid peroxidation in the glandular tissue (69). This results in enzymatic spillage and cell lysis. The parotid glands are more susceptible to injury (70). Sullivan et al. evaluated the histology of radiated human submandibular glands and found that both serous and mucinous acinar cells are equally destroyed by high doses of radiation, whereas previous animal models have suggested that serous acini are more susceptible to radiation injury (69,71,72). Zymogen granules have been implicated as a mechanism for the higher susceptibility of acinar cells to radiation, compared to mucinous acini (71,72). Acute inflammatory reaction causes a purulent exudate within the ducts and the parenchyma. The acute inflammatory reaction subsides without treatment provided that irradiation is stopped. Continued irradiation leads to complete destruction of the serous acini and subsequent atrophy in the gland. Radiation-induced thyroid neoplasms are well documented, and there is similar evidence that salivary and parathyroid tumors are also induced. Both pleomorphic adenomas and malignant neoplasms are increased in incidence (73,74).

Radioactive Iodine-Induced Sialadenitis

Sialadenitis is the most common complication of I-131 treatment for well-differentiated thyroid malignancy, with a reported incidence of 10% to 60% (52,75). The sodium–potassium–chloride transporter in salivary tissue concentrates I-131 to levels that are 30 to 40 times higher than plasma levels, which is sufficient to cause glandular damage (76). In patients with radioactive iodine (RAI)-induced sialadenitis, the parotid glands are affected more frequently than the submandibular glands with an approximate ratio of 9:1 (52,77). Caglar et al. (77) used Tc-99m pertechnetate salivary gland scintigraphy to assess salivary function in patients with RAI-induced sialadenitis and control patients, and found that the development of RAI-induced sialadenitis is dose dependent. Preventative measures have been shown to be effective at reducing the likelihood of developing RAI-induced sialadenitis. For patients with persistent symptoms, sialendoscopy and irrigation (with or without steroid instillation) has found to provide symptom relief in majority of patients. Typical findings at the time of endoscopy include ductal stenosis, presence of cellular debris and mucous plugs as well as the absence of vascular marking on the mucosa of the salivary duct with a generalized blanching suggestive of chronic inflammation (52,53).

Trauma

Penetrating injuries to the parotid glands may involve the duct or facial nerve. Any penetrating injury posterior to the anterior border of the masseter muscle should be suspected of causing a ductal injury. Inspection of the wound directly often allows adequate assessment of the duct. If the duct cannot be identified, a probe may be passed transorally and located in the wound. This should confirm the status of the duct. If the duct has been transected, optimal treatment is end-to-end anastomosis over a polyurethane catheter or salivary duct stent with 6-0 or finer sutures (Fig. 48.12). The catheter is then sutured in place to the buccal mucosa, to be removed in 2 weeks. If the proximal end of the duct cannot be readily identified, compression of the gland often produces enough saliva from the cut end to allow its identification. Alternately, if the primary duct is long enough, it may be sutured directly into the oral cavity through a puncture wound. If this is not possible, the duct may be ligated or a new duct may be created from buccal mucosa. In all these situations, except ligation, repeated dilation with lacrimal probes may be necessary to achieve a satisfactory final result. The Marchal dilator system used for sialendoscopy can be used as well for duct probing. Interventional sialendoscopy to check integrity of ductal repair via endoluminal irrigation of saline can be helpful.

Laceration of the parenchyma can usually be managed conservatively. Closing the parenchyma and the capsule with a few interrupted sutures generally suffices. If a salivary cutaneous fistula develops, healing can generally be ensured by repeated aspiration and a pressure dressing. Resolution may take 1 to 2 weeks to allow for the traumatized ductal system to reopen. Persistence of a fistula strongly suggests duct obstruction rather than parenchymal injury alone (78). In this setting, sialography or MR

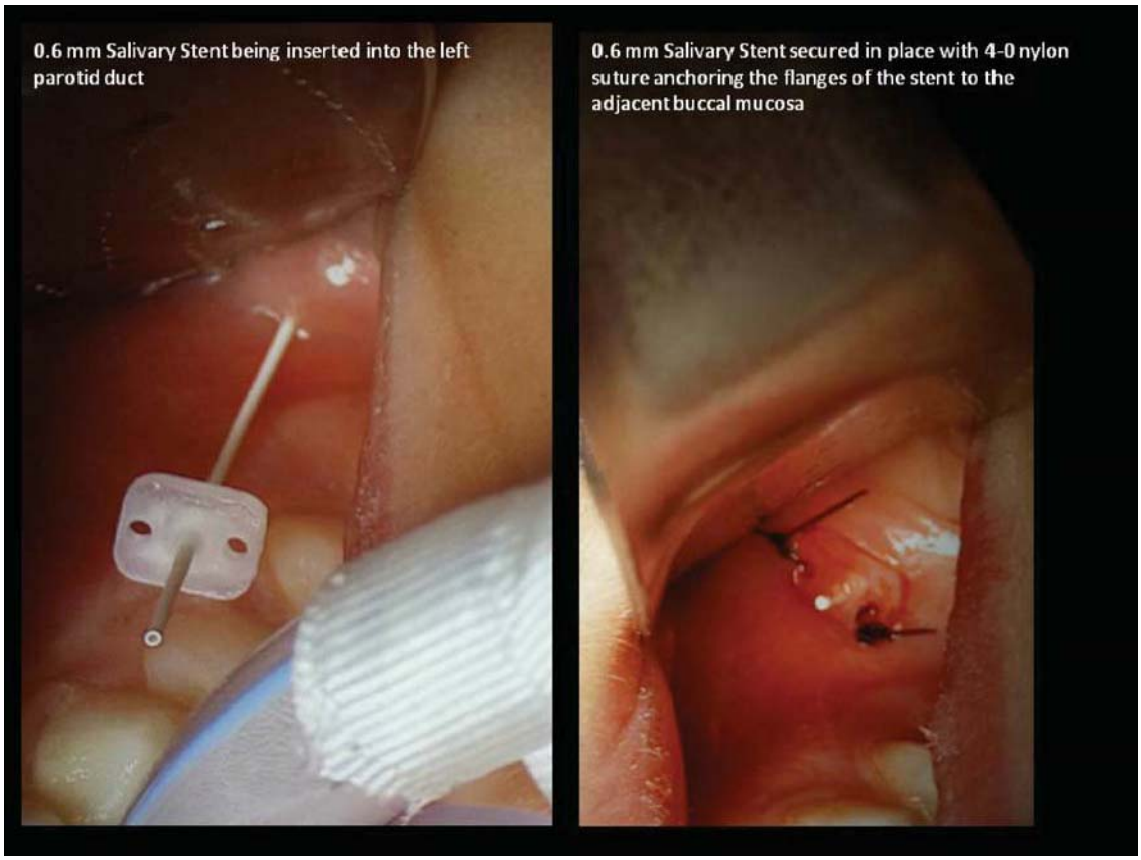


Figure 48.12 Salivary stent 0.6 mm (Hood Laboratories, Pembroke, MA).

sialography should be performed. If duct obstruction is found, repair should be performed, if possible. If conservative treatment fails, excision of the gland is curative as is administration of radiation of sufficient dose to destroy the gland. The latter is probably ill-advised except in extraordinary circumstances. Injection of botulinum toxin has been shown to be effective in case of refractory salivary fistula (79–81).

Injury to the facial nerve may also occur from penetration wound. A thorough evaluation of facial nerve function should be performed on any patient suffering a penetrating injury to the face. If the patient cannot perform volitional testing, a nerve stimulator may be used. If the wound is anterior to a vertical line from the lateral canthus to the mental foramen, repair is probably unnecessary (even with clear dysfunction) because recovery is likely.

Injuries posterior to this line should be repaired immediately. Whereas delayed repair has some possible theoretic advantages, these advantages are overshadowed by the importance of being able to find both ends of the nerve and the ability to do so through the open wound itself. Additionally, some believe that delayed repair does not really have advantages. Repair must be meticulous and with magnification.

Blunt trauma may also injure the gland with resultant concussion, edema, or hemorrhage. These usually resolve without treatment, although temporary duct obstruction may occur. A large hematoma should be drained before it becomes organized because subsequent fibrosis and scarring may lead to duct obstruction and to a cosmetic deformity.

The submandibular and sublingual glands are managed in a similar manner to that of the parotid gland, but ductal injuries here are much less common because of the protection afforded by the mandible.

Sialadenosis

Sialadenosis is a nonspecific term used to describe a noninflammatory nonneoplastic enlargement of a salivary gland, usually the parotid. In most cases, the mechanism is unknown, but there are many associations. The salivary gland enlargement is generally asymptomatic. Bilateral parotid gland swelling is common in obesity secondary to fatty hypertrophy. However, a complete endocrinologic and metabolic workup should be performed before this diagnosis can be made. This is important because obesity is frequently associated with other disorders such as diabetes mellitus, hypertension, hyperlipidemia, and menopause.

Malnutrition is also commonly associated with sialadenosis. This can occur in the form of pellagra, cirrhosis, diabetes mellitus, beriberi, anorexia nervosa, and bulimia. Sialadenosis has been reported in kwashiorkor and

hypovitaminosis A. In these conditions, the enlargement is secondary to hypertrophy.

Parotid swelling is intimately associated with alcoholic cirrhosis. It is so rare in nonalcoholic cirrhosis that it can be used as a differential diagnostic feature, occurring in 30% to 80% of cases of alcoholic cirrhosis. Evidence suggests that this enlargement is based on protein deficiency, and histologic changes are similar to those in general malnutrition.

Any disease that interferes with the absorption of nutrients may also lead to parotid gland hypertrophy. Reported diseases include celiac disease, bacillary dysentery, carcinoma of the esophagus, Chagas disease, and ancylostomiasis. Sialadenosis may also occur in uremia, hypothyroidism, myxedema, testicular or ovarian atrophy, pregnancy, lactation, and chronic relapsing pancreatitis.

The prognosis is generally good if the underlying disease can be corrected. In this setting, the parotid glands generally return to normal.

OTHER DISORDERS

Pneumoparotitis may occur with any episode of increased intrabuccal pressure. It has been reported in glass blowers and after intubation and endoscopy. Cheilitis glandularis is an uncommon disease manifested by enlargement of the labial salivary glands, which then secrete a clear, thick, sticky mucus (82). The glandular hypertrophy may occur to such a degree that eversion of the lower lip occurs, in which case vermilionectomy is usually curative. In Kussmaul disease (sialodochitis fibrinosa), a mucous plug causes obstruction in a collecting duct. This commonly occurs in a dehydrated patient and is manifested by recurrent swelling with associated pain. The appearance of a mucous plug at the duct orifice is diagnostic. Treatment consists of gentle massage and sialogogues to extrude the plug in addition to rehydration when appropriate. A number of drugs may cause salivary gland enlargement as a side effect. These include isoproterenol, ethambutol, phenbutazone, phenothiazine, iodine compounds, and heavy metals.

Necrotizing sialometaplasia is a disease of cryptogenic origin, although some cases appear to occur as a reaction to injury. It is generally manifested as a mucosal ulceration most commonly found in the hard palate, but it may occur in any salivary tissue. There is a male preponderance. Necrotizing sialometaplasia may be mistaken histologically for squamous cell or mucoepidermoid carcinoma, hence the importance of verifying the correct diagnosis. Mucosal ulceration with pseudoepitheliomatous hyperplasia, ischemic lobular necrosis, and dissolution of acinar walls with a release of mucous occur. This causes a subsequent inflammatory granulation tissue response combined with squamous metaplasia of the acini and ducts. The lesion is self-healing and requires no treatment. Clinical correlation with history of duration of illness, risk factors of head and neck cancer and clinical presentation as well as progression are key to identifying these conditions that mimic head and neck cancer but clearly have a more favorable prognosis. If the clinical presentation does not correlate with the history extreme care must be taken to assure the correct diagnosis prior to undertaking a major resection. If the diagnosis is in doubt, a repeat biopsy should be performed (83).

A disease that may be a variant has recently been described. It has been termed "subacute necrotizing sialadenitis." The lesion presents as a painful, nonulcerated, erythematous swelling of the posterior hard palate. Histologically, most of the acinar cells are lost, and there is atrophy or necrosis of the ductal cells. The lesion is self-healing in 2 to 4 weeks.

Aberrant salivary gland tissue may occur in a variety of locations. It is particularly common within lymph nodes in the parotid area. It has also been reported to occur in the mandible, lower neck, hypopharynx, middle ear, sternoclavicular joint, thyroglossal duct, and pituitary gland. In the mandible, the tissue may be on the surface or in a central location. If on the surface, the lesion appears to be merely ectopic submandibular tissue and is always benign. Central lesions are uncommon and even less common in the maxilla. When these tissues become neoplastic, the type of tumor may be a mucoepidermoid carcinoma, adenoid cystic carcinoma, or adenocarcinoma, in that order (84).

Finally, parotid gland enlargement may occur in patients with HIV infection. It usually occurs as a symmetric diffuse enlargement of both parotid glands. This clinical presentation in a young person should raise suspicion of HIV infection. Table 48.2 summarizes diagnosis and management of SGDs.

COMPLICATIONS

Complications of nonneoplastic SGD usually stem from the underlying condition or etiology that causes salivary gland involvement. For example, viral diseases affecting the salivary glands rarely lead to a complication related to the salivary glands, but may cause serious injury, either temporary or permanent, to other organ systems. Certain conditions, however, have the capability of causing direct consequences. For example, patients with acute sialadenitis may progress to abscess formation that in some cases may lead to life-threatening upper airway edema due to spread of infection into deep neck spaces.

The long-term consequences of chronic SGDs include xerostomia and the development of benign LE lesions. Xerostomia can lead to severe dental caries, dysphagia, odynophagia, hoarseness, and reduced quality of life. Benign LE lesions are associated with the development of lymphoma, pseudolymphoma, and anaplastic carcinoma. Sarcoidosis may be associated with facial paralysis and with severe systemic illness (Heerfordt syndrome). Sialolithiasis can be asymptomatic but can cause recurrent salivary gland swelling and obstruction of salivary flow leading to acute

TABLE 48.2 DIAGNOSIS AND MANAGEMENT—DISEASES OF THE SALIVARY GLANDS

Disease	Features	Management
Viral	Acute onset; associated symptoms	Symptomatic
Acute suppurative sialadenitis	Acute onset; postoperative or debilitated patient; purulent saliva from duct; diffusely swollen and painful gland	Hydration: massage: antistaphylococcal antibiotic
Chronic sialadenitis	Painful recurrent swelling; decreased saliva production	Sialogogues; massage; antibiotics for acute exacerbations
Tuberculosis	Painless swelling, often with drainage	Long-term antibiotics
Sarcoidosis	Usually asymptomatic swelling	Symptomatic
SS	Painless swelling of multiple salivary glands; may be associated with another autoimmune disease	Symptomatic
Sialolithiasis	Painful swelling, usually associated with eating	Removal of calculus
First branchial cleft cyst	Repeated acute suppurative swelling	Excision, usually with parotidectomy
Penetrating injury	Obvious defect with appropriate history	Careful evaluation; repair
Sialadenosis	Asymptomatic swelling	Workup to find underlying cause

suppurative sialadenitis. As described above, this in turn may lead to the development of more severe neck infection and to septicemia. The same may occur with first branchial cleft cysts. Penetrating injuries may lead to the development of salivary cutaneous fistula or to partial or total facial paralysis.

Finally, since many patients with nonneoplastic salivary gland disorders are now being managed in a minimally invasive fashion with sialendoscopy and hybrid approaches, it is important to be aware of some of the complications associated with these procedures. Extravasation of fluid into the floor of mouth and cheek can lead to swelling and edema. In some cases, this can cause airway compromise. Salivary duct tears are also reported. In case of minor tears, conservative management with antibiotics and anti-inflammatory medication is satisfactory. In the event of a major duct avulsion, salvage gland resection is often required. Residual stones, scarred papilla of the gland, ductal stenosis, and ranula formation are procedure-related complications that can also present as acute suppurative sialadenitis and must be borne in mind. Major bleeding, infection, and facial nerve damage are uncommon (34,54).

HIGHLIGHTS

- The majority of nonneoplastic disorders of the salivary gland can be categorized based on clinical history and physical examination.
- Classification of the SGD process helps direct treatment and prognostication.
- Diagnosis of autoimmune and granulomatous conditions often requires special laboratory tests and salivary gland biopsy to detect underlying disease process.
- Ultrasonography is an excellent imaging tool that is under utilized and can provide cost-effective dynamic feedback to the surgeon.
- The possibility of underlying neoplastic disorders must be considered while treating nonneoplastic disease processes.
- Patients with salivary gland cysts should undergo a complete work up to determine the cause and direct therapy.
- Salivary gland surgery, especially parotidectomy, must be recommended with caution in patients with inflammatory diseases given the high probability of postoperative facial nerve paresis.
- The diagnosis of sialadenosis requires further investigation to identify an underlying cause.
- Necrotizing sialometaplasia mimics carcinoma; clinical presentation must be correlated with history. Biopsy must be obtained prior to planning major surgical resection.
- Newer minimally invasive surgical, medical, and diagnostic options such as botulinum toxin injection, ultrasonography, and sialendoscopy should be considered to complement traditional treatment algorithms.

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49 Outcomes, Effectiveness, and Quality of Life: Measuring Clinical Effectiveness

Maureen Hannley

HEALTH STATUS ASSESSMENT

Within the last 25 years, the measurement of health-related quality of life (HRQOL), medical- and patient outcomes, and clinical effectiveness has moved beyond its origins in health care research to find wider application across specialties and practice settings. Our society has grown and changed, and with it the need to allocate health service resources rationally across diverse health programs has steadily grown as well, prompting the evolution of new health policy decisions in both the public and private sectors. To assist in formulating those new decisions, caregivers, health care institutions, and even drug and device manufacturers have been called upon to develop and apply measures of the broad effects of illness states on patients' lives, the effectiveness of intervention options, and their outcomes. Granted, some general instruments have been in use in the United States for 30 years or more, and millions of such questionnaires have been distributed. However, changes in delivery systems, advances in technology, new issues in health care payment systems, and a shift in patient management to include more chronic care and care of the aged have increased the importance of patient participation in assessment of their health care using contemporary health status assessment instruments.

In the past, simple biomedical indicators of change in health status, such as morbidity and avoidable mortality, survival rates, adverse reactions, complications, symptom relief, pain, and physical and biochemical markers of recovery, were the standard metrics of treatment outcome. Although it took an act of Congress and subsequent changes in research funding by the National Institutes of Health (NIH) (Patient Outcomes Research Act of 1989, S. 702), changes in health policy and allocation of health care resources have gradually moved to define health outcomes of intervention in the broadest sense, specifically those focused on the impact of the condition and its treatment on the patient's emotional and physical functioning and lifestyle. At the center of this trend is the theme that a definition of health can no longer be limited to the absence of disease as measured by the traditional quantifiable criteria, but must also define the impact of disease and disease intervention on overall quality of life (QOL) and satisfaction with care (1,2).

THE "QUALITY OF LIFE"

"Quality of life is a vague and ethereal entity, something that many people talk about, but which nobody knows very clearly what to do about" (3).

A paradox of measuring "quality of life"—a widely-recognized concept in the social and health sciences—is that it has no standard, uniformly accepted definition. While there is general agreement among experts that QOL is subjective and highly individual, its criteria and indicators reflect a similarly wide range of perspectives. These range from the lyrical—"the perceived discrepancy between what is and what might have been"—to the pragmatic—"evaluation of (personal) well-being with physical symptoms, sexual function, work performance, emotional status, etc." (4). A multitude of operational definitions exist that reflect philosophical, psychological, sociologic, economic, or biologic perspectives, but the inescapable conclusion is that the perception and achievement of QOL is personal, unique, and dependent on one's own preferences, circumstances, values, and priorities in life. This has important implications that are explored in a later section.

HRQOL research was first conducted in cancer treatment settings where the balance between quality and duration of life was a pivotal issue in decisions to use new drugs or combinations of drugs of either partial or unknown efficacy but with very serious side effects (5). Since then, QOL has become an important goal of treatment and marker of success in health interventions of all kinds. By definition, HRQOL is more focused than general QOL and thus

lends itself more readily to criteria for measurement, at least from a functional perspective, related to the ability to perform activities of daily living (ADL) and fulfill role functions adequately. Moreover, sophisticated health technology and treatments have expanded the life span, meaning that more people live—and live longer—with chronic health conditions. Thus, HRQOL includes perceptions of physical, emotional, and social well-being, before, during, and after treatment and the impact of those factors on the ability to lead a satisfying life.

However, it is a double-sided concept, incorporating positive as well as negative aspects of well-being and life, and is multidimensional, encompassing social, psychological, and physical health (1). Although not routinely explored, a thorough profile of HRQOL would also include some assessment of the patient's satisfaction with treatment (especially as it relates to the symptoms of greatest personal concern), and prospects for future well-being. In today's environment of crushing health care costs, issues related to concerns about economic stability might well be included. To be useful, HRQOL must be a personal construct and it must be dynamic for, as health changes for the better or the worse, perspectives on life, roles, relationships, and experiences change. But poor health or the presence of disease is not invariably associated with poor HRQOL; rather, it can be shaped by factors such as coping, expectancy, and adaptation (6) and studies have shown repeatedly that doctors' and patients' assessment of outcome do not always coincide. It is important to understand as well that although health is usually an important component of overall QOL, health status is neither a predictor nor a determinant of QOL: each can vary independently, even paradoxically.

In the most idealistic sense, the goal of medical or surgical treatment is to extend life and to optimize the patient's health-related quality of that life, however he or she might define it. This is not a new concept. What *is* relatively new is the interest in formalizing its definition and measurement, and in using it as the unifying theme for assessing the burden of disease, the efficacy or effectiveness of treatment for that disease, and the individual outcome of treatment on the patient.

If HRQOL includes perception of physical, emotional, and social well-being and the impact of those factors on the ability to lead a satisfying life, many of the diseases and disorders treated in otolaryngology—head and neck surgery have an undeniable impact. Who would debate the pleasure of being able to smell a beautiful flower or the bouquet of a fine wine? Allergic or nonallergic rhinosinusitis can deprive patients of this sensation and impose other uncomfortable symptoms such as nasal congestion, fatigue, and pain. Evidence of hearing loss appears on an audiogram but does not reveal how it affects the ability to enjoy music, participate in a conversation in a crowded restaurant, or listen to a child's whispered secrets. Loss of these elements of QOL can result in depression, anxiety, and withdrawal. The list continues: voice and the ability to speak, to sing, to tell the world who we are; sleep-disordered breathing; the gastroesophageal reflux disorders; the loss of facial symmetry and expression; and the cruel spectrum of head and neck cancers, some of the most visually obvious and functionally disabling cancers of all. The biomedical intervention outcomes for these conditions and others have been documented and reported; a few clinical trials have been completed, enough so that meta-analyses are becoming possible. But if ever there were multitudes of reasons to make measurement of HRQOL and patient-related outcomes a part of the clinical picture, otolaryngology—head and neck surgery has them!

WHY MEASURE HEALTH-RELATED QUALITY OF LIFE AND FUNCTIONAL STATUS?

Given that compassionate patient care of the highest quality is the goal of every health care provider, there is a need to understand the process from the perspective of the patient. While clinical outcomes are certainly important—indeed, would be considered the primary outcome in medical and surgical interventions—they are not always related to how the patient feels about the disease, its impact, the intervention, and *its* impact. Those are issues that may influence not only patient satisfaction, but the recovery process itself (7). The recent social imperative for individuals to take more responsibility for their personal health through prevention, healthy living, and self-education has made awareness of HRQOL a fact of life: most people are not familiar with the traditional biomedical markers of health and disease, but they do consider health an essential part of QOL. And quite simply, patients like to talk about themselves—they *like* to be asked that most basic of questions: "How do you feel?" Thus, including both clinical and patient-based outcome allows health care quality to be measured in a meaningful way for both clinicians and patients.

Apart from the humanistic issues related to increasing awareness of the patient's experience of health, disease, and treatment, there is a growing number of circumstances in which such measurements will play a key role: First, decisions about allocation of resources from third-party payers, managed care, and government agencies are increasingly requiring evidence of the effectiveness of health care interventions in the broadest sense—euphemistically termed "outcomes-adjusted reimbursement." That is, data will be expected on whether the treatment leads to a life worth living, by providing a more patient-oriented baseline against which the medical effects of the intervention can be evaluated (1,8). For example, two or more drugs may have comparable medical effectiveness against the same condition but produce very different HRQOL results; this could prove to be a significant factor for both the patient and the provider in the decision-making process.

Second, the US Food and Drug Administration (FDA) now encourages drug and pharmaceutical manufacturers to develop and use patient-reported outcome measures (PROMs) to support labeling claims, especially those

that are "best known or best evaluated from a patient perspective" as a part of the approval process for new drugs and devices (9). While evidence of this nature could be an asset to prescribing physicians when counseling patients in the United States, in Europe it is used to determine availability and pricing of medications. It is not unreasonable to anticipate that such a practice will become more widespread here as patient-reported HRQOL data become more influential in health policy and reimbursement decisions.

Another way in which HRQOL data can be used, and which has been somewhat sensationalized, is to assist in determining quality-adjusted life years (QALYs), an approach which has become one of the key considerations in allocation and reimbursement decision processes. A QALY is the arithmetic product of life expectancy and quality of the remaining years. A QALY places a weight on time in different health states: a year of perfect health is worth 1 and a year of less than perfect health is worth less than 1. Death is considered to be equivalent to 0. QALYs can be used to compare the extent of benefits gained in a broader sense from a variety of interventions when compared to their costs, side effects, and survival time (10). Only a small number of HRQOL measures are used for this application and it remains a subject of considerable controversy when used in the context of governmental control of health care benefit allocation.

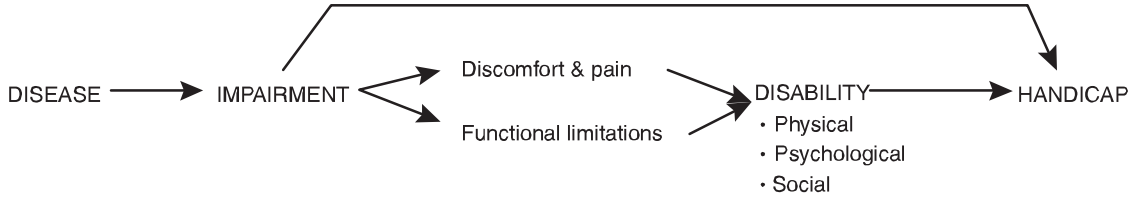
Fourth, health technology assessments (HTAs) are used in many European countries to determine the benefits or added value of new technologies for the purpose of reimbursement and pricing decisions and/or the establishment of clinical guidelines. In the United States, HTA is carried out through the Agency for Healthcare Research and Quality. The recent interest in comparative effectiveness research has prompted US expert advisors to call for the HTA process to include not only clinical and biomedical outcomes, but also "… important measures of effectiveness such as patient-reported outcomes, including health related quality of life, patient satisfaction, activities of daily living, and work productivity as relevant to the various USA stakeholders" (11). A large NIH project, the Patient Reported Outcomes Measurement Information Service (PROMIS) offers tools that can be used as primary or secondary endpoints for clinical studies of treatment effectiveness in a wide variety of chronic diseases and in the general population.

Finally, contract research organizations use patient-reported HRQOL instruments routinely as a part of their protocols when conducting large-scale clinical trials and field studies for drug and device manufacturers, in preparation for submitting new drug applications to the FDA.

FUNCTIONAL STATUS

The conceptual framework for measuring multidimensional functional health status is related to the World Health Organization (WHO) classification of impairment, disability, and handicap, and seeks to address the functional and psychosocial outcomes of diseases, disorders, and conditions (2). Although "impairment," "disability," and "handicap" are interrelated concepts, they are not interchangeable. Their relationship is shown in Figure 49.1. An *impairment* is a problem in body structure or function, which can manifest itself as a functional limitation, for example, difficulty in hearing and/or discomfort and pain. Impairment describes the biologic status: loss of a body part, dysfunction secondary to trauma, disease, malformation, etc. If severe enough, the impairment can also—but does not invariably—result in a *handicap*, which prevents the individual from carrying out life roles. Functional limitations or discomfort and pain produced by an impairment can lead to a *disability*—restriction in performing all or some of the ADL due to physical, psychological, and/or social issues, including such problems as fear, embarrassment, feelings of isolation, or loss of independence. This can be seen with disorders such as Ménière disease and head and neck cancer. While restriction in performing ADL can be measured objectively, the patient's QOL experience is subjective, affected by how he or she feels about those restrictions. Awareness of how the patient feels about his or her impairment can give useful insights into its life impact, leading to some therapeutic enablement strategies (12). Disabilities can also lead to handicap (although use of the word "handicap" has fallen into disfavor, imparting some negative psychosocial connotations) (10).

These broad definitions of biologic states and their associated physical, mental, and social consequences set the stage for the structure common to the tools we use to measure health status, including physical health, mental health, social health, role function, and overall well-being. Most can be characterized in terms of the range and focus of the information they collect. Although there are several



Allen PF. Assessment of oral health related quality of life. 2003. Health & QOL Outcomes 1:40

Figure 49.1 Relationship of impairment, disability, and handicap. (From Allen PF. Assessment of oral health related quality of life. *Health Qual Life Outcomes* 2003;1:40, with permission.)

ways in which to group the hundreds of available PROMs and HRQOL measures, for this discussion, we consider the instruments in the broadest sense: *generic*, *symptom-specific*, and *disease-specific*. While these three categories of health status and QOL instruments each have their own properties, advantages, and disadvantages (see Table 49.2), they have an additional important property in common. Because the goal is to learn the impact of disease and interventions on the patient's HRQOL and functional status, they are designated patient-reported outcome measures (PROMs). As officially defined by the US FDA, a PROM is "… an instrument of any aspect of a patient's health status that comes directly from the patient (i.e., without interpretation by a physician or anyone else)" (13). A PRO can describe health status, disability, handicap, a functional outcome, or a factor contributing to QOL in a standardized measure; these data provide a useful supplement to the medical assessment. In a very real sense then, the patient becomes the clinician's partner in achieving balanced insights into clinical effectiveness.

TYPES OF HEALTH-RELATED QUALITY OF LIFE MEASURES

Generic HRQOL instruments are designed to be applicable across a broad range of diseases, disorders, and conditions. Similarly, they can be used with different groups of patients and to assess the impact of a range of different interventions, making them valuable for comparative effectiveness studies. Both general QOL and HRQOL can be addressed with generic instruments. Some of the most widely used generic scales are the Medical Outcomes Survey SF-36 (MOS SF-36); the Glasgow Benefit Inventory (GBI); and the World Health Organization Quality of Life Assessment Inventory (WHOQOL-BREF). Just as a number of factors contribute to overall QOL, HRQOL instruments are designed to measure those perceptions by separate questions organized into *domains*, with the goal of parsing out individual influences on the overall quality score. Over the years, consensus has been established that HRQOL is a multidimensional concept, divided for measurement into three core domains: physical, social, and psychological. It is important, however, to distinguish between *functional* scales and HRQOL scales. In the physical domain, perception of normal or disrupted function such as mobility, pain, and sensory function are evaluated. In the social domain, questions are centered on items such as ADL, interactions with family and friends, and responsibilities in and out of the home. The psychological domain would involve emotional and mental functioning, including mood, distress, memory, self-image, special concerns, etc. While these three domains are fundamental, some instruments contain other domains, such as vitality, spirituality, sexuality/intimacy, financial concerns, and role function. Each domain is comprised of a series of questions that are scored separately and/or contribute to an aggregate score. An overall global HRQOL will yield an estimate of the patient's subjective evaluation of his or her own health; this may be different than simply the sum of the domain scores (14). A brief list of some of the more commonly used generic HRQOL instruments is presented in Table 49.1.

TABLE 49.1 GENERIC QUALITY OF LIFE INSTRUMENTS

Atkinson Life Satisfaction Scale
BDI Fast Screen (BDI-FS)
Child's Perception Questionnaire
Children's Depression Inventory
Dartmouth Primary Care Cooperative Information Project (COOP) Charts
Disease Repercussion Profile
EuroQol (EQ-5D)

Functional Assessment of Chronic Illness Therapy (FACT)
Functional Independence Measure
Functional Limitations Profile
General Health Questionnaire (GHQ-12)
General Health Rating Index (GHRI)
Generalized Anxiety Disorder
GBI
Glasgow Children's Benefit Inventory
Health Utilities Index (HUI)
Health Utility Index-3
Hospital Anxiety and Depression Scale
Illness Perception Measure (IPM)
London Handicap Scale (LHS)
Medical Outcome Study SF-36
Nottingham Health Profile (NHP)
Patient Generated Index
Patient Health Questionnaire
Pediatric QOL Inventory
Pediatric Quality of Life Questionnaire (PedsQL)

Performance Status Scale
Pictorial Representation of Illness and Self Measure-Revised 2 (PRISM-R2)
Postsurgical Patient Satisfaction Questionnaire
Psychological General Well-Being Index (PGWB)
QOL Index
Quality of Well-Being Scale (QWB)
Questionnaire on Life Satisfaction
Rosenberg Self Esteem Index
Sense of Coherence (SOC)
Sickness Impact Profile (SIP)
State–Trait Anxiety Inventory (STAI)
WHO Quality of Life Assessment Inventory (WHOQOL-BREF)
WHO Well-Being Index (WHO-5)

Although generic instruments have been in widespread use longer than any other type and thus have very stable psychometric properties and reliability, they often lack the sensitivity to evaluate subtle changes or mild disease, lack relevant subdomains, or fail to demonstrate health impact of certain conditions such as rhinosinusitis or mild to moderate hearing impairment. Disease-specific or possibly symptom-specific instruments might be a better choice to overcome these shortcomings.

Disease-specific scales are designed to assess specific diagnostic or patient populations; they are not generalizable to other patient populations in the same way that generic instruments are. Disease-specific scales have the goal of detecting the impairments associated with specific diseases or conditions, and/or to be responsive to clinically significant changes related to interventions or the natural history of the disease. They will frequently include scales both for evaluating functional impairment and for evaluating HRQOL. In contrast to the generic instruments, they have the advantage of containing statements and domains that are relevant only to the clinical condition in question. Because they are designed to assess HRQOL in investigative groups or patient populations, they are likely to be more reactive to treatment-related changes than are the generic instruments. Disease-specific instruments should always have a means of establishing the severity of the condition to allow accurate interpretation of the results, assessment of change, and case-mix adjustment when evaluating group data. Disease-specific scales may be structured with subdomains or they may have a single focus; selection of one instrument over another will be guided by the user's clinical or research goals.

As the term denotes, *symptom-specific instruments* are designed to focus exclusively on symptoms produced by a particular disease or condition (there is some debate as to whether these are actually HRQOL scales) and thus are extremely well suited to measure intervention-related changes. They have the additional advantage of being brief, reducing the patient burden considerably, and minimizing interference with clinical routine. The five-question Nasal Obstruction Symptom Evaluation (NOSE) Scale is a case in point (15).

If generic instruments lack the sensitivity of disease- and symptom-specific instruments to subtle life impact and treatment-related changes, the more specific instruments have the disadvantage of being so focused that they fail to evaluate problems in other life domains that may interact with the condition of interest, yielding a score that does not take into account the impact of the disease on the individual's global QOL—or whether other life factors exacerbate the impact of the disease. It is important to be sensitive to how seriously the condition under study affects specific functions or aspects of a patient's life. This is especially true of the emotional and social domains. For example, deafness or hearing loss may be associated with feelings of depression or isolation; vertigo with loss of control; voice disorders with embarrassment, reduced self-image, and diminished participation in group interactions. However, disease- and symptom-specific scales have a substantial advantage: with further questioning by the clinician they allow the patient to identify those items that are of greatest significance to him or her, or with the relative importance of relief that treatment could bring, perhaps improving satisfaction with care (16). Several validated scales have been developed to measure individual problems, severity, and expectations of relief, but inter-test consistency has been found suboptimal even in the same patients (17). The way in which questions are structured in each domain could influence the patient's decision of how to rank the items. A summary of the three types of HRQOL instruments' advantages and disadvantages appears in Table 49.2.

TABLE 49.2 COMPARISON OF GENERIC, SYMPTOM-SPECIFIC, AND DISEASE-SPECIFIC HEALTH MEASURES

	Example	Advantages	Disadvantages
Generic	SIP	Comparisons can be made between populations with different problems Psychometric properties are known Can capture a wide range of dysfunction in different areas not specific to disease Better for resource allocation, as it addresses "whole person"	Not sensitive to subtle changes in specific conditions Discriminant validity and responsiveness may be poor May be too long to be practical for patient and for scoring/analysis
Symptom-specific	NOSE	Focus on specific symptom(s) in order to measure change	Misses impact on whole organism that may have prognostic value for intervention
Disease-specific	Head and Neck Quality of Life (HNQOL) Scale	More likely to detect subtle changes Greater responsiveness to disease-specific interventions Contain domains and statements related uniquely to condition of interest	Cannot compare with general population May have lesser sensitivity to impact of comorbidity May not capture items or issues of greatest concern to patient

CHOOSING HEALTH STATUS ASSESSMENT INSTRUMENTS IN PRACTICE

Literally thousands of HRQOL instruments of every description have been published in all categories and are available to users. The Patient Reported Outcomes and Quality of Life database (PROQOLID: http://www.proqolid.org) includes 654 instruments, 500 of which are condition-specific. The database can be searched alphabetically, by condition, or by specialty (the otolaryngology listings are rather sparse). The Online Guide to Quality-of-Life Assessments (OLGA: http://olga-qol.com) is said to include thousands of PRO instruments in its database.

Most experts agree that choosing one generic and one disease- or symptom-specific questionnaire is the best strategy for achieving a well-rounded and precise picture of a patient's HRQOL and functional status. The most important factor to keep in mind is the goal of using a health status assessment instrument. Different instruments will be used for different goals, even if they are used with the same condition. For example, if the purpose of administering the HRQOL instrument is to compare the impact of a selected intervention in two or more patient populations that fall within the same general category (e.g., auditory disorders, voice disorders), a broader scale (e.g., Hearing Handicap Index, Voice Handicap Index) would be appropriate. If the aim is to determine whether a specific treatment improves symptoms, a short, symptom-specific index would be sufficient. For more serious, perhaps life-threatening illnesses, use of a measure of depression (e.g., the Beck Depression Inventory [BDI]) and/or anxiety (e.g., State/Trait Anxiety Index) may be appropriate.

Some general properties should be considered in the selection process. These would fall into three main categories: (a) Is (the instrument) relevant? (b) Is it practical? (c) Is it methodologically sound?

Relevance is the extent to which the content of the instrument is applicable to the condition or the patient under study. If it was validated on individuals under the age of 50 years, it may have limited value for a geriatric patient; an allergic rhinitis questionnaire may not be the best choice for evaluation of a patient with chronic rhinosinusitis (CRS). Obviously, if the problem is a relatively straightforward disease or symptom, an instrument with a broad array of life domains related to mobility, ADL, role fulfillment, etc., would be irrelevant to the clinical goal. Patient-reported instruments that have the greatest relevance to the patient/group being studied will yield the highest quality data. Examine the instrument carefully before administration to assure that it is the most relevant choice, with content and format appropriate for the goals of the clinical or research application. Care must be taken also when administering the instruments to populations with unique cultural values, such as immigrants from other parts of the world who have not yet become completely acculturated, and those whose lifestyle is shaped by ethnic, religious, or sexual orientation (18). Most of the major HRQOL instruments now have been translated into other languages and validated; Spanish versions of the instruments are useful additions to practices where significant numbers of the patient population are Hispanic.

Earlier in this chapter, reference was made to the fact that there is no generally accepted definition or criteria for "quality of life," a quite idiosyncratic construct—yet, hundreds of instruments have been developed to measure it. Many of these existing measures of QOL fail to take into account the individuality of one's own unique criteria by imposing standardized models of QOL and domains selected by the instrument developers. The question arises then: Do they simply describe QOL as health professionals and society believe it to be for people who are ill, something that may have little relevance to the patients who respond to the questions? (19). Undoubtedly, there are a number of universal factors that contribute to QOL, but they would probably be accorded different weights in different societies and cultures; and, QOL being the dynamic construct that it is, would change with time and social and health status. The most important and relevant contributors to an individual's QOL at a given moment in time, however, may not be captured by a standardized QOL questionnaire. Moreover, if the factors being measured with a standard questionnaire do not coincide with those that are important to the patient, it is unlikely that intervention will produce evidence of change since the instrument is not measuring what is important to the patient (19). Irrelevant questionnaire content can also succeed in alienating the patient, making him feel his issues are of no consequence and perhaps weakening adherence to treatment. There are several individualized QOL scales available, but they are far from ideal: they are not validated, cannot be used across patients to compare results, may be complex to interpret and analyze, and patients may not be completely forthcoming about their more personal feelings and priorities.

PROMs and HRQOL measures will not be added to a busy clinical practice if they are not practical. Of foremost consideration is the length of the instrument: it must be straightforward and not so long that it delays the patient's appointment, or creates an undue burden on the patient, especially the very ill patient, requiring no more than about 10 minutes to complete, if possible (14). In addition, unreasonably lengthy questionnaires may be only partially completed and their usefulness thus undermined. They should be easy to understand, and be self-administered, requiring few instructions or clarification from support staff. The instrument should be easy to score and to interpret with norms provided, ideally so that it can be completed by a nurse or other personnel with minimal training. All of these factors should minimize the cost of adding this procedure to the practice: the form can be mailed to the patient in advance of the appointment (risky, since many

will forget to bring it to their appointment), completed in the waiting room, or in the examining room.

A PRO instrument is of value only if it is well-designed and methodologically sound. A well-designed PROM is capable of assessing patients across a broad spectrum of disease severity; conversely, a poorly designed instrument may misrepresent the impact of the disease and treatment or fail to identify significant intervention outcomes, especially those associated with very mild or very severe disease. Whatever the instrument or battery of instruments selected, PROM of HRQOL and health status should have four essential properties: reliability, validity, sensitivity, and responsiveness. Of these, validity and reliability are the fundamental properties and the most crucial.

Reliability is an important attribute for a test measure. It is a measure of the reproducibility of the results—or that it will give the same results in different situations (e.g., different situations, different days). Reproducibility, of course, is the cornerstone of the scientific method. Reliability provides significant information for either research or clinical purposes in that it indicates how much of the variability in the measures that might be caused by different situations is caused by variability among patients (20). So the reliability is the efficiency with which a test can differentiate among patients on some given features. Some other valuable aspects of reliability are its *test–retest reliability*: the correlation between performance on two separate occasions; and *interobserver reliability*: the degree of agreement in test results when administered by two different observers (20). The latter attribute would, of course, not be of concern for PROMs.

Validity is the extent to which an instrument measures what it claims to measure. This is also known as *face validity*. Related to face validity is the *content validity*: does the scale tap all contents, behaviors, and elements of the feature to be measured? Another aspect of validity is *criterion validity*, or the extent to which the measure correlates with a "gold standard." This is somewhat problematic because there is no gold standard for HRQOL as such; but if the measure is compared to another generally accepted measure of the same construct, a correlation coefficient between the two scores will enable assessment of the criterion validity. A frequently used, but rarely defined measure is the *construct validity* of the attribute under study, used when there is no other measure of the same attribute for comparison. It refers to the extent to which the instrument succeeds in operationalizing the theoretical relationship between the attribute of interest and other related attributes (20).

The *responsiveness* of an instrument is an important attribute for it is this property that indicates the extent to which changes in values correlate with true changes in status. This is highly significant when obtaining intervention-related change scores. The responsiveness of a HRQOL scale is largely dependent on patients' initial health status. For example, a patient's health may be so poor that further deterioration will go undetected since he or she already reported the lowest score ("floor effect"). The importance of magnitude of change depends on baseline status and must be compared to an independent criterion for interpretation (21). Closely related to responsiveness is *sensitivity*, the amount of change an instrument is able to detect.

APPLICATIONS IN OTOLARYNGOLOGY—HEAD AND NECK SURGERY

Given the number of subspecialty practice areas within otolaryngology—head and neck surgery, it should not be surprising that there is a similarly broad range of disease-specific QOL and functional outcome measures related to these areas. A list of a variety of useful instruments (which is by no means comprehensive) is presented in Table 49.3. Many have been developed and validated by otolaryngologists; others by audiologists, speech—language pathologists, physical therapists, nurses, sociologists, health science researchers, and other physicians such as plastic surgeons, allergists, pulmonologists, pediatricians, neurologists, gastroenterologists, and oncologists. These tools represent the full range of health status measurement formats: while most are PROs, they may measure functional status, HRQOL, self-perceived well-being, symptom status, overall QOL, satisfaction with care, or a combination of two or more of these. They may be multidimensional, with questions in several domains or a very brief disease-specific functional index. Several indices of general comorbidity have been included in the list, reflecting the role of comorbidity in head and neck cancer, rhinosinusitis, gastroesophageal reflux disease (GERD), and sleep-disordered breathing. A significant number have been translated into other languages, and validation processes have been repeated to assure the instruments' cross-cultural and cross-linguistic validity. The international availability of HRQOL and functional outcome measures should have the benefit of encouraging international collaborative clinical research efforts, constructing databases, and facilitating meta-analyses.

The use of health status and HRQOL instruments has supported the clinical value of a variety of procedures and addressed controversies with data. Clearly, the index disease for which both functional status and HRQOL measures are appropriate is head and neck cancer, with its impact on speech, swallowing, breathing, taste, and often appearance. Not surprisingly, reports on HRQOL describe high rates of depression and anxiety in these patients, varying somewhat with the cancer site and stage, treatment modality, and patient variables such as age, gender, support system, and comorbidity. These associations are uniform across domestic and international papers and instruments used—the most common being the EORTC—HN35, the University of Washington quality of life instrument (UW-QOL-R), and the Functional Assessment of Cancer Therapy (FACT-HN). Testing specifically for depression can guide the clinician to consideration of a referral for psychosocial counseling or, as one paper suggests, distinguish medical and treatment

TABLE 49.3 DISEASE-SPECIFIC HRQOL AND FUNCTIONAL OUTCOMES INSTRUMENTS

ALLERGY

Allergic Rhinitis
Allergy outcome survey (AOS)
Caregiver treatment satisfaction questionnaire for allergic rhinitis (CGTSQ-AR)
Nocturnal rhinoconjunctivitis quality of life questionnaire (NRQLQ)
Patient benefit index for allergic rhinitis (PBI-AR)
Pediatric allergic disease quality of life questionnaire (PADQLQ)
Pediatric rhinoconjunctivitis quality-of-Life questionnaire (PRQLQ)
Rhinitis symptom utility index (RSUI)
Rhinoconjunctivitis quality of life questionnaire (RQLQ)

RHINOLOGY

Nasal Obstruction
Nasal health survey (NHS)
NOSE scale
Nasolacrimal duct obstruction symptom score (NLDO-SS)

Rhinosinusitis
Chronic sinusitis survey (CSS)
Rhinitis symptom utility index (RSI)
Rhinosinusitis disability index (RDI)
Rhinosinusitis QOL survey (Rhino-QOL)
Sinonasal assessment questionnaire (SNAQ-II)
Sinonasal outcomes test (SNOT-16; SNOT-20, SNOT-22)

Olfaction
U. Penn. smell identification test (UPSIT)

OTOLOGY/NEUROTOLOGY

Otitis Media
Chronic ear survey (CES)
Chronic otitis media (COM-5)
Otitis media clinical severity index (OM-CSI)
Otitis media diary (OMD)
Otitis media functional status questionnaire (OM-FSQ)
Otitis media outcomes (OMO-22)
Otitis media survey (OM7-27)
Otitis media-6 (OM-6)
Parents' questionnaire on consequences of OM on family life (PARENT-QOL)

Ménière Disease
Ménière disease outcomes questionnaire (MDOQ)
Ménière disease patient-oriented symptom-severity scale (MD-POSI)

Hearing Impairment
Effectiveness of auditory rehabilitation (EAR)
Hearing disability handicap scale (HDHS)
Hearing evaluation and auditory evaluation (HEAR-14)
Hearing handicap inventory for adults (HHI-A)
Hearing handicap inventory for the elderly (HHI-E)
Hearing satisfaction scale (HSS)
Single sided deafness questionnaire
Youth quality of life instrument-Deaf and hard of hearing module (YQOL-DHH)

Tinnitus
Tinnitus annoyance index (TAI)
Tinnitus handicap inventory (THI)
Tinnitus questionnaire
Tinnitus reaction questionnaire
Tinnitus severity questionnaire (TSQ)

Vertigo/Dizziness
Activity balance confidence questionnaire (ABCQ)
Dizziness handicap inventory (DHI)
Dizziness patient-oriented severity index (D-POSI)
European evaluation of vertigo questionnaire
UCLA dizziness questionnaire (UCLA-DQ)
Vertigo handicap questionnaire (VHI)
Vertigo symptom scale (VSS)
Vertigo, dizziness, imbalance questionnaire (VDI)
Vestibular activities of daily living (VADL)

Vestibular Schwannoma
Penn acoustic neuroma quality of life scale (PANQOL)

Facial Paralysis
Facial clinimetric evaluation scale (FaCE)
Facial disability index (FDI)

Cochlear Implants
Nijmegan cochlear implant questionnaire
Speech intelligibility ratings
Speech perception categories

Hearing Aids
Abbreviated profile of hearing aid benefit
Glasgow hearing aid benefit profile (GHABP)

LARYNGOLOGY

Voice Disorders
Consensus auditory-perceptual evaluation of voice (CAPE-V)
Pediatric voice handicap index (pVHI)
Pediatric voice-related quality of life (PVRQOL)
Singing voice handicap index (SVHI)
Voice function outcome measure (VFOM)
Voice handicap index 10 (VHI-10)
Voice outcome survey (VOS)
Voice-related quality of life (VRQOL)
Voice symptom scale (VSS)

HEAD AND NECK

GERD/EERD
Gastroesophageal reflux disease health-related quality of life (GERD HR-QL) scale
Gastroesophageal reflux disease quality of life (GERD-QOL) scale
Gastrointestinal symptom rating scale
GERD symptom frequency questionnaire (GSFQ)
Pediatric gastroesophageal reflux disease symptom and quality of life questionnaire (PGSQ)
Pharyngeal reflux symptom questionnaire
Quality of life in reflux and dyspepsia (QOL-RAD)
Quality of life questionnaire in gastroesophageal reflux (Reflux-qual)
Reflux disease questionnaire (RDQ)
Reflux questionnaire (ReQuest)
Reflux symptom index (RSI)
Supraesophageal reflux questionnaire

Adenotonsillitis
Pediatric throat disorders outcome test (PTDOT)
Tonsil and adenoid health status instrument (TAHSI)

Sleep-disordered Breathing
Empirical sleepiness scale
Epworth sleepiness scale (ESS)
Functional outcomes of sleep questionnaire (FOSQ)
Obstructive sleep apnea-18 (OSA-18)
Obstructive sleep apnea patient-oriented symptom severity scale (OSA-POSI)
Obstructive sleep disorders-6 (OSD-6)
Pittsburgh sleep quality index (PSQI)
Sleep apnea quality of life index (SAQLI)
Sleep disorders questionnaire (SDQ)
Snore outcomes survey
Symptoms of nocturnal obstruction and related events (SNORE)

Head and Neck Cancer
Distress inventory for cancer (DIC)
Dysphagia handicap index
EORTC QOL (HN-35)
Functional assessment of cancer therapy (FACT-HN)
Halitosis associated quality of life (HAQOL)
Head and neck oncology outcome assessment
Head and neck quality of life (HNQOL) scale

TABLE 49.3 DISEASE-SPECIFIC HRQOL AND FUNCTIONAL OUTCOMES INSTRUMENTS *(Continued)*

Mayo Clinic postlaryngectomy questionnaire (MCPQ)
MD Anderson dysphagia inventory (MDADI)
Neck dissection impairment index (NDII)
Parotidectomy outcome inventory (POI-8)
Quality of life radiation therapy instrument (QOL-RTI)
Speech handicap index (SHI)
University of Washington quality of life instrument (rev) (UW-QOL-R)
Washington University head and neck comorbidity index (WUHNCI)
Xerostomia specific questionnaire

Anterior Skull Base Surgery
Anterior skull base surgery QOL

FACIAL PLASTIC SURGERY
Blepharoplasty outcomes evaluation
Cleft evaluation profile
Derriford appearance scale
Facelift outcomes evaluation
Facial appearance sorting test (FAST)
Facial injectables, longevity, late and early reactions and satisfaction questionnaire (FILLERS Q)
Facial lines outcomes questionnaire
Facial lines treatment satisfaction questionnaire
Midface dysfunction scale
Observer-rated facial disfigurement 9 point Likert scale
Lip reanimation outcomes questionnaire
Observer scar assessment scale
Obturator functioning scale
Patient-rated facial disfigurement analogue scale
Rhinoplasty outcomes evaluation
Skin rejuvenation outcomes evaluation

COMORBIDITIES
Adult comorbidity evaluation 27 (ACE 27)
Charlson comorbidity index (CI)
Cumulative illness rating scale (CIRS)
Index of coexistent disease (ICED)
Klabunde index
Modified Kaplan-Feinstein index
World Health Organization international classification of functioning, disability, and health (ICF)

side effects from true depression (22). The impact of comorbidity on functional outcomes, QOL, and prognosis for disease-specific survival is widely acknowledged as well. Recognition of this strong association has led to recommendations for integration of tumor-specific staging systems with comorbidity in order to develop better instruments for prognostication (23). As previously discussed, it is important to solicit patients' input to assessment of their status. If asked to prioritize the importance of their functional impairments, for example, patients with oral or oropharyngeal cancer in one study identified speech, chewing, and swallowing function as being more important than all other domain scores (24). Traditional functional assessments continue to be a part of the management process: speech, swallowing, hearing, balance, quality of sleep, and facial movement. More validated functional scales have been developed, with the capacity to quantify the level of function, that are responsive to change, and can be analyzed in the context of both clinical status and impact on HRQOL. Used with generic QOL scales, these measures can form a battery that paints a broader picture of the disease and intervention impact on the patient as a person.

Functional assessments and HRQOL studies have been used to great advantage in other areas of otolaryngology—head and neck surgery. A series of systematic reviews has demonstrated rather conclusively that endoscopic sinus surgery is effective in relieving the symptoms of CRS, notably nasal obstruction, postnasal discharge, facial pain, bodily pain, and fatigue, while improving the HRQOL in several domains (25–27). Headache and hyposmia are less affected. While these findings may not be news for many clinicians, they take the results out of the realm of personal experience and into the desired area of evidence-based management when accompanied by consensus-based management guidelines (28) and provide a solid foundation for patient counseling.

The American Academy of Otolaryngology—Head and Neck Surgery Foundation (AAO—HNSF) has sponsored a series of practice-based patient outcomes and HRQOL studies on a range of topics: nasal obstruction (Nasal Obstruction and Septoplasty Effectiveness study [NOSE]), obstructive sleep apnea (Studying Life Effects and Effectiveness of Palatopharyngoplasty study [SLEEP]), tonsillectomy in children and adults (TO TREAT), rhinosinusitis, and tympanostomy tubes. All showed improvement in symptoms and QOL, adding to the evidence base for effectiveness of common otolaryngology procedures. PROMs and HRQOL measures have yielded equally valuable information about otitis media, Ménière disease, vestibular schwannoma, and spasmodic dysphonia, which contribute to greater understanding of disease impact and clinical decisions to some extent.

However, a theme of health status, effectiveness, and HRQOL studies in rhinosinusitis, as well as a number of other otolaryngic diseases and disorders, is that symptom outcome is studied inconsistently in many studies, even if there is a consensus-based standard to guide such studies (28,29). Thus, the credibility of some of the clinical research literature is weakened by being under-powered, lacking consistent inter-study operational definitions, failing to consider all variables or symptoms related to a disease entity, including inappropriately heterogeneous groups, and marred by a lack of replicability. The Cochrane Database of Systematic Reviews (http://www2.cochrane.org/reviews) provides an exceptionally high-quality series of regularly updated systematic reviews of the effects of health care. Frequently, the conclusion of the review is that

there is insufficient evidence of adequate quality to support claims of effectiveness of an intervention, contrary to what may be the "conventional wisdom." The data are often subjected to meta-analysis to increase the power of the findings of numerous studies that would be too small to produce reliable results individually. Finally, benefits and potential harms of interventions are identified, as well as conditions in which they should be used. One valuable feature of the reviews is that they identify the type of studies needed to demonstrate effectiveness; recommendations may include study design, types of patients to be included, variables, etc. The Cochrane Database could be considered the definitive source for evidence-based information about health care effectiveness, and for planning studies in this area.

FEEDBACK, EFFECTIVENESS, AND QUALITY OF PRACTICE

The ultimate test of whether incorporating HRQOL measures into clinical practice is productive, valuable, or even necessary lies in two questions: (a) did use of the measures increase patient satisfaction? and (b) did they improve health outcomes? (30). As previous discussion has illustrated, there is a growing body of literature documenting symptom and QOL improvement following treatment. While the health status or HRQOL scale used in the study is routinely identified, and domain scores may be summarized, mention is rarely made of whether the questionnaire results were discussed with the patient, whether they improve doctor–patient communication, or whether they influence the clinical decision process.

The application and analysis of *functional outcome measures* are well established, both for clinical research and for clinical use. They are reported regularly in the literature as structured studies and as observational series, as provider-reported outcome and as PROs. Objective medical criteria for successful outcomes are satisfied: audiometric thresholds improve, apnea/hypopnea indices decrease, and number of episodes of rhinosinusitis is reduced. Patient-reported functional outcomes are improved: they can hear better in more conditions, they can sleep through the night and no longer have daytime sleepiness, and they can breathe better and are not bothered by post-nasal drip. Those functional outcomes could be anticipated on the basis of the medical outcomes, obtained informally from the patient, or quantified by means of a validated questionnaire; the latter will allow comparisons across patients with attention to patient- and medical variables and measurement of intervention-related change. Patient satisfaction is good—not as a result of the health measure, but as a result of the successful intervention. Health care outcomes could be improved by the use of formal functional outcomes instruments to improve patient selection criteria for a given intervention approach with analysis of group data. If the study is concerned with a novel intervention, however, the provider- and patient-reported functional outcome measures become more significant and have the potential to improve health care in the sense of providing more options for management of specific diseases or conditions.

One issue should be considered more closely, however: what to do *with*, and *about*, available HRQOL information as an entity. There is little uncertainty about following up on functional impairment of swallowing, breathing, or speaking; inclusion of referral for psychiatric or psychosocial support is a less consistent feature of action plans. With short-term management, for example, septoplasty, tympanostomy tubes, tonsillectomy, the utility of HRQOL information is as a useful supplement to medical- and patient-reported functional outcome data. For long-term or chronic disease management, the potential contribution of HRQOL information is greater.

In the hierarchy of cancer treatment objectives, disease control is the primary issue, and preserving or restoring function would be a key consideration as well, with patient-reported HRQOL occupying an unspecified position in many health care environments. Although patients report that they are in favor of completing QOL questionnaires in clinic and that it assists in describing their health problems to their doctors, its importance is not rated as highly by clinicians (31). Murphy et al. (32) notes appropriately that in order for QOL measurements to have meaning to clinicians, they should be linked with clinical benchmarks and that both generic and head and neck cancer-specific measures should be included in the assessment battery to provide a comprehensive assessment of global health and tumor-specific issues. These authors concluded by expressing some reservations about whether the routine use of QOL measures in the clinical setting is beneficial to patients, suggesting that methodologic issues need further study and refinement.

The use of HRQOL information in the clinical setting is far from limited. Used appropriately, it can serve as a screening tool, a monitoring tool, as a method of promoting patient-centered care, in assisting the decision-making process, as a method of facilitating communication among multidisciplinary teams, and as a means of monitoring the quality of patient care (33). HRQOL measures also have short-term clinical application to supplement medical- and patient-reported functional outcomes for documentation of intervention effectiveness. Evidence from randomized clinical trials has demonstrated that the use of patient-reported HRQOL information is valuable in improving discussion and detection of HRQOL problems but has less impact on how clinicians manage patient problems or on subsequent patient outcomes. This may be related to the introduction of a new component into the clinical machine that has no established place in how patients and clinicians communicate with each other or how clinical decisions are made.

In addition to the lack of a traditional place in the clinical routine, other barriers to adoption of HRQOL information in clinical care may exist. First, the time constraints of

busy clinicians, particularly surgeons, do not give them the opportunity for extended consultations with their patients. Second, while clinicians are comfortable discussing physical functioning and symptoms with their patients, they may be less comfortable discussing emotional functioning and daily living activities, even if both topics derive from the same QOL questionnaire. Third, clinicians may not view the information from the patient as being sufficiently important to warrant a change to the treatment plan, although at least one European study reported that QOL was considered as essential as survival for head and neck cancer patients by many of the 500 otolaryngologists surveyed (30,34). Head and neck cancer patients are a highly symptomatic and complex group with multiple QOL issues that merit consideration. There is evidence that nurse specialists can provide more holistic care for such patients and make an important contribution through discussion and follow-up of their HRQOL issues (35). This may be considered an attractive feature of a management plan for caregivers and patients alike.

SUMMARY AND CONCLUSIONS

During the 20th century, average life expectancy in the United States increased more than 30 years, much of it due to advances in health care (36). Expectations for a healthier life at older ages have increased and with them the perspective of health as a positive contributor to the QOL, not simply an absence of disease. Patient-reported QOL and functional outcome assessments as supplements to the more traditional clinical indicators are becoming more common and represent a paradigm shift in measuring the health outcome of clinical interventions. This approach defines a more patient-led baseline against which intervention effectiveness can be assessed, imposing fundamental and positive changes on health care delivery, policy, research, and economics.

HIGHLIGHTS

- The concept of general QOL is highly individual, with no set definition or criteria. It is subject to change with age and circumstances. HRQOL includes perceptions of physical, emotional, and social well-being, before, during, and after treatment and the impact of those factors on the ability to lead a satisfying life. To be useful, HRQOL must be a personal construct and it must be dynamic for, as health changes for the better or the worse, perspectives on life, roles, relationships, and experiences change. Although health is usually an important component of overall QOL, health status is neither a predictor nor a determinant of QOL.
- The conceptual framework for measuring multidimensional functional health status is related to the WHO classification of impairment, disability, and handicap, and seeks to address the functional and psychosocial outcomes of diseases, disorders, and conditions. Functional outcomes and HRQOL can be assessed using PROMs.
- PROMs fall into three categories: generic, disease-specific, and symptom-specific. *Generic HRQOL instruments* are designed to be applicable across a broad range of diseases, disorders, and conditions. They can be used with different groups of patients and to assess the impact of a range of different interventions, making them valuable for comparative effectiveness studies. *Disease-specific scales* are designed to assess specific diagnostic or patient populations; they have the goal of detecting the impairments associated with specific diseases or conditions, and/or to be responsive to clinically significant changes related to interventions or the natural history of the disease. *Symptom-specific instruments* are designed to focus exclusively on symptoms produced by a particular disease or condition and thus are extremely well suited to measure intervention-related changes.
- Functional outcome and HRQOL instruments must be methodologically sound for confident clinical and research use. They must be validated and shown to have adequate reliability, validity, responsiveness, and sensitivity. *Reliability* is a measure of the reproducibility of the results; *validity* is the extent to which an instrument measures what it claims to measure; *responsiveness* indicates the extent to which changes in values correlate with true changes in status; *sensitivity* is the amount of change in status that the instrument is able to detect.
- The potential of HRQOL and functional outcome measures to increase satisfaction with care and improve health outcomes must be demonstrated before they will be accepted as routine components of the health care delivery system. Although functional outcomes measurements will be easier to implement, HRQOL measures are valuable tools, especially in the care of patients with chronic diseases or those requiring long-term care. HRQOL measures can serve as a screening tool, a monitoring tool, as a method of promoting patient-centered care, in assisting the decision-making process, as a method of facilitating communication among multidisciplinary teams, and as a means of monitoring the quality of patient care; nurse-specialists can be invaluable partners in identifying and discussing HRQOL problems with patients.

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50 Taste

Natasha Mirza

The goal of the chemosensory system is the detection and discrimination of foods and the initiation and sustenance of ingestion. This system is present in both vertebrates and invertebrates and well developed even in a newborn infant. It is estimated that more than 2 million Americans have some kind of chemosensory disorder (1). What is proven so far has been that a loss or alteration of taste affects nutritional intake and leads to multiple nutrition-related medical problems (2). For this reason, it is important to understand the mechanism of taste and to identify some of the effects of taste dysfunction and the means of reducing them. This chapter briefly reviews the anatomy and physiology of taste including taste transduction; clinical evaluation of the taste system; the impact of aging, medications, and other disease states; and discusses some of the methods to help decrease some of the harmful effects of taste loss on both nutrition and quality of life.

DEVELOPMENT OF THE TASTE SYSTEM

Morphologic evidence shows that there is a functional taste system present *in utero*. Even premature infants respond pleasurably to sucrose and glucose. The hedonic system of pleasantness is also well developed in infants (3). The acceptance of sweet and rejection of bitter seem to be hardwired while the effect associated with odors depends much more on experience.

ANATOMY OF THE TASTE SYSTEM

In mammals, taste buds are located throughout the oral cavity, in the pharynx, the laryngeal epiglottis, and at the entrance of the esophagus. Taste buds on the dorsal lingual epithelium are the most numerous (total number of taste buds, all classes, approximately 4,600 per tongue). Here, taste buds are contained within three major classes of papillae, the fungiform, foliate, and circumvallate, while the filiform papillae are nongustatory. Fungiform papillae are most densely distributed on the tip and sides of the tongue. These papillae generally contain one to several taste buds per papilla (4). They are innervated by the chorda tympani branch of the facial (VII cranial) nerve and appear as red spots on the tongue because they are richly supplied with blood vessels. The total number of fungiform papillae per human tongue is around 200. The foliate papillae are situated on the edge of the tongue slightly anterior of the circumvallate line. They are predominantly sensitive to sour tastes and are innervated by the glossopharyngeal (IX cranial) nerve and average five foliate papillae per side of the tongue with approximately 120 taste buds per foliate papillae. Circumvallate papillae are sunken papillae, with a trough separating them from the surrounding wall. The taste buds are in tiers within the trough of the papillae. They are situated on the surface of the circumvallate line and form an inverted V on the posterior of the tongue. They confer a sour/bitter sensitivity to the posterior one-third of the tongue. They are innervated by the glossopharyngeal (IX cranial) nerve. There are 3 to 13 circumvallate papillae per tongue with about 250 taste buds per papillae. The filiform papillae are mechanical and nongustatory. In addition, there are 2,500 taste buds on the epiglottis, soft palate, and laryngeal and oral pharynx.

In mammals, taste buds are aggregations of 30 to 100 individual elongated "neuroepithelial" cells (50 μm in height, 30 to 70 μm in width) (5). At the apex of the taste bud, microvillar processes protrude through a small opening, the taste pore (4 to 10 μm in diameter) into the oral milieu. Just below the taste bud apex, taste cells are joined by tight junctional complexes. Taste cells are bipolar cells, which connect to the epithelial surface of the oral cavity via dendritic processes and to a nerve axon at the base which invades the bud and ramifies extensively, with each fiber

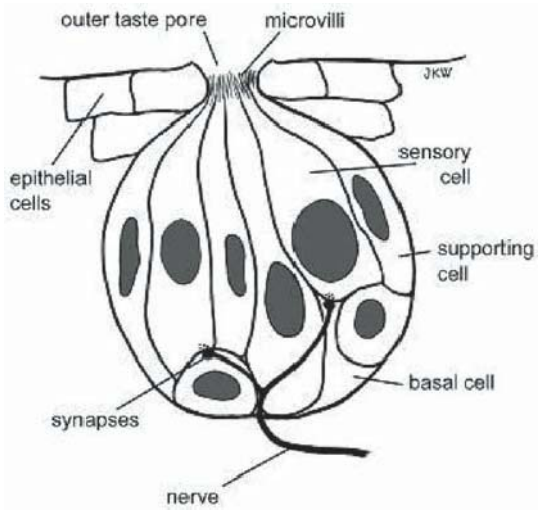


Figure 50.1 Anatomy of a taste bud. (From Geriatric Otolaryngology, eds. Eibling and Calhoun, 2006, Published by Taylor and Francis group.)

typically synapsing with multiple receptor cells within the taste bud (Fig. 50.1). There are at least three different types of taste cells although the function of these cells overlaps. The lifespan of a mammalian taste cell is approximately 10 days. As a cell ages, a nerve terminal detaches, finds a developing cell, and forms a new synapse. The new cell has to be of the same taste specificity as the old dying cell; in other words, taste receptor cells act as surface markers to guide nerve fibers to the right cellular target. Cells in each taste bud contain the sensory receptor cells, supporting cells, and basal cells that differentiate into new receptor cells. A single taste bud is all that is needed to provide sensation for all the four tastes so that even the decrease in number of lingual papillae does not necessarily lead to a significant loss of taste.

TASTE TRANSDUCTION

It is important to understand some of the basic science that is involved in taste transduction to understand the effects of pathologic conditions on this mechanism (6). Stimuli entering the mouth first interact with sites on the microvilli within the taste pore. Salts and sour acidic stimuli use ion channels while sweet and bitter substances react with protein compounds. Taste receptors trigger transduction cascades, which then activate synapses and cause the excitation of nerve fibers. A signal is produced, which is then carried to the brain, relaying information on the identity and intensity of the gustatory stimulus. Receptor proteins are located on the apical surface of cells and from there the stimulus enters the cell either via an ion channel as it does for the salty and sour tastes or via second messenger systems like cyclic AMP for bitter and sweet. Once the stimulant enters the cell there is a change in the internal electrical state of the cell, which leads to the secretion of a neurotransmitter and activation of a nerve fiber.

Each taste serves a specific purpose in the maintenance of health of an individual. Salt taste guides the intake of sodium chloride and thus the salt–water homeostasis. Sour helps with the recognition of complex foods. At low concentrations, it is pleasant but once it reaches high concentrations it becomes an unpleasant taste and leads to avoidance. It guides acid–base regulation and is sensitive to extracellular pH changes. The sweet receptor is a classical proteinaceous molecule analogous to an olfactory receptor. It responds to soluble carbohydrates in the oral cavity and regulates caloric intake, nutrition, and energy balance. It uses a second messenger like cAMP to activate a cyclic nucleotide cascade. Sweet taste has a strong hedonic effect and is well developed in infants. Bitter taste like sour is bearable and even to some extent pleasant in low concentrations but is repulsive when strong. Bitter receptors belong to the second messenger system of G proteins. They set off a G-protein–coupled receptor (GPCR)-mediated signal that leads to dual signaling of cAMP and cGMP within the cell. Bitter taste serves as a warning system designed by nature to protect against the ingestion of harmful compounds. Even newborn infants are seen to respond to bitter compounds, like quinine, with distaste (7). Umami as a taste was discovered about 100 years ago and is somewhat similar to sweet taste. It is derived from L-glutamate and is the taste present in Monosodium glutamate (MSG), chicken broth, meat extracts, and aging cheese. Umami receptors act much the same way as bitter and sweet receptors (they involve GPCRs), but not much is known about their specific function. It is thought that the amino acid L-glutamate binds to a type of GPCR known as a metabotropic glutamate receptor (mGluR4). This causes the G-protein complex to activate a secondary receptor, which ultimately leads to neurotransmitter release. The intermediate steps are not known. This taste helps guide the intake of peptides and proteins.

INNERVATION OF THE TONGUE

Taste receptor cells do not have an axon. Information is relayed onto terminals of sensory fibers by transmitters. These fibers arise from the ganglion cells of three cranial nerves. Over the anterior tongue the chorda tympani (a branch of the facial nerve) is sensory for taste and the lingual nerve, a branch of the trigeminal nerve serves general sensation. The chorda tympani "hitchhikes" along the lingual nerve travels through the middle ear and joins the facial nerve in the fallopian canal, then to the geniculate ganglion and terminates in the upper portion of the nucleus solitarius.

Over the posterior tongue, taste is conveyed via the glossopharyngeal (IX cranial) with some branches of the vagus providing additional taste sensation. In this region of the tongue, general sensation is also provided by the same two nerves. The IX nerve travels through the jugular foramen and terminating in the tractus solitarius

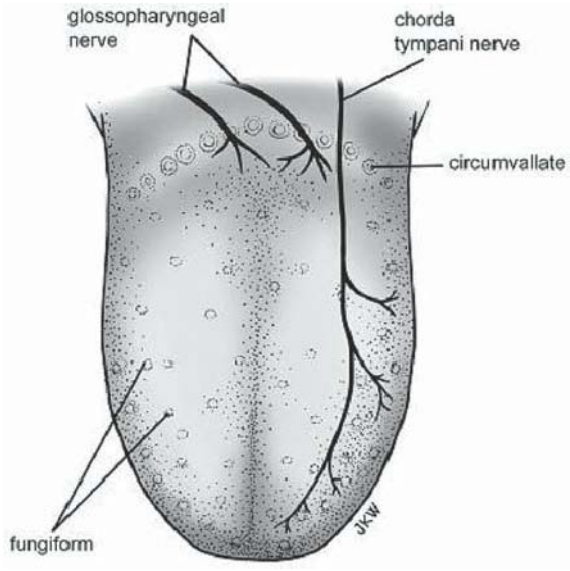


Figure 50.2 Innervation of the tongue. (From Geriatric Otolaryngology, eds. Eibling and Calhoun, 2006, Published by Taylor and Francis group.)

(gustatory nucleus). The trigeminal nerve is responsible for detecting the burning sensation caused by certain foods, for example, peppers. The superior laryngeal nerve, a branch of the vagus, innervates taste buds on the laryngeal surface of the epiglottis. Its role in taste is unknown (Fig. 50.2).

Central Pathways

Taste fibers from cranial nerves VII, IX, and X form part of the fasciculus solitarius and synapse centrally in the medulla (in a thin line of cells called the nucleus of the solitary tract). From there, the information is relayed to the somatosensory cortex for the conscious perception of taste and to the hypothalamus, amygdala, and insula, giving the so-called affective component of taste. This is responsible for the behavioral response, for example, aversion, gastric secretion, and feeding behavior. Nature has provided some of the compensation mechanisms that make taste very robust. These depend on the fact that there is inhibition among the central projections of the taste nerves. Taste nerves normally inhibit one another across the midline. Therefore, when a nerve is damaged there is a decrease in inhibitory impulses from that side, which in turn leads to an increase in responses from the opposite side. This disinhibition of the damaged nerve leads to an overall preservation of taste and total ageusia or loss of taste is very rare. On the other hand, the olfactory system depends on one nerve and is therefore more vulnerable to injury. It is also interesting to note that damage to taste releases inhibition on the trigeminal nerve and causes intensification of sensations like oral burning and oral touch and also makes certain foods, for example, fatty foods less palatable (8).

Genetic Variations

Phenylthiocarbamide and 6-n-propylthiouracil (PROP), chemically related compounds, are probes for genetic variation in bitter taste. Tasters and nontasters are identified based on the individual's ability to perceive PROP. The perceived intensity grades tasters into medium tasters (PROP is bitter) and supertasters (PROP is very bitter). Compared with supertasters, nontasters have fewer taste papillae on the anterior tongue (fungiform papillae) and experience less negative (e.g., bitterness) and more positive (e.g., sweetness) sensations from certain foods and beverages like alcohol.

Pain and other propriosensation are also more intense in these people and their thresholds for chili peppers and a fatty food is also more intense. According to some studies, the preference for and consumption of various (bitter-tasting) foods, recognized for their cancer-preventive properties, are also linked to an individual's PROP status (9,10). According to Bartoshuk, variations in oral sensation alter not only the intake of foods but also habits like smoking and alcohol consumption. She has found that for supertasters vegetable intake is lower leading to various pathologic states, for example, colon cancers. On the other hand, high-risk foods and habits tend to be less in supertasters as they generally do not like the taste of fatty foods, alcohol, or cigarette smoke (11).

TASTE TESTING AND BACKGROUND

Verification of taste loss is an important aspect of testing when a patient comes to the doctor complaining of taste loss. It is often found that the sense of taste maybe normal but the sense of smell is impaired leading to a loss of flavor. Flavor is a complete sensory experience arising from ingested stimulant molecules and involves taste, smell, texture, and temperature. Taste studies looked at two primary aspects of taste: acuity and intensity. Taste acuity measures two different parameters: (a) taste detection or threshold testing, which is a measure of the concentration at which a distinction can be made between a taste substance (tastant) and water, and (b) taste recognition, that is, which is sweet, sour, salty, or bitter. Taste intensity is a suprathreshold measure of taste qualities. Whole mouth testing is used to assess the individual's ability to detect, identify, and evaluate the intensity of different concentrations of the four taste substances. Spatial taste testing is used to assess different areas of the tongue to identify if there is localized impairment of taste.

The methods used in taste testing involve an evaluation of taste identification and taste intensity. For most individuals everyday taste-related experiences involve suprathreshold experiences. In the *whole-mouth taste testing*, five concentrations of sucrose, sodium chloride, citric acid, and caffeine are presented in a solution form. The subject sips, swishes, and expectorates it. The subject then

indicates whether the solution tasted sweet, salty, sour, or bitter and rates its intensity on a segmented visual analog scale (VAS) with the extremes labeled as very strong and very weak and with a background logarithmic gradation of shading.

The regional taste test described below is a well validated taste test used by the several chemosensory centers to assess gustatory dysfunction (12,13). It employs four suprathreshold stimulants: namely NaCl for salty, sucrose for sweet, acetic or citric acid for sour, and quinine sulfate or caffeine for bitter. A drop of the tastant (sweet, sour, salt, and bitter) is placed on the tongue with a micropipette and the subject is asked to identify the solution. These taste solutions are applied to four areas of the tongue: anterior right and left and posterior right and left. About 15 mL aliquots of single concentrations of sucrose (0.49 M), sodium chloride (0.31 M), citric acid (0.015 M), and caffeine (0.04 M) are presented in random order to selected regions of the tongue. Each taste solution is presented to each tongue region six times, in random order, for a total of 96 trials. This is a forced choice test in which patients are asked to identify solutions, with their tongue extended from their mouths, by pointing to a card labeled, "sweet," "sour," "bitter," and "salty." When a patient is unable to identify a solution, he or she is encouraged to guess. Patients are asked to rinse their mouths with distilled water between presentations. A total of 96 trials are employed (4 tastants × 6 trials × 4 tongue regions) and is generally administered over 45 minutes.

Threshold or intensity testing is much more difficult. Intensity testing involves a VAS, which is a 9-level scale of increasing shades of gray with the minimum at one end and maximum at the other. The problem with such testing is that the strength of a tastant is likely to vary across individuals, for example, the most intense sweet experienced by a supertaster is much more intense than the same concentration experienced by a nontaster.

Electrogustometry

Electrogustometry utilizes a weak electric stimulus to produce a sour taste when applied to taste receptors. It is useful to measure taste in specific loci of the anterior tongue. Its main disadvantage is the inability to measure specific tastes.

Videomicroscopy

This procedure was described by Miller and Reedy (14) in 1990. It is a noninvasive procedure designed to provide a 50- to 100-fold magnification to resolve the number and location of taste pores on the lingual papillae without destructive tissue preparation. Videomicroscopy (VM) allows the study of taste perception in terms of quantified taste receptor organs. Studies by Miller and Reedy have confirmed that taste pore staining is a valid method for counting taste buds. VM has the capability to successfully view, capture, and store high-resolution digital images. Fungi from papillae are approximately 0.1 to 1 mm in diameter and each taste pore has a diameter of 5 to 10 µm in fixed dehydrated tissues but is larger in living tissues. There are three to four taste pores per papilla. This method affords the advantage of being a nondestructive method allowing one to study dynamic changes in taste receptor populations over time. It also allows comparison of the anatomy with function in living subjects. The images obtained facilitate documentation, storage, and analysis of the papillae and pore images (Figs. 50.3 and 50.4).

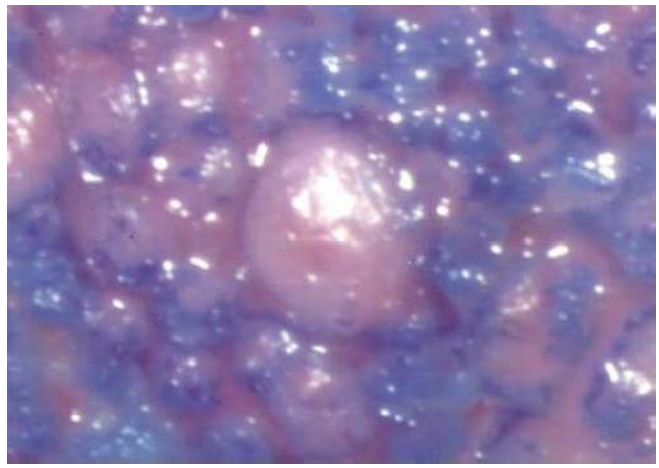


Figure 50.3 High power view of lingual fungiform papilla. *Arrow* shows taste pore. (From Laryngoscope. Lippincott Williams and Wilkins, 2008.) Mirza N, Machtay M, Devine P, Troxel A. Gustatory impairment in patients undergoing head and neck irradiation. Laryngoscope 2008; Jan 118(1):24–31.

TASTE ALTERING CONDITIONS

It is important to remember that when the taste system is damaged it may result in either a loss of taste or more often a distortion of taste or "phantom taste." Some of the conditions mentioned below are common causes of taste dysfunction and are discussed in greater detail here.

Aging

While age causes a decrement in all taste sensitivities, sweet taste in almost all studies reviewed seemed the most robust and survived the longest (15,16). Most studies have also found that males were much more vulnerable to the effects of aging compared with age-matched females both for taste thresholds and intensities. The relationship of the density of taste buds to taste sensitivity has demonstrated that NaCl threshold is inversely related to the number of fungiform papillae (more papillae = more sensitivity, lower threshold) (17,18). Arey et al. (19) found degenerative changes in taste receptors with a regression of gustatory papillae. Olfaction is more affected than taste and leads to a decrease in flavor overall.

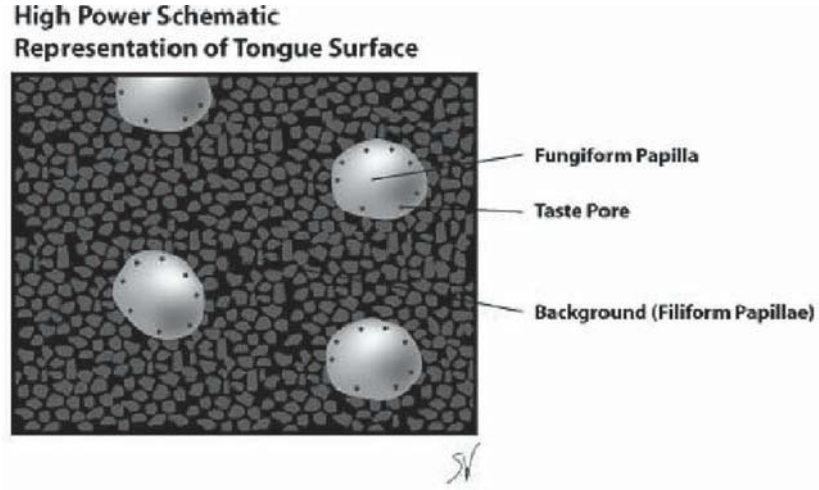


Figure 50.4 Schematic view of videomicroscopy. (From Laryngoscope. Lippincott Williams and Wilkins, 2008.) Mirza N, Machtay M, Devine P, Troxel A, Abboud SK, Doty RL. Gustatory Impairment in patients undergoing Head and Neck Irradiation. Laryngoscope. 2008. Jan 118(1): 24-31

Sucrose being the most robust of the tastes accounts for changes in eating habits of the elderly with a preference for cakes and pastries and hence deleterious health effects. However, there was no significant age-associated deterioration in somatic sensations such as touch and burning pain in the tongue, showing that aging affects taste perception and oral somatic sensations differently. Reasons for taste loss may also be related to decrease in the flow of saliva, which in turn leads to decreased taste receptor stimulation. Gingivitis and periodontal disease increase taste thresholds. In fact, several studies have shown a lowering of taste thresholds with an improvement in oral hygiene. Trials of antifungal troches and antibiotics have therefore been tried in an effort to improve oral health.

Systemic Diseases

Systemic diseases like diabetes, gastric disease, hypothyroidism, liver disease, chronic renal failure, Alzheimer and Parkinson disease affect taste. For example, uremia may introduce toxins into the blood stream leading to taste alterations and the problem improves with dialysis. Similarly, diabetics may develop neuropathies, which may affect the gustatory nerves and lead to abnormalities of taste. Perimenopausal women often complain of "the burning mouth syndrome," which is believed to be related to a lowering of the bitter taste threshold and a release of oral pain inhibition (20,21).

The use of systemic medications especially antihypertensive drugs and chemotherapeutic agents affect taste. Medications are suspected of introducing tastable substances into the blood and thereby altering taste thresholds; for example, chemotherapy drugs are well known to lower the bitter threshold and account for an aversion to certain foods like meats. Schiffman found that certain drugs can modify taste transduction or the turnover of cells and alter taste perception. The taking of more than one medication (so-called polypharmacy) is becoming more common and this compounds the problem with taste dysfunction.

Smoking affects taste especially the bitter sense. Hsu and Davis (22) found that smoking decreased gustatory sensitivity. Mirza et al. (23) performed a longitudinal study on the effects of radiation on the gustatory system and found that radiation adversely affected sour taste the most and also caused damage to the taste pores. Recovery took approximately 6 months.

Nerve Damage

This can occur from surgery involving pressure on the gustatory nerve, for example, during a tonsillectomy, middle ear surgery, or from a resection of the nerve involved with a tumor. Such losses are generally temporary as there is overlap in taste fibers and nerve damage leads to a release of inhibition of the contralateral nerves so everyday taste is generally not affected. Taste phantoms occur with some conditions like Bell palsy and acoustic neuromas. Generally, these phantoms last for about 6 months and then resolve spontaneously. Review of the literature suggests that possible indirect damage to the lingual branch of the glossopharyngeal nerve could be the cause of the taste disturbance after a tonsillectomy (24).

This symptom may be reversible within 2 years after tonsillectomy. Patients should be informed of the risk of postoperative taste disturbance after tonsillectomy as being one of the rare complications of this surgery.

Radiation and Chemotherapy

Taste dysfunction, which includes a partial loss (hypogeusia), complete loss (ageusia), and abnormal taste (dysgeusia), for example, a metallic taste, is a well-known complication of radiation and chemotherapy for head and neck cancer. This dysgeusia impacts both nutritional intake and the quality of life, with patients developing mouth sores and inflammation. Mirza et al. conducted a prospective, longitudinal study on newly diagnosed head and neck cancer patients and found that sour taste

was most affected after radiation and chemotherapy. The number of taste buds was also significantly decreased after radiation. While taste generally recovered after 6 months of therapeutic radiation, the number of taste buds did not return to the preradiation levels. Taste damage was independent of the decrease in saliva production although xerostomia has obvious deleterious effects on taste as well. Efforts to avert radiation injury are therefore needed and include dose sculpturing techniques to decrease radiation to nontarget tissues, altered fractionation schedules to decrease normal tissue injury, replenishment of stem cells through the administration of growth factors and the need for the development of mucosal protectants, along with the need to alter the diet of radiation patients (with food additives, flavorants, avoidance of very high-temperature foods), to decrease the impact of taste alterations in this population.

EFFECTS OF TASTE LOSS

What most individuals complain of is a loss of flavor and enjoyment of foods, which is most often related to the well-known loss of olfaction combined with some taste loss (25). The effect is a loss of appetite which puts the individual at higher risk for depression, anorexia, and weight loss. Institutionalized individuals, for example, often show an increase in taste thresholds, which may account for the poor intake and nutritional status of some of these people. Poor taste perception combined with olfactory loss puts the individual at risk for food poisoning from the ingestion of spoiled foods.

THERAPY FOR TASTE LOSS

No specific therapy or pharmacologic agents are available to reverse the loss of taste with aging and in general the prognosis is poor. Awareness of taste alteration and decrement is paramount in making sure individuals get a balanced diet and prevent health problems, which are secondary to a poor and unhealthy diet.

Flavor amplifiers have been developed to enhance the flavor by adding an extra ingredient to the food. Examples of these are seasoning salts, fruit juices, meat stocks, and gravy. MSG also helps as a flavor enhancer especially for protein-based dishes, for example, meat loaf, casserole, etc., because it adds a savory taste to these foods. Other food enhancers include vinegars, sun-dried tomatoes, herbs, and spices. Color enhancers make the food more appealing and enjoyable to people who have a poor appetite.

Anecdotal evidence also exists that lack of the trace elements can lead to decreases in metabolic functions. Chauhan et al. (26) has therefore suggested that zinc supplementation be tried to enhance taste along with vitamins A, B_{12}, and folic acid for the maintenance of taste bud integrity. For individuals suffering from oral pain, the use of capsaicin as a desensitizer of pain receptors and clonazepam as a gamma-aminobutyric acid agonist has been shown to help, for example, sufferers of the "burning mouth syndrome" (27).

CONCLUSION

Current research is geared toward the development of drugs containing taste ligands, which activate or inhibit taste receptor proteins. These, in turn, can then increase or decrease specific tastes (e.g., artificial sweeteners like saccharin and aspartame). Awareness of the loss or alteration of taste should be an important part of education for individuals suffering from a taste dysfunction so that a conscious effort is made toward the preparation of a nutritionally balanced diet. When an individual notices a loss of taste, a referral to a chemosensory center should be made where a multidisciplinary team approach can help with the elimination of the reversible causes of taste loss. Protectants of taste should be researched for and avoidance of drugs and harmful habits like smoking should be encouraged as they will help preserve the natural taste function. Keeping the sense of taste strong is essential for the enjoyment of life and for the survival of the human race as a whole.

HIGHLIGHTS

- Sensory cells in taste buds do not have axons. Rather, they process chemical signals and activate sensory neurons via synapses.
- Individual taste sensitivity is genetically determined and is highly variable.
- Taste sensitivity is quantifiable utilizing standardized testing.
- Taste is affected by many diseases such as diabetes, chronic renal failure, Parkinson, and Alzheimer.
- Some common medications affect taste, such as antihypertensives and chemotherapy drugs.
- Taste may be affected by interruption of the sensory neural pathways such as chorda tympani and lingual nerve.
- No specific treatment exists for taste dysfunction. Adjunctive measures such as food color and flavor enhancers (MSG, etc.) may benefit affected patients.

ACKNOWLEDGEMENT

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51 Stomatitis

Richard O. Wein *Miriam O'Leary*

This chapter covers the broad category of diagnoses that fall under the diagnosis of stomatitis. The term "stomatitis" indicates an inflammation and potential breakdown of the oral cavity mucosal surfaces and is typically symptomatic. The clinical presentation may extend to the oropharynx or the external perioral region. The etiologies are multiple and include treatment-related, infectious, immunologic, systemic, nutritional, and idiopathic causes.

The diagnoses that fall under this classification can be challenging to identify and require a detailed assessment of a patient's history of presentation and associated conditions. Additionally, these presentations are not solely seen in the adult population and some forms of stomatitis are unique to the pediatric population.

Given that many of these diagnoses are localized manifestations of systemic diseases, collaborative management of patients with our Dermatology, Infectious Disease, Oral Medicine, and/or Rheumatology colleagues is expected.

Interestingly, despite being encountered daily in general practice, the etiology of many of these oral lesions remains unclear. Many of the advocated treatment options vary dramatically within the medical literature and may only offer symptom control and not affect cure of the underlying diagnosis. As such, this chapter attempts to summarize some of the common perspectives relative to these diagnoses; however, for those seeking more detail on any one condition, the reader is encouraged to review the articles cited within the chapter's reference list.

CLINICAL ASSESSMENT

The clinical appearance of stomatitis is variable. Presentations can differ from simple localized to fulminant manifestations and may include components of mucosal erythema, hyperkeratosis, ulceration, pseudomembrane, and/or vesicle formation.

The rate of epithelial turnover in the oral cavity ranges from 3 to 7 days. As a result, this anatomic location is quick to demonstrate visible signs of a metabolic disturbance from a systemic condition or in relation to treatment (1).

Throughout this chapter, a theme should develop relative to the importance of a thorough history of presentation and the assessment for associated diagnoses. Some of the conditions that are discussed are diagnoses of exclusion, while others may represent the earliest presentation of a more significant systemic process.

Pertinent issues that should be addressed in the history include the circumstances and the time course surrounding the onset of symptoms, recent changes in medications, aggressiveness of oral hygiene and product use, palliating/provoking factors, quality of pain and any prodromal symptoms.

A full head and neck examination is necessary in these cases in an effort to assess for synchronous findings beyond the oral presentation. Dentures should be removed and assessed for quality of fit while asking the patient about the original date of manufacture in addition to visits for modification. In cases of buccal mucosal lesions, the relationship of the ipsilateral dentition and any amalgam that contacts the mucosa in a closed mouth position should be identified. Additionally, the quality of salivary production should be assessed.

Exudative lesions should be considered for gram stain and culture (with fungal cultures additionally requested). Tzanck smear and viral cultures should also be considered in patients with vesicular lesions.

Laboratory assay, in cases where a wide differential diagnosis continues to exist after history and physical examination, can include a complete blood count (CBC) with differential, erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), and cytoplasmic-antineutrophil cytoplasmic antibodies (c-ANCA) in addition to levels

for iron, ferritin, total iron-binding capacity, folate, thiamine (B1), riboflavin (B2), pyridoxine (B6), cobalamin (B12), zinc, and magnesium (2). In xerostomic patients, anti-SSA and anti-SSB can be drawn to assess for Sjogren disease.

Biopsy remains a powerful tool for establishing a definitive diagnosis in patients with stomatitis of unclear etiology. Patients with vesiculobullous lesions should have perilesional tissue sent for direct immunofluorescence (DIF) for deposition of IgG, IgA, and/or complement C3. Biopsy should be considered in patients with suspected recurrent aphthous stomatitis (RAS), oral lichen planus (OLP), or graft-versus-host disease (GVHD) to rule out oral squamous cell carcinoma because of the potential for similarity in appearance.

Patients with a history and findings highly suggestive of an inflammatory bowel condition, such as Crohn disease or ulcerative colitis (UC), should be considered candidates for colonoscopy.

ETIOLOGY

Our understanding of the etiology of treatment-related mucositis at the cellular level continues to evolve. Some aspects may be genetically predetermined and explain the heterogeneity of response between patients to different treatments.

Theories on the development of mucositis have traditionally stated that it was the result of direct damage to the basal epithelial cell layer leading to an impairment of the renewal capacity of the surface epithelium. The resultant clonogenic cell death would result in atrophy and consequent ulceration with the clinical presentation of mucositis.

Additional evidence has suggested that an acute microvascular injury resulting from endothelial apoptosis may play a more significant role in the etiology of mucositis than previously considered. Electron microscopy has demonstrated that endothelial and connective tissue damage precede epithelial changes in irradiated oral mucosa. This finding suggests that the development of treatment-related mucositis is not just an epithelial process.

Sonis et al. (3) describe the five phases of mucosal barrier injury as a result of chemotherapy and/or radiation therapy as:

1. Initiation with generation of reactive oxygen species
2. Up-regulation with generation of messengers including nuclear factor-κB
3. Signaling and amplification with proinflammatory cytokines including tumor necrosis factor-alpha (TNF-α)
4. Ulceration with inflammation with bacterial colonization and pain
5. Healing with epithelial proliferation and the return of local microbial flora

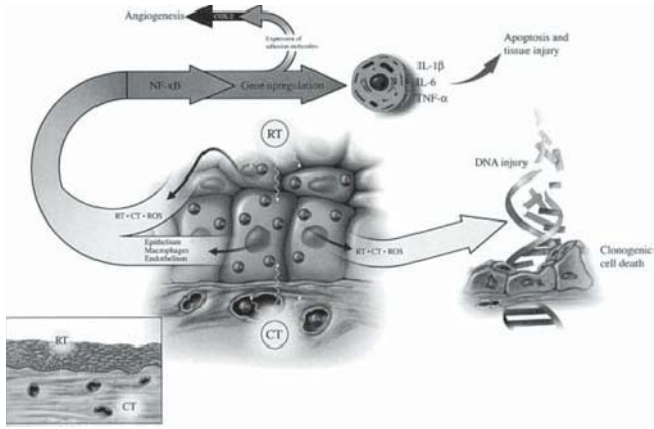


Diagram 51.1 Mucositis as a result of radiation therapy or chemotherapy occurs as a result the creation of reactive oxygen species (ROS) and the stimulation of transcription factors (such as nuclear factor-κB). Resultant double-stranded DNA breaks leads to clonogenic cell death. Up-regulation of TNF-α and the interleukins (IL-6 and IL-1β) leads to apoptosis of cells in the basal epithelium. Additional expression of factors, cyclooxygenase-2, stimulates reactive angiogenesis. (From Sonis ST, Elting LS, Keefe D, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer* 2004;100(9 Suppl):1995–2005, with permission.)

TREATMENT-RELATED STOMATITIS

Stomatitis can occur as a result of multiple forms of therapy; however, it is most evident and has the greatest impact in the treatment of cancer. It is expected that with chemotherapy and radiation therapy some degree of stomatitis, also known as mucositis, development will be experienced. Strategies for prevention, assessment, and treatment of treatment-related mucositis have been well documented; however, variation in findings and recommendations exist.

Assessment tools typically categorize the severity of a presentation by assessing a patient's well-being, utilizing mouth and throat soreness (MTS) scores, and defining the patient's functional capacity. Oral function can be assessed through dietary capacity, the ability to eat in public, and overall speech quality. An example of a quality-of-life instrument used in this setting is The Oral Mucositis Weekly Questionnaire—Head and Neck Cancer. It has been shown to be a reliable and valid means for assessing the impact of mucositis on patients undergoing treatment (4).

Administration of 5-fluorouracil, with or without leucovorin, is associated with oral mucositis in as many as 40% of patients with grade 3 and 4 presentations occurring in 10% to 15% of patients (5). In a double-blind randomized study by Sorensen et al., patients undergoing chemotherapy with 5-fluorouracil and leucovorin received prophylactic chlorhexidine or cryotherapy in attempt to decrease treatment-associated mucositis. Prophylactic chlorhexidine (10 mL at 0.1% concentration) was utilized three times per day with 1-minute oral rinses. Cryotherapy was performed with crushed oral ice 10 minutes before and

35 minutes after administration of chemotherapy. The frequency and duration of oral mucositis were significantly improved with both treatment options. Combined use of cryotherapy and chlorhexidine were not examined during this study (6).

Another preventative treatment option, frequently reported in patients with hematologic malignancies, is palifermin. Palifermin is a recombinant human keratinocyte growth factor-1 (hKGF-1) that is considered to offer mucosal protection by inducing epithelial hyperplasia. Typical administration is in multiple pre- and posttreatment administrations of 60 μg/kg. Use of single-dose palifermin was studied in sarcoma patients receiving doxorubicin chemotherapy in a randomized, double-blind, placebo-controlled trial. Single-dose intravenous palifermin (180 μg/kg body weight), administered before each cycle, was noted to significantly reduce the incidence and severity of mucositis experienced. During the trial, the drug was well tolerated and majority of patients experienced thickening of oral mucosa and tongue. Biopsies of the affected areas noted increased levels of proliferative marker Ki-67 suggesting a palifermin-associated etiology (7).

The medications associated with treatment-associated mucositis are not limited to the conventional chemotherapeutic options but also include agents like hydroxyurea (8) and the newer targeted therapies such as imatinib mesylate (9), cetuximab, panitumumab, gefitinib, erlotinib, rapamycin, sorafenib tosylate, and lapatinib (10).

Mucositis associated with radiation therapy is a common finding that tends to be self-limited after the completion of treatment. Mucositis typically peaks between weeks 5 to 6 during treatment as assessed by MTS scores (11). Radiation-associated mucositis is worse in patients undergoing radiation with accelerated regimens (5). Grade 3 and 4 mucositis requiring gastrotomy tube placement is more significant with chemoradiation protocols (38%) than compared to radiation alone (18%). The risk of developing mucositis is the same for patients undergoing treatment of an oral cavity and oropharyngeal cancer as those treated for a laryngeal and hypopharyngeal cancer.

Prophylactic pilocarpine has been shown to decrease the incidence and severity of treatment-associated mucositis that is presumed through the up-regulation of salivary function during treatment (12). However in contrast, in a randomized phase III prospective trial of bethanechol, which has a similar ability to stimulate salivary function, prophylactic treatment did not prevent mucositis or candidiasis in head and neck cancer patients undergoing radiotherapy (13).

In 2004, the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) offered a consensus statement with recommendations on treatment-associated mucositis.

In the setting of radiation therapy, the MASCC/ISOO advocated the use of benzydamine, a nonsteroidal anti-inflammatory that inhibits TNF-α (not available in the United States), and did not support the use of chlorhexidine as a prophylactic for mucositis (5).

In patients treated with chemotherapy, the prophylactic use of acyclovir was not recommended. Cryotherapy was not advocated in the setting of treatment with 5-fluorouracil, with or without leucovorin. Additionally, the panel did not support the prophylactic use of pentoxifylline or low-level laser therapy in patients preparing for stem cell transplant (5).

Novel agents requiring additional evaluation include Gelclair, AES-14, and human keratinocyte growth factor-1 (hKGF-1) and hKGF-2. Gelclair, a mixture of polyvinylpyrrolidone, sodium hyaluronate, and glycyrrhetinic acid, has demonstrated improved pain scores during treatment yet clinical trial data were lacking. AES-14, a proprietary form of administering L-glutamine, demonstrated the capacity to decrease grade 2 or greater mucositis when compared to placebo. Repifermin (hKGF-2) was shown to reduce grade 2 to 4 mucositis in clinical trials, and head and neck cancer patients receiving palifermin (hKGF-1) experienced a lower incidence and shorter duration of mucositis when compared to placebo (5).

The Cochrane Collaboration reviewed 131 studies with over 10,000 randomized patients in assessing treatment options for the prevention of oral mucositis in patients receiving cancer treatment. Less than 10% of the studies were considered to have a low risk of bias associated with their performance. The therapies shown to offer some benefit compared to placebo included: aloe vera, amifostine, cryotherapy, granulocyte-colony stimulating factor, intravenous glutamine, honey, keratinocyte growth factor, polymyxin/amphotericin antibiotic paste, and sucralfate. The strength of the evidence was described as variable (14).

Graft-Versus-Host Disease

Acute GVHD is dependent upon type I cytokine-driven CD8 effectors, while chronic graft-versus-host disease (cGVHD) has traditionally been associated with type II CD4 T cells (15). The median onset of GVHD is 6 months after transplantation with oral manifestations seen in up to 80% of patients.

The clinical presentation includes xerostomia, oral ulceration, altered capacity for taste, and recurrent candidal infections (16) (Fig. 51.1A and B). The clinical appearance can mimic oral squamous carcinoma. Of note, patients who have undergone hematopoietic stem cell transplant are at increased risk of developing oral squamous cell carcinoma and should have regular surveillance exams with biopsy performed for suspicious lesions (17). Histologic findings of GVHD on biopsy include hydropic degeneration of the basal layer of the epithelium, intracellular edema, apoptotic bodies, fibrosis, and lymphocytic infiltrate in the submucosa (18).

The current therapy for cGVHD is nonspecific immunosuppression.



Figure 51.1 GVHD of the lateral **(A)** and dorsal **(B)** tongue in a patient with prior history of bone marrow transplant.

Contrary to conventional belief, Imanguli et al. believe that cGVHD is not a type II cytokine driven disorder. They advocate a model that oral cGVHD results from type I interferon (IFN)-driven proliferation and differentiation of Th1/Tc1 differentiated effectors. This concept was supported by the finding of T cells in cGVHD infiltrates expressing T-bet, a transcription factor critical for Th1/Tc1 polarization and the production of IFN-γ and granzyme B. With these new findings, the authors suggest that new treatment approaches for cGVHD should focus on affecting the IFN-mediated inflammatory axis (15).

Lichenoid Reactions

Lichenoid reactions of the oral cavity represent an immunologic response to a systemic or local stimulus. Reactions can present as a contact stomatitis, as seen in the buccal mucosa opposing a dental amalgam (Fig. 51.2), or may represent a drug reaction from the initiation of a common medication. An extensive number of oral medications have been associated with lichenoid drug reactions (Table 51.1). The most common agents responsible for oral lichenoid drug reactions are nonsteroidal anti-inflammatories, antihypertensives, and HIV antiretrovirals. Presentation of a lichenoid reaction can vary widely but typically occurs within 2 to 3 months after initiation of a medication (19).

In addition to dental amalgam, contact lichenoid stomatitis has been reported with cinnamon flavoring (as a result of cinnamic aldehyde) and other flavorings commonly found in mints and mouthwashes. A history of a recent change in the use of oral hygiene products or variation in the habitual use of a mint or gum brand may help elucidate this risk factor.



Figure 51.2 Lichenoid contact reaction from local amalgam.

TABLE 51.1 MEDICATIONS ASSOCIATED WITH ORAL LICHENOID DRUG REACTION

Tetracycline	Chloroquine
Carbamazepine	Quinine
Phenytoin	Quinidine
Valproic acid	Isoniazid
Chlorpropamide	Rifampin
Glipizide	Streptomycin
Insulin	Zidovudine
Tolbutamide	Imatinib
Bismuth	Dactinomycin
Amphotericin B	INF-α
Ketoconazole	Gold salts
Atenolol	Penicillamine
Enalapril	Aspirin
Hydrochlorothiazide	Ibuprofen
Methyldopa	Naproxen
Metoprolol	Benzodiazepines
Lithium	Tricyclic antidepressants
Indomethacin	Allopurinol

Adapted from Schlosser BJ. Lichen planus and lichenoid reactions of the oral mucosa. *Dermatol Ther* 2010;23(3):251–267.

Individuals with contact allergy to inorganic mercury amalgam present with an oral mucosal lesion within 1.0 cm of the suspected offending restoration, and they lack associated cutaneous lichen planus (CLP). Patch testing to inorganic mercury has been advocated for recalcitrant presentations and should be read on days 7, 10, and 14 in an effort to identify late reactions. In the setting of a positive patch test, subsequent improvement of oral lesions is highly likely with removal and replacement of the restoration. Contact lichenoid reactions are not unique to mercury and may also occur to gold and palladium (20,21).

INFECTIOUS

Candidiasis

Oral candidiasis is the most common form of fungal stomatitis. Approximately 30% to 60% of individuals carry candidal species as part of their normal oral flora (22,23). *Candida albicans* is the most common candidal species in the oral cavity and accounts for up to 80% of oral isolates.

Multiple local and systemic factors can lead to candidal overgrowth. Recurrent oral candidiasis is typically seen in patients with poorly controlled diabetes, HIV-positive patients (with decreased CD4 counts), at the extremes of age (premature and elderly), and in patients with xerostomia. Use of broad-spectrum antibiotics and topical or inhalational steroids can also predispose to candidal overgrowth (22–24).

The most recognized clinical presentation of *Candida* is readily diagnosed but other forms of oral candidal infection may be more difficult to identify. The category of erythematous candidiasis is actually the most common form of oral candidiasis and presentations under this subheading are varied. Erythematous candidiasis includes acute and chronic atrophic candidiasis, angular cheilitis, median rhomboid glossitis, and chronic multifocal candidiasis (22,23).

Multiple classifications are reported for oral candidal infections. Table 51.2 presents a system that delineates candidal infections into five categories (24).

Pseudomembranous candidiasis, also known as thrush, is common in immunocompromised populations and may be diagnosed in all age groups. White creamy plaques on an erythematous mucosal base may be seen throughout the oral cavity with various degrees of associated symptoms. Extension of thrush to involve the pharynx and esophagus may also occur and present with dysphagia and odynophagia (23,24).

Acute atrophic candidiasis is also known as "antibiotic sore mouth." It occurs as a result of use of broad-spectrum antibiotics. Patients complain of oral burning and present with an erythematous patches on the buccal mucosa or dorsal tongue with papillary atrophy noted on examination. Chronic atrophic candidiasis is seen with denture use and is discussed in greater detail below.

Chronic hyperplastic candidiasis, also known as candidal leukoplakia, is the least common form of oral candidal infection. It presents on the buccal mucosa as a superficial white lesion that is incapable of being wiped away from the underlying mucosa. If the lesion does not resolve with use of antifungal therapy, leukoplakia should be viewed as more likely representing the diagnosis and biopsy considered (23,24). Candidal-associated diagnoses include actinic cheilitis, median rhomboid glossitis, and linear gingival erythema.

Angular cheilitis, also know as perleche (Fig. 51.3), represents a combination of fungal (*C. albicans*) and bacterial (*Staphylococcus aureus*) infections. Pain and erythema with fissuring at oral commissure are noted. This finding is common in denture wearers and is the result of the loss of alveolar bone height over time with the pooling of secretions at the oral commissure. In young dentate patients, infection with HIV should be considered as a potential diagnosis in recurrent presentations (23,24).

Median rhomboid glossitis, also known as central papillary atrophy, presents at the midline dorsal oral tongue.

TABLE 51.2 CLASSIFICATIONS OF VARIOUS TYPES OF ORAL CANDIDIASIS

Pseudomembranous (exudative) candidiasis
(Exudative candidiasis)
Acute atrophic (erythematous) candidiasis
Median rhomboid glossitis
Oral candidiasis
Chronic atrophic candidiasis
(Denture stomatitis)
Chronic hyperplastic candidiasis
(Candidal leukoplakia)
Candida-associated diagnoses
Actinic cheilitis
Median rhomboid glossitis
Linear gingival erythema

Parentheses indicate additional names used to describe the above-listed entity.
Adapted from Sharon V, Fazel N. Oral candidiasis and angular cheilitis. *Dermatol Ther* 2010;23(3):230–242.



Figure 51.3 Angular cheilitis.



Figure 51.4 Median rhomboid glossitis in a patient with a history of Sjogren disease and immunosuppression.

The smooth or lobular demarcated region anterior to the circumvallate papillae is typically asymptomatic in presentation (Fig. 51.4). A mirrored palate lesion may be seen from direct contact with the tongue (23,24).

The diagnosis of chronic multifocal candidiasis, separate from the classification above, is assigned to those patients with more than one form of candidal infection (e.g., angular cheilitis and denture stomatitis) that is present for greater than 4 weeks with the lack of predisposing risk factors (immunosuppression, xerostomia, medications) for candidal infection (23).

The diagnosis of oral candidiasis can be established solely on clinical exam or may be augmented with the use of exfoliative cytology, culture, or biopsy. On smear, budding oval yeast forms with nonbranching septate pseudohyphae with blastocysts are noted. On biopsy specimens, fungal elements invading the parakeratin layer of the epithelium can be seen (Fig. 51.5) (23,24).

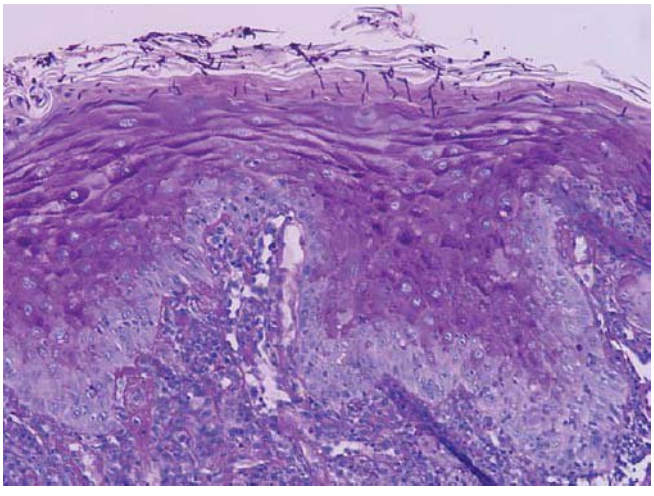


Figure 51.5 Periodic acid-Schiff staining of a biopsy specimen with candidal invasion of the parakeratin layer of epithelium.

A wide variety of topical and systemic treatment options are available. For the limited common forms of acute infection, topical agents are typically employed prior to use of to systemic antifungal agents. Topical therapies come in the form of lozenges (clotrimazole), tablets (miconazole), suspensions (nystatin and amphotericin B), and creams (ketoconazole). Oral agents typically include the azole class of antifungals (fluconazole, ketoconazole, and itraconazole) (23,24).

The length and type of treatment is dependent upon the presentation (acute vs. chronic), patient characteristics (immunocompromised), and response to the initiation of therapy. Although the length of treatment varies with respective medication, treatment for at least 2 to 3 weeks is common with most agents. Drug resistant forms of *Candida* may be seen in patients requiring longer courses of antifungal therapy. Oral agents are typically used in patients at recalcitrant presentations or when a significant risk of developing systemic infection exists (22–24).

Denture-Related

Denture-related stomatitis occurs in up to 70% of denture wearers and is highest in the elderly, women, smokers, and individuals with compromised immune function. Causes include includes poor hygiene and continual (night-time) denture use. Colonization with *C. albicans* and with the formation of resistant biofilms on the denture result in a presentation that is resistant to use of nystatin oral rinses. Culture of the denture can help confirm the diagnosis (24,25).

Denture stomatitis, also known as chronic atrophic candidiasis, has been described to have three subtypes of presentation that include:

Type I—localized inflammation
Type II—diffuse erythema involving the denture-bearing mucosa
Type III—papillary hyperplasia on mucosa (Fig. 51.6) (23,24).

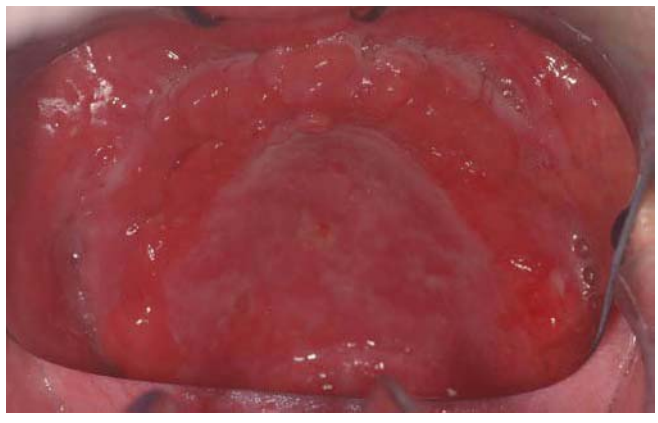


Figure 51.6 Erythema and papillary hyperplasia seen with denture stomatitis.

Poor fitting dentures exacerbate oral trauma through rough edges and inadequate contact spots and should be addressed with routine maintenance. The importance of sanitization with commercially available denture cleaners needs to be emphasized to address the formation of biofilms. Treatment with oral fluconazole or topical clotrimazole cream and nystatin (to the mouth and denture) may require 1 month of treatment for resolution (25).

Noncandidal Fungal Etiologies

Noncandidal etiologies of fungal infections of the oral cavity that can present as stomatitis include paracoccidioidomycosis, histoplasmosis, and mucormycosis.

Paracoccidioidomycosis is primarily seen in South America (Brazil, Colombia, and Venezuela) and is associated with smoking, poor nutrition, and alcohol abuse. It affects the mucous membranes, lymph nodes, lungs, and bones. Chronic presentations are more common than subacute and more likely to be associated with mucosal lesions. Painful oral cavity lesions are seen in about 60% of patients. The gingiva is the most commonly affected site with involvement also seen in the soft palate, lower lip, and tongue (26). The classical clinical presentation is a superficial ulcer with granular appearance and hemorrhagic points (Table 51.3). Treatment involves use of antibacterials (sulfamethoxazole) and antifungals (itraconazole and amphotericin B) and is dependent upon the clinical presentation (27).

Histoplasmosis is caused by the organism *Histoplasma capsulatum*. It is most commonly found in the Ohio and Mississippi River Valley regions of the United States and in South America (Argentina and Brazil). Infection results from inhalation of fungal spores that can be found in caves, as a result of birds and bats, or from working around chickens. Infection is most problematic in immunocompromised patients. Mucocutaneous lesions are more common in South America than is seen with the North American HIV-infected patients (27). Oral lesions vary and may present as papules, patches, ulcers, or vegetations. Patients may present with only oral ulceration without the finding of extraoral manifestations of histoplasmosis (28). The clinical appearance of the oral findings may mimic squamous cell carcinoma. Treatment involves antifungals, such as itraconazole and amphotericin B, and may require lifetime suppressive therapy in immunocompromised populations (27).

Mucormycosis is a life-threatening invasive fungal infection that occurs predominantly in patients with diabetes who are prone to ketoacidosis. It may also present in neutropenic and posttransplant patients or associated with malignancy (leukemia). Palatal ulceration and necrosis are classic for the rhinocerebral presentation of mucormycosis (29). Vascular invasion by hyphae with thrombosis and infarction of tissue is seen on biopsy specimens. A mortality rate of greater than 40% exists. Treatment requires the removal of the underlying risk factor, aggressive surgical intervention, and systemic antifungal therapy (27).

TABLE 51.3 LIST OF THE MOST COMMON CAUSES OF GRANULOMATOUS ORAL/PERIORAL CONDITIONS

Foreign body reaction (suture, amalgam)
Tuberculosis
Leprosy
Cat-scratch disease
Tertiary syphilis
Histoplasmosis
Cryptococcosis
Blastomycosis
Paracoccidioidomycosis
Sarcoidosis
Crohn disease
ORG

Adapted from Alawi F. Granulomatous diseases of the oral tissues: differential diagnosis and update. *Dent Clin North Am* 2005;49: 203–221.

Viral

Herpes Simplex Virus

Primary herpetic gingivostomatitis is predominantly the result of herpes simplex virus-1 (HSV-1) and occurs in 25% to 30% of children (30). Clear yellowish pinhead vesicles develop after a prodrome of fever, anorexia, and malaise. Vesicles appear on keratinized tissue such as the attached gingiva, hard palate (Fig. 51.7), and the lip at the vermillion border. The vesicles contain active virus and are considered very contagious; however, the contagion potential drops rapidly after rupture. Rupture occurs within hours revealing irregular ulcers covered by a yellow-gray membrane. The oral presentation is variable in extent but is typically asymptomatic. Lymphadenitis and odynophagia may accompany the presentation. Healing typically occurs in 7 to 10 days. Primary herpetic gingivostomatitis in an adult may present very similar to mononucleosis with predominantly pharyngotonsillar symptoms (22,30).



Figure 51.7 Herpes ulceration of the hard palate.



Figure 51.8 Herpes labialis.

During the asymptomatic latent state, the virus resides within the sensory ganglion of the trigeminal nerve. Exposure to a stressor leads to viral replication and reexpression with a subsequent vesicle formation. Stressors may include fever, radiation, chemotherapy, HIV infection, UV light exposure, pregnancy, and surgery (22,30).

Secondary or recurrent herpes affects labial and perilabial surfaces (cold sores) in the majority of cases and is typically unilateral (Fig. 51.8). Secondary presentations within oral cavity are uncommon yet when present occur on gingiva or palate mucosa and do not occur on mobile soft tissues. Multiple small vesicles may coalesce to larger lesions. Treatment is dictated by symptoms. Lubrication may reduce crusting of overlying lesions and enhance healing.

Treatment options include the use of topical agents and systemic antivirals; however, therapy primarily directed to symptom control. When treatment is initiated at the time of prodromal symptoms, reduction in healing time and pain reduction has been reported. Antiviral therapy is unnecessary in the setting of primary infection unless concern over progression to encephalitis arises. Long-term clinical ulceration should prompt investigation for other vesiculobullous conditions rather than an HSV-associated diagnosis (30).

HIV-Associated Stomatitis

HIV-positive patients presenting opportunistic oral lesions are likely to have higher viral loads and lower CD4 counts. Stomatitis may be the first manifestation of an undiagnosed HIV infection. Awareness of this association can prompt HIV testing and facilitate early diagnosis and treatment (31). In the HIV-positive patient undergoing treatment, emergence of stomatitis can signify the failure of an existing antiretroviral regimen.

Oral presentations seen in the HIV-positive population includes candidiasis, oral hairy leukoplakia, recurrent aphthous-like ulceration, orolabial HSV, oral warts, and HIV-associated periodontal disease such as linear gingival erythema (32).

Pseudomembranous candidiasis is the most common form of stomatitis seen in HIV-positive patients (31). Prophylactic fluconazole is not recommended except for in severe or recurrent cases because of concerns it could lead to multidrug resistance. Topical agents are recommended for patients with a CD4 counts greater than 200 cells/mm^3. Culture and sensitivity is advised if the candidiasis does not respond to initial therapy (32,33).

For RAS, initial treatment approaches with topical and systemic steroids is the same for HIV-positive as for HIV-negative patients. Thalidomide has been used in severe refractory aphthous stomatitis in two randomized, double-blind, placebo-controlled trials; however, drug toxicity can limit treatment. Cytomegalovirus (CMV) may also present with painful oral ulcerations and can be associated with the subsequent development of CMV-associated retinitis and encephalitis (32).

In HIV-positive patients with orolabial herpes, if the CD4 T-cell count is greater than or equal to 200 cells/mm^3, topical treatments should be considered first and continued until lesions resolve. Use of a systemic antiviral agent is advocated if CD4 counts are below 200 cells/mm^3, when lesions are extensive, or if a patient did not respond to topical therapy (32).

Epstein-Barr virus is the causative factor in the development for oral hairy leukoplakia in HIV-positive and immunocompromised patients. It has the pathognomonic appearance of elongated filiform papillae associated with white plaques that typically present on the lateral aspect of the tongue. The morbidity of oral hairy leukoplakia is usually low and treatment is reserved for symptomatic presentations (32,33).

Acute necrotizing ulcerative gingivitis, commonly known as trench mouth, can be seen in HIV-positive patients and can spread to involve surrounding oral mucosa causing a necrotizing stomatitis. Fortunately, this condition responds rapidly to local debridement and disinfectants like chlorhexidine or povidone–iodine (33).

Immune reconstitution inflammatory syndrome (IRIS) can be seen in patients with AIDS with oral opportunistic infections, such as candidiasis, that are initiating highly active antiretroviral therapy (HAART). Cell-mediated immunity is suddenly raised and results in an exaggerated response against the opportunistic infections and paradoxically worsens the patient's symptoms. It is recommended to treat the opportunistic infections before starting HAART in order to avoid IRIS (33).

Tuberculosis

Although uncommon, primary pulmonary tuberculosis infection can disseminate to the head and neck region. Primary tuberculosis of the head and neck is also rare and can occur due to direct contact with infected sputum at sites of mucosal trauma in the oral cavity. The clinical presentation of tuberculosis in the oral cavity varies and

may present as a chronic nonhealing ulceration or a discrete submucosal mass. Biopsy demonstrates a granulomatous inflammation and mycobacterial organisms. Sputum cultures assessed with mycobacterial DNA amplification may be used to discriminate between differing strains of *Mycobacterium* that can present in the oral cavity. Chest imaging and tuberculin skin testing are required in the assessment of these patients. Treatment typically requires multiple months of combination antimycobacterial therapy until three consecutive posttreatment sputum cultures are negative (34).

IMMUNOLOGIC

Vesiculobullous Lesions

Diagnoses in this category can be divided into oral intramucosal and submucosal bullous diseases. The submucosal diseases include mucous membrane pemphigoid (MMP), bullous pemphigoid (BP), and epidermolysis bullosa acquisita (EBA). The most notable intramucosal disease that is discussed is pemphigus vulgaris (PV).

Mucous Membrane (Cicatricial) Pemphigoid

MMP, also known as cicatricial pemphigoid, is a chronic autoimmune subepithelial blistering disorder. It has an incidence between 1 in 12,000 to 20,000 and is typically diagnosed in the fifth to sixth decade of life. It is more common in women (1.5:1 ratio) and does not appear to have a racial or geographic predilection (16,35).

MMP can affect both cutaneous and mucosal surfaces and varying degrees of presentation. It most commonly affects the oral and ocular mucosa but may also occur in nasopharynx, esophagus, larynx, and urogenital tract (Fig. 51.9). The majority of patients present with a desquamative gingivitis (Fig. 51.10) and mucosal involvement of the buccal mucosa, palate, alveolar ridge, tongue, and lower lip is common.

After bullae present and rupture, irregular-shaped erosions are present. The term "cicatricial" describes the severe



Figure 51. 9 Blistering in the oral cavity seen in MMP.



Figure 51.10 Desquamative gingivitis of MMP.

adhesions that can form with healing. Resultant webs and stenosis can occur within the aerodigestive tract. Up to 40% of patients will develop scarring of the conjunctiva with scleral fusion, entropion, with potential loss of vision (16,35).

On biopsy, a subepithelial separation with inflammatory infiltrate is noted (Fig. 51.11). DIF of perilesional skin shows linear deposition of IgG, IgA, and/or C3 along the epithelial basement membrane zone. Autoantibodies to multiple components of the basement membrane including BP antigen, laminin 5 and 6, and type VII collagen result in the immune response. Indirect immunofluorescence reveals serum autoantibodies binding to the epidermal or dermal side of salt-split skin (16,35).

Patients who present solely with oral lesions have a better prognosis than those in whom a significant cutaneous component also exists. The mainstay for treatment for MMP has traditionally been corticosteroids. Treatment-related side effects have lead to interest in corticosteroid-sparing regimens that have utilized azathioprine, mycophenolate mofetil, cyclophosphamide, and methotrexate. Patients who are unresponsive to conventional treatment options

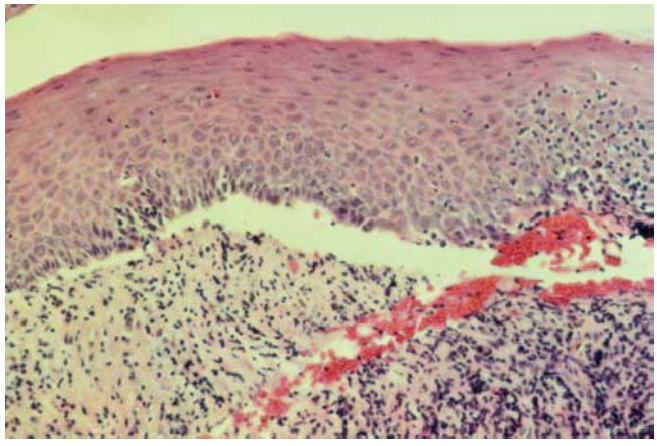


Figure 51.11 H and E histopathology demonstrating the subepithelial split of MMP with resultant blister formation and inflammatory infiltrate.

may be considered candidates for intravenous immunoglobulins, plasmapheresis, and "biologic" therapy (rituximab, etanercept, infliximab) (35,36). Patients require ophthalmology consultation because of the potential complication of symblepharon formation.

Bullous Pemphigoid

BP is a cutaneous subepidermal autoimmune disorder. Oral manifestations can be seen in 10% to 40% of patients and ocular involvement is atypical. BP is uncommon in the United States and is diagnosed most frequently in Europe in patients over 60 years of age (16).

The blistering skin presentation can be widespread and several subtypes of the clinical presentation exist (Fig. 51.12). Onset can be associated with exposure to ultraviolet light, radiation therapy, or as a reaction to selected medications (nonsteroidal anti-inflammatory drugs, antibiotics, etc.).

Diagnostic findings are similar to MMP with DIF studies on biopsy specimens. Treatment alternatives also parallel those offered patients with MMP, yet topical therapies play greater role in management because the advanced age of many patients and the potential side effects with prolonged use of systemic agents. In most patients treated for the condition, the disease remits in 2 to 5 years yet can be life threatening in debilitated patients (16,36).

Epidermolysis Bullosa Acquisita

EBA is a rare bullous condition where autoantibodies develop to type VII collagen of the basement membrane of skin and the mucosa of the upper aerodigestive tract. The inherited form of this disease is called EB. In both conditions, mechanical trauma causes blistering and resultant scarring and severe atrophy of the affected tissues. The scarring and disability seen with EBA is far less than that seen with EB.



Figure 51.12 Cutaneous manifestations of BP.

The clinical presentation of EBA does not manifest until early adulthood and can be easily mistaken for other blistering conditions that present later in life. The diagnosis should be confirmed by biopsy with DIF to rule out other mucocutaneous bullous diseases. High-dose corticosteroids, in combination with other immune-modulating agents, can be effective in addressing these conditions. Unfortunately, the oral scarring and atrophy can lead to debilitating microstomia (37).

Pemphigus Vulgaris

PV is a potentially fatal autoimmune mucocutaneous bullous disease caused by IgG autoantibodies binding to desmoglein 3 and desmoglein 1.

Variants of PV exist and include mucosal-dominant PV (target antigen is desmoglein 3) and mucocutaneous PV (target antigen is both desmoglein 1 and desmoglein 3). The incidence is 1 to 6 per million per year with mean onset at 50 to 60 years of age with a slight female predilection (35). There is a strong association with certain ethnic groups including Ashkenazi Jews and individuals from the Mediterranean and Southern Asia. PV may be seen in association with other autoimmune disorders such as rheumatoid arthritis, myasthenia gravis, systemic lupus erythematosus (SLE), and pernicious anemia (16).

Oral involvement is the hallmark of the clinical presentation of PV and is seen in up to 90% of patients. Most patients present with oral disease for greater than 1 year prior to manifesting to the cutaneous findings of PV. All mucosal surfaces within the body can demonstrate involvement. Lesions present as fluid-filled blisters that break and expose erythematous irregular ulcerated lesions that are painful. The typical oral sites involved include the buccal and palatal mucosa, ventral tongue, and lips (Fig. 51.13). In severe presentations, all sites may be involved and give the appearance of a desquamative gingivostomatitis with cheilitis (Fig. 51.14A and B). Other mucosal surfaces that may be involved include the pharynx, esophagus, conjunctiva, nasal cavity, vagina, penis, and anus (16,35).

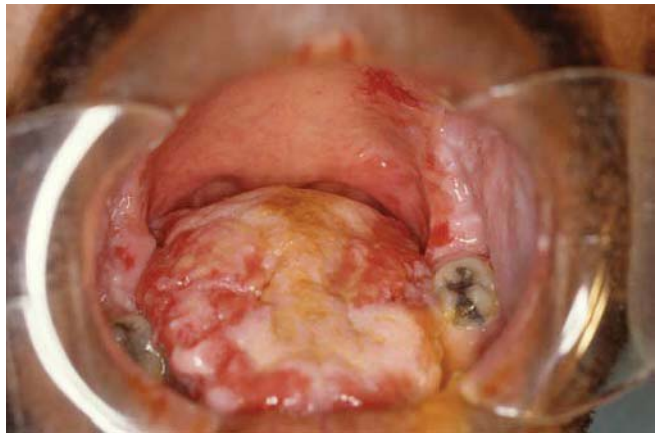


Figure 51.13 Oral findings of PV.



A B

Figure 51.14 Desquamative gingivitis **(A)** and cheilitis **(B)** of PV.

A positive Nikolsky sign, where slight rubbing of the skin or mucous membranes leads to bullae formation or sloughing of epithelium, may be seen. This is the result of the loss of cell-to-cell adhesion through damaged desmosomal proteins and results in bullae formation. The oral epithelium expresses cadherin-type cell adhesion molecule desmoglein 3 to which autoantibodies form. Bullae in PV develop immediately above the basal cell layer (suprabasal bullae). A "tombstone appearance" of a single row of cuboidal basal cells is typically seen below the bullae (16).

Diagnosis is established through a perilesional biopsy that allows for DIF assessment for intercellular deposits of IgG and complement C3. Assays by indirect immunofluorescence microscopy or enzyme-linked immunosorbent assays can assess serum antibody titers (Fig. 51.15) (35).

Systemic immunosuppression with corticosteroids is the mainstay of treatment to achieve control and long-term remission (16). A consensus statement from the International Pemphigus Committee was published 2008 on the definitions of disease and therapeutic response in an attempt to facilitate future clinical advances. The group defined the failure of therapy as the continued development of new lesions, extension of old lesions, or failure of established lesions to begin to heal despite 3 weeks of therapy with 1.5 mg/kg/day prednisone equivalent with or without the following therapies (for 12 weeks): cyclophosphamide 2 mg/kg/day, azathioprine 2.5 mg/kg/day, methotrexate 20 mg/wk, and mycophenolate mofetil 3 g/day. (38).

Pulse therapy of steroids (isolated high-dose noncontinuous dosing) has been postulated as method to decrease the side effects of conventional steroid administration in populations requiring long-term therapy. Mentink et al. assessed the utility of high-dose pulse steroid therapy in PV in a randomized placebo-controlled trial. Dexamethasone was given (300 mg three times per month) in addition to conventional therapy (prednisolone 80 mg/day with taper over 19 weeks and azathioprine 3 mg/kg/day). The trial showed no benefit to pulse therapy compared to placebo in the treatment of PV (39).

In another randomized, double-blind placebo controlled study, dapsone was utilized as a glucocorticoid-sparing agent in individuals unable to tolerate previous steroid taper. Although not statistically significant, dapsone did allow for a decrease in patients' steroid dosing levels. However, because of the expected side effect of methemoglobinemia, patients require close monitoring and were discontinued from therapy if hemoglobin levels fell below 9 g/dL (40).

Additional treatment options for recalcitrant disease are similar to those discussed with MMP and may include

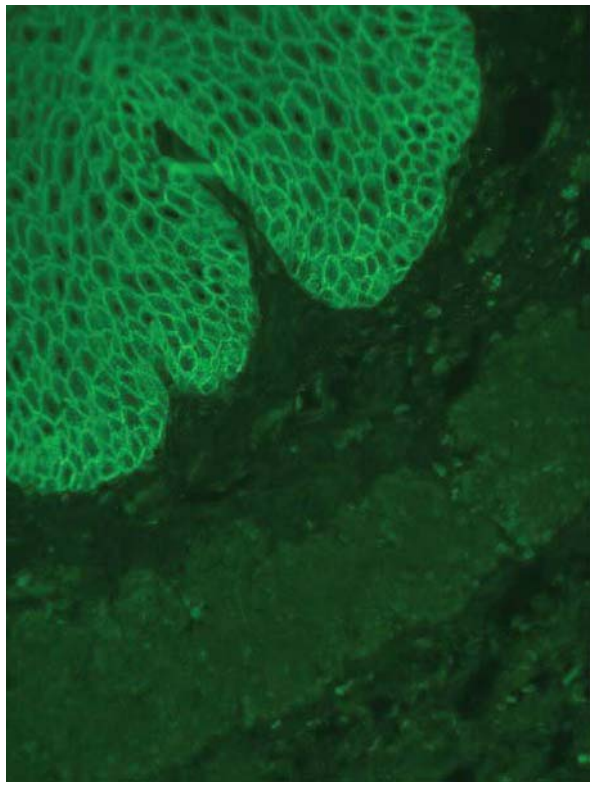


Figure 51.15 DIF microscopy findings seen in PV with cell surface deposition of IgG.

TABLE 51.4 LIST OF NEOPLASTIC AND PROLIFERATIVE CONDITIONS ASSOCIATED WITH PARANEOPLASTIC PRESENTATION OF PEMPHIGUS

Non-Hodgkin lymphoma
Chronic lymphocytic leukemia
Thymoma
Castleman disease
Waldenstrom macroglobulinemia
Hodgkin lymphoma
Monoclonal gammopathy
Systemic mastocytosis
Squamous cell carcinoma—tongue, vagina, skin
Bronchogenic carcinoma
Endometrial carcinoma
Liposarcoma
Poorly differentiated sarcomas
Leiomyosarcoma
Dendritic cell sarcoma
Malignant nerve sheath tumor

(Bold type indicates most common etiology.)
Adapted from Said S, Golitz L. Vesiculobullous eruptions of the oral cavity. *Otolaryngol Clin North Am* 2011;44:133–160.

plasmapheresis, cyclosporine, or cyclophosphamide (16,35). PV can be fatal if blisters denude large areas of skin and mucous membranes. The mortality has declined to 10% with the use of steroids; however, complications secondary to treatment remain a problem (16).

Paraneoplastic pemphigus can occur as a result of a number of malignancies.

Table 51.4 lists the proliferative conditions associated with this entity. Hematologic neoplasms are responsible for greater than 80% of all presentations (16).

Chronic Ulcerative Stomatitis

Chronic ulcerative stomatitis (CUS) is a rare disease of the oral mucosa that typically presents on the tongue of postmenopausal women as painful nonhealing ulcers. The appearance of the lesions can be mistaken for OLP and biopsy is required to differentiate the two entities. Diagnosis requires direct autoimmunofluorescence studies for autoantibodies to the p63 transcription factor, a member of the p53 family of proteins. The etiology of CUS is unknown. As opposed to lichen planus, which is primarily treated with steroids, CUS is responsive to treatment with antimalarials such as hydroxychloroquine (41,42).

SYSTEMIC CONDITIONS

Lupus

SLE is an autoimmune condition that has a broad range of clinical manifestations including the presentation of stomatitis. Oral ulceration is reported in 5% to 25% of patients with recurrent lesions primarily affecting the palate, buccal mucosa, and gingiva. Oral findings can vary in appearance with focal lesions demonstrating lichenoid or granulomatous changes. Biopsies show epithelial acanthosis with focal basal cell liquefaction and lymphocytic infiltrate. Patients can experience stomatodynia, xerostomia, and recurrent candidiasis. "Lupus cheilitis" involving predominantly the lower lip may also be seen (16,43).

Discoid lupus erythematosus (DLE), a variant of SLE limited to the skin, can present with oral lesions that appear similar to erosive lichen planus (43). The oral lesions of DLE are frequently unilateral yet may be multiple, whereas with lichen planus is typically bilateral and symmetric (37). DIF studies and/or histopathologic examination of cutaneous lesions may aid in differentiating between the two diagnoses (44).

Wegener Granulomatosis

Wegener granulomatosis (WG) is a systemic condition of unknown etiology that is characterized by acute necrotizing granulomas of the aerodigestive tract, a focal vasculitis of small to medium sized vessels, and glomerulonephritis. Oral involvement is characterized by a "strawberry gingivitis" resulting from a friable granular hyperplasia of the gingiva. Erosion of the underlying alveolar bone may result in dental instability and need for extraction. Involvement of the buccal mucosa and palate may also occur but the clinical appearance of these lesions is variable and may mimic aphthous ulceration (43,45). Diagnosis is aided by assay for antineutrophil cytoplasmic antibodies with the majority of WG patients demonstrating c-ANCA positivity.

Crohn Disease

Crohn disease is an inflammatory bowel disease (IBD) of unknown etiology that is characterized by recurring episodic inflammation of the bowel that can result in strictures and fistulae. Greater than 50% of patients present with oral findings that can be nonspecific and include cobblestone changes to the buccal mucosa; granulomatous ulceration; and a firm, painless lip swelling (34,43). Deep linear ulcerations embedded within the base of hyperplastic tissue folds in the gingivobuccal sulcus are considered pathognomonic for the disease (34). The oral lesions typically precede the intestinal lesions by years. Additional potential findings include angular cheilitis or a mucogingivitis with erythematous macules (34,43).

A prospective study by Harty et al. revealed that greater than 40% of patients had oral findings at the time of initial diagnosis of their Crohn disease. A subset underwent biopsy of the oral lesions and noncaseating granulomas were noted in all cases. The authors concluded that the oral cavity could be a source of diagnostic tissue for this disorder but did not demonstrate a correlation between presence of oral lesions and overall disease severity (46).

Colonoscopy is necessary to establish the diagnosis and demonstrates skip lesions that differentiate the Crohn from UC. Laboratory assay is nonspecific (34).

Ulcerative Colitis

UC is an IBD of unknown etiology that is characterized by recurring episodic inflammation of the mucosal layer of the large intestine that is associated with rectal bleeding, colitis, and abdominal pain. Extraintestinal manifestations of disease are common but presentation of oral lesions is more frequent in Crohn than with UC. In one case series, the most common initial presentation of UC was oral aphthae in a patient with anemia (with or without abdominal symptoms) (47).

Patients with UC and Crohn disease may also develop a rare condition called pyostomatitis vegetans. Referred to as a "snail-track," on exam it presents as a line of elevated yellowish pustules on an erythematous mucosa that typically occurs on the buccal and labial mucosa (43). Biopsy demonstrates intraepithelial and subepithelial microabscesses and focal acantholysis. Given that this may be the first sign of an IBD, prompt recognition of this presentation can lead to early evaluation by colonoscopy and initiation of treatment before the onset of abdominal complications. After diagnosis, the clinical course for patients with oral manifestations tends to parallel the activity of the IBD. As a result, a patient's oral examination may be used as a reflection of their response to treatment (47).

Pregnancy

There are several physiologic changes that occur in the oral cavity during pregnancy. "Pregnancy gingivitis" can affect approximately 50% of women with a resultant inflammation and hyperplasia of the gingival mucosa. This can range widely from asymptomatic to severe in presentation with pain and bleeding that can necessitate surgical intervention. Elevated estrogen and progesterone levels are responsible for the increased vascular permeability and decreased immune resistance, which can exacerbate worsening of a preexisting gingivitis (48).

Lobular capillary hemangiomas, also known as pyogenic granulomas, occur in 2% of pregnant women in the oral cavity. They are asymptomatic pedunculated lesions that grow rapidly and bleed easily. Dental plaque and pregnancy-associated gingivitis may trigger the formation of these lesions at any point during the pregnancy and spontaneous resolution after delivery is typically seen (48).

Impetigo herpetiformis, considered by some a variant of pustular psoriasis, is a rare serious condition that can develop the third trimester that is associated with hypocalcemia. This diagnosis has a distinctive cutaneous appearance that initiates on flexural and intertriginous areas of the body and then spreads with erythematous patches and grouped sterile herpetiform pustules that erode and crust. The tongue and oral cavity may become involved with erosive lesions and demonstrate an appearance similar to geographic tongue. The condition continues to worsen during the pregnancy and can pose a significant risk to the fetus and requires early diagnosis, intravenous hydration and treatment with antibiotics, steroids, and may necessitate the induction of labor. Resolution of symptoms is noted to occur rapidly after delivery (48,49).

Oral manifestations of diseases such as PV and Behcet can be exacerbated by pregnancy (48).

Behcet Disease

Behcet disease is a disorder characterized by a classic triad of findings including recurrent aphthous ulceration, uveitis, and genital ulcers. It is most common in the Mediterranean region and in nations along the ancient "Silk Road" (Turkey, Iran, Korea, and Japan). Human leukocyte antigen (HLA) subtype B51 is associated with susceptibility to the disease and a relationship to streptococcal infection has been postulated yet the etiology of this disease remains unknown. The recurrent oral ulcers, typically the first manifestation of the disorder, are painful and can severely limit oral hygiene. This, in turn, can result in an increase in bacterial colonization and worsen the existing ulceration. Oral health (plaque accumulation, probing depth, gingival inflammation, and number of extracted teeth) has been shown to correlate with overall disease severity (50).

The typical oral presentation of Behcet disease is recurrent aphthous ulceration (greater than 3 episodes in 12 months) persisting for up to 6 weeks with each episode. Multiple ulcers of varying sizes with surrounding erythema appear on the soft palate, buccal mucosa, and tongue and can heal with significant scarring. Of note, the ulcerations with Behcet are painful unlike those seen with other connective tissue disorders such as SLE. Mucosal involvement may extend to include the hypopharynx and larynx and result in stenosis. Diagnosis relies on clinical findings and no specific laboratory assay is characteristic of the disorder. Treatment involves topical and systemic steroids with immunosuppressives utilized in severe cases. Low-dose colchicine can effectively aid management of the mucocutaneous manifestation of the disease (51).

Sarcoidosis

Sarcoidosis is a multisystem disorder of unclear etiology. Both genetic and environmental factors appear to play a role in development. Oral findings may be the first evidence of the disease in patients. Submucosal nodular swelling and painless ulceration of the tongue, buccal mucosa, and palate may be seen. Patients may also demonstrate diffuse gingival enlargement. Lupus pernio, presenting a chronic violaceous indurated lesions, may occur on the lips. Biopsy of oral ulcerations will demonstrate noncaseating granulomas and that are nonspecific relative to the differentiation

from other granulomatous disorders. There is no definitive test for sarcoidosis and diagnosis is based on a constellation of signs and symptoms (34,43).

Hematologic Diseases

Cyclic hematopoiesis is a rare disorder that is secondary to episodic bone marrow failure that results in wide fluctuations in neutrophil, platelet, and reticulocyte counts. Patient also experience transient fever, aphthous ulceration and gingivitis, and recurrent skin infections in conjunction with the neutropenia at intervals of approximately every 3 weeks. It most commonly occurs in children and resolve with age but may also present in adults (1).

Stomatitis may be associated with any of the leukemias but is most common with acute and myeloid presentations (1). Oral findings parallel the hematologic disturbance of the individual patient such that oral petechial hemorrhages of the palate are seen with thrombocytopenia and deep mucosal ulcerations and candidiasis will occur in the neutropenic patient. Gingival hyperplasia from the infiltration by the malignant cells of leukemia or lymphoma can also be seen (1,43).

NUTRITIONAL

Malnutrition and Deficiencies

Iron-deficiency anemia can present with angular cheilitis and atrophic glossitis. With the development of atrophic glossitis, the dorsal surface of the tongue appears smooth and red with the loss of fungiform and filiform papillae. The clinical presentation may be preceded by glossodynia. These findings are seen in the setting of a microcytic, hypochromic anemia in conjunction with decreased serum iron and ferritin and elevated total iron-binding capacity (1,52).

Plummer-Vinson syndrome is a rare disorder that presented with a spectrum of iron-deficiency anemia, dysphagia, and esophageal strictures in middle aged women who were associated with an increased risk of oropharyngeal cancer. The iron deficiency associated with the syndrome would result in patients presenting with glossitis, glossodynia, and angular cheilitis at the time of evaluation (1).

Megaloblastic anemia occurs as a result of B12 or folate deficiency and may present in the elderly or in individuals on a vegetarian diet. It may also be seen in patients with HIV, with pernicious anemia, and with gastrointestinal disorders. Patients will typically present with atrophy of oral mucosa, glossitis, and angular cheilitis (1,52).

Water-soluble vitamins that impact the health of the oral mucosa are B2 (riboflavin), B3 (niacin), B6 (pyridoxine), B9 (folic acid), B12 (cyanocobalamin), and C (ascorbic acid). The water-soluble vitamins require regular intake or supplementation because of the lack of durable storage within the tissues that is seen with fat-soluble vitamins. Patients with a deficiency of one of the various B vitamins can present with atrophic glossitis, glossodynia, and angular cheilitis. Vitamin C deficiency presents with mucosal petechiae and hemorrhagic gingivitis with hypertrophy (1).

IDIOPATHIC

Recurrent Aphthous Stomatitis

RAS is defined as recurrent ulcers confined to the mouth and seen in the absence of systemic disease. RAS typically first appears in childhood and abates by the third decade of life (53). There is a familial tendency with a HLA predilection (53). The reported prevalence ranges from 5% to 21% and a lower incidence is noted in smokers (2,22). It is more common in women, in Caucasians, and in people of high socioeconomic status (2).

Independent risk or causative factors of RAS have not been clearly established in population-based studies. The causative factors for an outbreak include trauma, food products (chocolates, nuts tomatoes, and wheat), stress, medications (NSAIDS, beta blockers, ACE-I), and vitamin deficiencies (B1, B2, B6, folate, zinc, and iron) (2,53). No relationship exists to herpes simplex infection. It is thought to be related to both cell-mediated immunologic causes and antibody-dependent cell-mediated cytotoxicity.

On clinical presentation, pain typically exceeds the size of the lesions that may be found on the buccal mucosa, ventral tongue, floor of mouth (Fig. 51.16), labial mucosa, soft palate, and tonsillar fossa. The lower vestibule most commonly affected and a predilection for nonkeratinized and mobile tissue is noted (2,53). The time between episodes could vary from weeks to months. Patients typically have one ulcer but may have up to three ulcers at any one time. Table 51.5 demonstrates a severity scale for RAS that can be used to qualify presentations (54).

The common ulcers of RAS are classified as minor, major, and herpetiform aphthae. Minor aphthae represent 80% of cases are less than 1 cm (2,22,55). Major aphthae are 1 cm

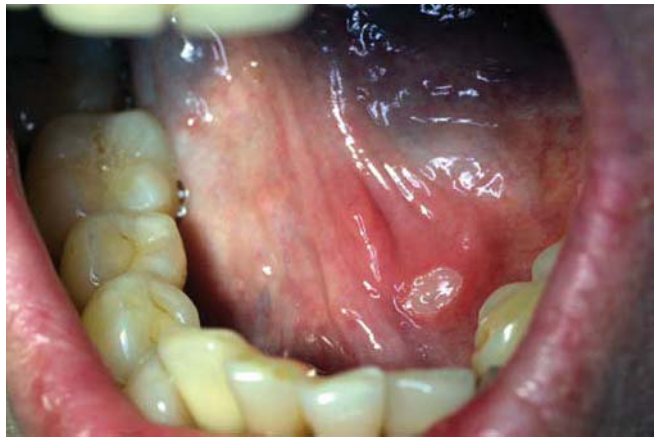


Figure 51.16 RAS ulcer on the floor of mouth.

TABLE 51.5 GRADES OF RAS

Grade	Severity	Findings
1	Mild	Limited number of ulcers with infrequent presentation. Mild functional impairment and pain. Near-normal oral intake
2	Moderate	Intermediate frequency and number of oral ulcers with moderate functional impairment and pain. Modest impact on oral intake with increasing social embarrassment
3	Severe	Frequent presentations with numerous ulcers resulting in major functional disability, severe dysphagia/odynophagia

Adapted from Hello M, Barbarot S, Bastuji-Garin S, et al. Use of thalidomide for severe recurrent aphthous stomatitis: a multicenter cohort analysis. *Medicine (Baltimore)* 2010;89(3):176–182.

or greater in size. Healing with simple recurrent aphthae occurs spontaneously in 10 to 14 days, and unlike vesiculobullous disease, the ulcers heal without scarring (53).

"Herpetiform" or clusterform aphthae (Fig. 51.17) are a misnomer given the lack of relationship to HSV. They are less common than simple recurrent aphthae. Patients exhibit multiple lesions at presentation (upward of 20) that may coalesce into what appears to be individual larger ulcers. Ulcers are not indurated and patients may be febrile during presentations. Lesions tend to be present more commonly than the intermittent presentation seen with simple aphthae. Treatment includes topical steroids in a cream or mouthwash (or use a tetracycline mouthwash if febrile).

An uncommon form of presentation includes craterform ulcers. These may last for months and are associated with deep necrosis and scar formation. Patients are febrile with adenopathy and very symptomatic during presentations. Acute episodes require oral antibiotics and steroids and patients may be transitioned to topical therapy between outbreaks.



Figure 51.17 Herpetiform RAS of ventral tongue.

The differential diagnosis for patients with recurrent oral ulceration is wide and requires careful consideration for alternative diagnoses. Recurrent HSV, Behcet disease, erythema multiforme (EM), periodic fevers with aphthous stomatitis, pharyngitis, and adenitis (PFAPA), Crohn disease, and UC may all present clinically with oral findings suggestive of RAS (2).

As with many sources of stomatitis, the mainstay of treatment of symptomatic patients includes the use of steroids. When using topical steroids, triamcinolone acetonide with Orabase is not considered as effective as more potent glucocorticoids, such as clobetasol propionate (0.05%) or fluocinonide (0.05%) (2). Perilesional injection of steroid is also an option for solitary major aphtha.

Treatment of patients with RAS also requires counseling on the avoidance of potential triggers, advocating for good oral hygiene, use of topical anesthetics for symptom control, and use of antimicrobial mouthwashes such as tetracycline or chlorhexidine. For more severe presentations, systemic therapies are varied and include oral steroids, colchicine, dapsone, clofazimine, levamisole, pentoxifylline, thalidomide, infliximab, and etanercept (2). However, it should be noted that few adequately powered clinical trials have tested the efficacy of therapeutic agents for RAS (53).

In a randomized, double-blinded, placebo controlled trial of pentoxifylline for RAS only a limited benefit with decrease in mean ulcer size was noted. The authors concluded that pentoxifylline may have a role in patients unresponsive to other treatment options but should not be considered first-line treatment for RAS (55).

In a double-blinded placebo controlled trial, vitamin B_{12} was assessed as a treatment option for RAS. Sublingual B12 (1,000 mcg) was given for 6 months. Significant improvement was noted regardless of serum levels of B12. During the last month of treatment, 74% had attained "no aphthous ulcer status" ($P < 0.01$) (56).

In a double-blinded randomized clinical trial, colchicine (0.5 mg/day) was compared to low-dose prednisolone (5 mg/day) for RAS. The study included a 3-month trial with 2-week assessment intervals. Both therapies were found to significantly reduce the presentation of RAS. However, less side effects were noted in the prednisolone group and it was considered by the authors to represent a better alternative for patients with frequent recurrence (57).

An uncommon variant of RAS is termed severe recurrent aphthous stomatitis (SRAS), also known as Sutton disease, that presents with overlapping attacks of craterform oral ulceration with deep necrosis (Fig. 51.18). Patients may be febrile with lymphadenopathy during episodes. SRAS also differs from RAS in that the time to healing is significantly longer and may result in problematic oral scarring. The effect on quality of life can be devastating as speech and swallowing are profoundly affected (54).



Figure 51.18 Crateriform ulcer of SRAS.

In a multicenter retrospective cohort study, thalidomide was found to be effective with 85% entering a complete remission within a median of 14 days of the start of treatment. Treatment was not without side effects with 84% of patients such as adverse events including somnolence (36%), paresthesia (18%), constipation (18%), and weight gain (16%). One in five adverse events was considered severe and included peripheral neuropathy, thromboembolism, and teratogenicity. After 40 months, 60% of patients were still receiving continuous or intermittent therapy.

The authors advocate the benefit of a low-dose maintenance regimen that appears to be effective and well tolerated in patients with SRAS (57).

Recurrent aphthous ulcers can be severe and refractory to treatment in patients with HIV. In some cases, HAART is the best treatment for intractable aphthous stomatitis in this setting (58).

Oral Lichen Planus

OLP is a chronic systemic disease of the skin and mucosal surfaces of unknown etiology. CD8+ T-cell-mediated autoimmune damage of epithelial basal cells is considered the mechanism of this disorder. The pathogenesis remains unclear (19,37,44). OLP occurs in 0.5% to 2.2% of the population and most commonly affects women over that age of 40 (37,44). OLP represents 9% of all white lesions affecting the oral cavity (37,44). It is a clinical diagnosis that may require histopathologic evaluation via biopsy in order to distinguish from dysplasia (37). The hypothetical risk of malignant transformation is controversial yet is considered to be very low (37). No association exists with OLP and habitual alcohol or tobacco use. Most patients diagnosed with OLP will not have associated CLP or involvement at any other mucosal sites in the body (44).

OLP most commonly affects the buccal mucosa (90%) but may also affect the dorsum of tongue, gingival, labial mucosa, and lower vermillion lip (Fig. 19A and B). With most cases of OLP, there are typically multiple lesions that are bilateral and symmetric. It may develop in sites of trauma in what is described as Koebner phenomenon (19). There are multiple described clinical presentations of OLP in the oral cavity and include reticular, popular, plaque-form, atrophic, ulcerative, and bullous forms (37).

OLP can be classified as reticular (white 23%), erythematous (atrophic 40%), and erosive (bullous, ulcerated 37%) (19). The reticular form is usually asymptomatic and exam reveals interlacing white lines (Wickham striae) on the buccal surface (Fig. 51.20). A variant of OLP, erosive OLP, demonstrates atrophic areas with erythema and varying degrees of ulceration and can present similar to desquamative gingivitis (19,22).

The differential diagnosis of OLP always includes oral lichenoid lesions, which can be caused by allergic reactions to dental restorative materials, drug reactions to certain medications, GVHD, or DLE (37). When biopsy is performed, OLP and oral lichenoid reactions share similar histologic features (dense of lymphocyte infiltration at the epithelium–connective tissue interface) and does not differentiate the two diagnoses (Fig. 51.21) (19).

CLP classically presents as pruritic, purple, polygonal, flat-topped papules, and plaques with predilection for the flexural wrists, dorsal feet, and pretibia. CLP does not preclude the finding of oral lesions and greater than 50% of patients with CLP will also have findings of OLP (19). It should be noted that a number of immune-mediated inflammatory dermatoses also cause notable oral manifestations, in addition to their more recognizable skin symptoms, and can be confused with CLP (37).

OLP is seen in 2.3% chronic hepatitis C patients and has been questioned as an extrahepatic manifestation of hepatitis C. In a study examining OLP and chronic hepatitis C in the general population of Brazil, a statistically significant relationship was noted between the two entities. However, other reports in literature dispute this association. Some authors advocate oral exam on hepatitis C patients and consideration for hepatitis C screening on OLP patients. Treatment of hepatitis C with IFN may induce or worsen lichen planus (59).

OLP runs its course over an average of 8 years, but can persist for decades. It often "burns out," but can leave the patient with permanent mucosal scarring. The risk of malignant transformation of lichen planus is very controversial because it has proven very difficult to measure, but is likely quite low. A high index of suspicion is necessary, however, on the part of the clinician, when lesions appear or behave atypically (37).

There is no cure and treatment is given to reduce the pain associated with presentation. Treatment should address oral hygiene and potential etiologies and include elimination of irritants, such as rough edges on dental restorations, spicy or acidic foods, and minimizing bacterial plaque with alcohol-free rinses (19,37). The aim of pharmacologic therapy is to control, rather than cure, the disorder. Reticular OLP does not typically require biopsy and may be treated with topical steroids if symptomatic (22).



Figure 51.19 OLP of the right buccal mucosa **(A)** and tongue **(B)**.

A variety of topical corticosteroids are available with variable efficacy. Preparations that contain adhesives with a steroid, such as triamcinolone in Orabase, will be more effective due to longer contact time with the affected mucosa. Candidal overgrowth can occur with the use of these agents. Systemic steroids can be used either as a high-dose short-term pulse or as a long-term low-dose to complement topical steroids (37,44).

Use of steroid-sparing agents, such as retinoids, topical cyclosporine, topical retinoids, topical calcineurin inhibitors and dapsone, have been reported but side effects may limit its use (19). Levamisole monotherapy is a treatment option for patients with chronic OLP who cannot take steroids (e.g., patients with diabetes, hypertension, malignancy) and has historically been used in combination with steroid therapy (60).

A Cochrane Collaboration review on the topic found that only a few therapies have ever been compared against placebo and no single agent's effectiveness has been confirmed in separate studies (61).

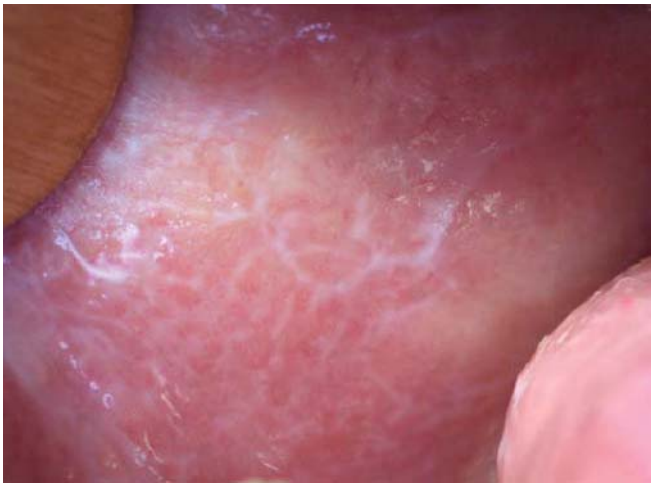


Figure 51.20 Wickham's striae of OLP.

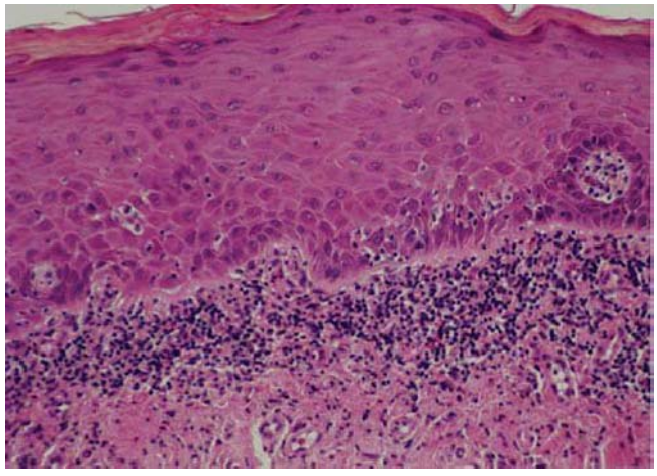


Figure 51.21 Hematoxylin and eosin staining on an OLP biopsy demonstrating a homogeneous band of lymphocytes at the epithelial–connective tissue interface.

"Burning Mouth" Syndrome

Primary burning mouth syndrome (BMS) is an idiopathic condition associated with a deep burning sensation of the oral mucosa with a lack of identifiable dental or medical pathology lasting for at least 4 to 6 months (62). The burning sensation is noted on the tongue in the majority of patients yet other affected areas include the palate (hard and soft), buccal mucosa, floor of mouth, and lips (63). Patients may also complain of oral dryness or alteration in taste. Symptoms can worsen with stress and exposure to hot food products and may improve with relaxation (62). There is a 7:1 female to male ratio and 90% of sufferers are perimenopausal women (62,63).

There are multiple diagnoses that may present with oral burning (secondary BMS) and include local malignancy, gastroesophageal reflux disease, hormonal disorders, nutritional abnormalities, and infection (Table 51.6). Diagnoses or treatments that result in xerostomia may predispose to the development of BMS.

Assessment of patients with a suspected diagnosis of primary BMS requires a full history and physical examination. A laboratory profile including a CBC, hemoglobin A1c, liver and thyroid function tests, iron, ferritin, vitamin B6/B12/D levels, ESR, ANAs, oral *Candida* swab, and antibodies to *Helicobacter pylori* can be used to fully assess these patients for alternative etiologies.

Reported treatment options are multiple and have included benzodiazepines, amitriptyline, paroxetine, gabapentin, and various topical agents (42). In a Cochrane Collaboration review, Zakrzewska et al. (64) found there was insufficient evidence to show the effect of painkillers, hormones, or antidepressants but there is some evidence that learning to cope with the disorder, anticonvulsants, and alpha-lipoic acid may help. Other authors have demonstrated a lack of efficacy of alpha-lipoic acid in this setting (65). Clonazepam is the only topical treatment studied in prospective double-blind, randomized fashion and has demonstrated efficacy in the reduction in the burning sensation in over one-half of patients treated (63). Treatment should include addressing any underlying xerostomia and psychiatric consultation is advocated (62,63).

The etiology of BMS is an area of debate. The most likely explanation is that it is neuropathy; however, it is unclear as to whether it represents a central or peripheral lesion. It has also been suggested that it may be variable in presentation (some patients central, some peripheral) as assessed by local lidocaine injection assessment. There is also an association of BMS and psychiatric diagnoses, such as depression and anxiety, which are seen in approximately one-half of all patients (62,63).

In terms of prognosis, 30% experience improvement of symptoms and 3% have spontaneous remission within 5 years of onset. Most patients have persistent symptoms for multiple years (62).

TABLE 51.6 ETIOLOGIES OF SECONDARY "BMS"

Classifications	Specific Causes
Contact allergy	Metals, acrylics
Dental	Recent procedure, dentures, poor hygiene
Infectious	*Candida*, bacterial, viral
Inflammatory	OLP, erythema migrans
Neoplastic	Squamous carcinoma, perineural invasion
Autoimmune	Sjogren, lupus
Endocrine	Diabetes, estrogen deficiency
Gastrointestinal	Reflux, Crohn
Pharmacologic	ACE inhibitors, antibiotics, antidepressants, diuretics, antiretrovirals, chemotherapy
Neurologic	Trigeminal neuralgia
Nutritional deficiency	Iron, B vitamins, folate, zinc
Depression	Various
Anxiety	Various

Adapted from Togerson RR. Burning mouth syndrome. *Dermatol Ther* 2010;23(3):291–298.

Orofacial Granulomatosis

Orofacial granulomatosis (OFG) is the term used for a number of conditions with similar characteristics and includes Melkersson-Rosenthal syndrome and Miescher cheilitis. The etiology is unclear and the entity is usually considered a diagnosis of exclusion after differentiation from similar entities such as Crohn disease and sarcoidosis (34,66).

Atopy is found in 12% to 60% of patients suggesting a relationship to a hypersensitivity disorder. The most frequent feature of this disease is persistent painless swelling of the orofacial tissues. This is most commonly manifested in the lips and may lead to vertical fissuring. The intraoral mucosa may develop diffuse edema, erythema, ulceration, and/or papule formation. In Melkersson-Rosenthal syndrome, patients present with fissured tongue, facial paralysis, and orofacial edema. Miescher cheilitis, also termed cheilitis granulomatosis, is characterized by chronic lip enlargement with granulomatous infiltration and lymphatic obstruction. Biopsy of OFG lesions will show noncaseating granulomas. Extensive testing is often needed to distinguish OFG from other granulomatous and allergic processes. Treatment can be challenging and is characterized by frequent recurrences. Local and systemic steroids are routinely used, although immunosuppressives have been used in refractory cases (34,66).

Erythema Migrans

Erythema migrans, also known as geographic tongue or benign migratory glossitis, has a reported incidence of approximately 3%. The etiology is unknown; however,

there is an association with atopy and psoriasis. The condition typically waxes and wanes and presents on the anterior two-thirds of the tongue. It is characterized by central erythema with surrounding raised yellow–white margins caused by nonuniform atrophy of filiform papillae of the dorsal tongue. Oral pain can be experienced with selected food products (acidic or spicy), but otherwise the condition is asymptomatic. Erythema migrans is more common in women and there is no uniformly effective treatment (22).

STOMATITIS UNIQUE TO CHILDHOOD

Marshall Syndrome

Marshall syndrome, also known as PFAPA, is a clinical syndrome of unknown etiology seen in children less than 5 years of age that present with periodic fever, aphthous stomatitis, pharyngitis, and adenitis. The periodic fevers of PFAPA recur every 3 to 6 weeks and the syndrome typically lasts for over 4 years. PFAPA is a diagnosis of exclusion and the differential includes cyclic neutropenia, hereditary periodic fevers, and Behcet disease (67).

Medical treatment has included steroids and cimetidine. Tonsillectomy has been advocated as an option to improve symptom control and may be considered in patients for which medical management is unsuccessful. In one study eight of nine patients experienced complete remission of symptoms within 3 months of tonsillectomy (67).

Traumatic Eosinophilic Granuloma/Riga-Fede Disease

Ulceration of the ventral surface of the tongue and/or lingual frenulum can be seen in newborns due to neonatal teeth. The ulceration can lead to the development of a fibrotic mass that is described as a traumatic ulcerative granuloma with stromal eosinophilia. This finding can be seen in infants with a tongue-thrusting habit or associated with familial dysautonomia (insensitivity to pain). Treatment involves filing or removal of the offending tooth, application of topical steroids to the oral lesion and may necessitate removal if an enlarged fibroma is present (68,69).

MULTIFACTORIAL

Erythema Multiforme

EM represents a spectrum of overlapping immune-mediated mucocutaneous diseases that are classified into four forms: EM minor, EM major, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). All forms of EM have an abrupt onset. Regardless of the inciting event, the common pathway for all of these conditions includes apoptosis and necrosis of the basal keratinocytes as a result of cytotoxic CD8+ T cells (37).

EM minor is defined by cutaneous involvement with classic "target" lesions. Hemorrhagic crusting of the lips is common and oral mucosal involvement with ulceration is seen in 25% of patients. EM major involves lesions of the skin, oral mucosa, and at least one other mucosal site apart from the oral cavity. The oral mucosal involvement is more prominent than that seen with EM minor and the length of the episode is longer (up to 6 weeks duration). Both of these two conditions are self-limited and usually caused by underlying infection from HSV-1, HSV-2, or *Mycoplasma pneumoniae* (16,37).

SJS is a severe form of EM and is characterized by stomatitis, conjunctivitis, and multiform skin lesions that can involve greater than 10% of the total body surface area. Oral findings include vesiculobullous lesions that rupture and result in painful ulcerations. SJS has a reported 10% mortality (37).

TEN is the most aggressive form of EM and involves epidermolysis of greater than 30% of the body surface area. Oral and pharyngeal involvement is common, and may result in extensive scarring. TEN has a reported 30% mortality (37).

Both SJS and TEN are the result of adverse drug reactions especially to anticonvulsants such as carbamazepine, phenytoin, phenobarbital, and sodium valproate (34,46). EM drug reactions have also been reported with sulfonamides, oxicam-type NSAIDS, pantoprazole, allopurinol, and tramadol (70).

DIF may be used to differentiate the presentation from other bullous conditions, but otherwise the diagnosis is based on clinical findings. After establishing the correct diagnosis, treatment is centered on determining the etiology of the presentation. With EM minor and major, if an infectious etiology is identified, therapy can be initiated. If an offending drug associated with SJS or TEN is identified, discontinuation is imperative. The extent of supportive care for the mucosal and cutaneous lesions matches the severity of the individual episode and the selective use of systemic corticosteroids can be considered (37).

SUMMARY

The presentation of stomatitis represents a wide spectrum of potential etiologies. A detailed history of presentation and assessment of associated conditions is critical in the diagnostic evaluation of these patients. Clinical presentations of a single diagnosis can vary widely between patients and making recognition on exam challenging.

Clinicians should remember that many of these diagnoses will require the collaborative management of the patient with other branches of medicine and that these colleagues can also be utilized in the diagnostic evaluation of the complicated patient without a clear etiology. Although some of the causes of stomatitis may be treated for cure, many are associated with chronic conditions where symptom control remains the focus of care.

HIGHLIGHTS

- As a result of the rapid turnover of oral epithelial cells, oral lesions may be the first manifestation of systemic disorders, such as sarcoidosis, Behcet disease, and IBD. Unfortunately, these oral lesions are often nonspecific to the disease entity.
- Mucositis remains a formidable challenge for patients undergoing radiation and/or chemotherapy, particularly as treatment regimens become more aggressive. Research efforts continue to focus on prevention, as this has been more successful than identifying new treatments. Overall, there is still a lack of data on effective therapies.
- *Candida* remains one of the most common forms of stomatitis seen in practice. Its incidence is rising due to increased numbers of chronically immunosuppressed patients and other factors. It has multiple varied presentations in the oral cavity, some of which can be challenging to recognize. Multiple treatment options exist, although resistant strains are becoming more common.
- Aphthous stomatitis can be a bothersome, although ultimately self-limited, process. The etiology remains unclear, although many aggravating factors and irritants have been described. Topical, systemic, and intralesional steroids are the cornerstone of treatment, although steroid-sparing agents have been used in severe and refractory cases.
- A number of vesiculobullous conditions present with oral cavity lesions. They can be differentiated on the basis of clinical course as well as direct and indirect immunofluorescence. Investigations into steroid-sparing agents for PV and BP have had promising results. The EM spectrum of diseases requires intensive supportive care for pain, dehydration, and prevention of secondary infection.
- Patients with HIV develop many of the same forms of stomatitis as the general community, but often require more intensive treatment, and earlier use of systemic, as opposed to local therapies. Institution of HAART in previously untreated HIV patients will ameliorate many forms of stomatitis found in this population.

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Pharyngitis

52

Stephen R. Hoff *Kay W. Chang*

Pharyngitis refers to inflammation of the pharyngeal mucosa, lymphoid tissue, musculature, and surrounding fatty and fascial tissues. This can be infectious or noninfectious, and can herald more extensive systemic diseases such as autoimmune disease or immunocompromise with human immunodeficiency virus (HIV). Acute pharyngitis is one of the frequent common causes of visits to a physician or health care provider, with over 15 million office visits per year for streptococcal pharyngitis alone (1). Approximately one-third of patients with upper respiratory infection (URI) have sore throat as the chief complaint. The abundance of lymphoid tissue in the pharynx, and the constant communication with the outside world during respiration, leads to the frequency of pharyngitis, and accounts for many of the symptoms.

Pharyngitis typically presents with sore throat, with odynophagia and dysphagia. This may be accompanied by fevers, hoarseness, nasal congestion, cough, halitosis, and malaise, depending on the etiology. Although there is a wide range of possible diagnoses, an accurate assessment of the time course, symptoms, and associated physical exam findings can rapidly and efficiently narrow the differential diagnosis (Tables 52.1 and 52.2). Viral infections are the most common cause of pharyngitis in both children and adults, but pediatric patients have a much higher rate of bacterial infection than adults (30% to 40% and 5% to 15%, respectively) (2,3).

Generally, most patients are treated supportively for the symptoms of pain and dysphagia, but antibiotics may be used when bacterial infection is suspected, or with opportunistic infections in the immune-compromised host. Of paramount importance is distinguishing pharyngitis from an acute infection with abscess formation, including peritonsillar, retropharyngeal, and parapharyngeal abscesses, which require more aggressive management. These are discussed further in Chapter 55. The symptoms of a pharyngeal malignancy may also mimic the clinical presentation of pharyngitis, and a high index of suspicion on the part of the physician is necessary, with biopsy and histologic examination as warranted.

Although there is overlap, the presentation and etiology of pharyngitis is different in the child and the adult. Therefore, this chapter discusses them separately, with a focus on the more common clinically encountered pathologies. Because adolescents tend to have pharyngitis profiles similar to adults, the pediatric section is specific to children less than 14 years of age. Adenotonsillar-specific disease, which obviously overlaps with pharyngitis, is discussed in Chapter 95.

ANATOMY

Anatomically, the pharynx has three divisions: the nasopharynx, oropharynx, and hypopharynx. These divisions are contiguous with each other, but contain different amounts of lymphoid tissue and unique specialized structures, and so are a helpful clinical distinction. The mucosal lining of the pharynx transitions from respiratory epithelium (pseudostratified ciliated) to stratified squamous from superior to inferior.

The nasopharynx is bounded by the nasal cavity and choanae anteriorly, soft palate inferiorly, sphenoid rostrum superiorly, and clivus posteriorly. The adenoidal lymphoid tissue sits on the roof of the nasopharynx, and is typically largest in children 5 to 7 years old. This may lead to obstruction between the nasal cavity and nasopharynx, with rhinorrhea, sleep apnea, and "adenoid facies" as a result. Typically, the adenoids begin to regress in late childhood, and are nearly absent in the adult. Presence of prominent adenoids in the adult should lead the physician to suspect pathologies such as HIV, lymphoma, or malignancy, and biopsy or testing may be warranted. Posterolaterally, the nasopharynx contains the eustachian tube orifices and associated muscles (salpingopharyngeus, levator veli palatini) and torus tubarius cartilage. Rosenmüller fossa (pharyngeal recess) is

TABLE 52.1 INFECTIOUS CAUSES OF PHARYNGITIS

Viral
Rhinovirus
Coronavirus
Adenovirus
Parainfluenza virus
Influenza virus types A and B
Measles virus
Respiratory syncytial virus
Coxsackie virus
EBV
CMV
HSV
HIV
Bacterial
GABHS (*S. pyogenes*)
Groups C and G Beta-Hemolytic Streptococcus
C. diphtheriae
N. gonorrhea
A. haemolyticum
Staphylococcus aureus
T. pallidum (Syphilis)
Fusobacterium
Francisella tularensis
Yersinia enterocolitica
M. tuberculosis
Mycobacterium leprae
C. trachomatis
Mycoplasma pneumonia
Fungal
C. albicans
Protozoal
Toxoplasma gondii

TABLE 52.2 NONINFECTIOUS CAUSES OF PHARYNGITIS

Autoimmune/Inflammatory
KD
Pemphigus
Pemphigoid
EB
Erythema Multiforme/Stevens-Johnson syndrome
Crohn disease
Sarcoidosis
Behcet syndrome
Reactive arthritis (Reiter syndrome)
Other
Foreign body
Trauma
PND
LPR
Neoplasm (squamous cell carcinoma, lymphoma, leukemia)
Caustic ingestion/thermal injury
Smoking/environmental exposures

located adjacent to the medial part of the eustachian tube orifice in the nasopharynx, and contains a small amount of lymphoid tissue known as Gerlach tonsil.

The oropharynx is bounded by the circumvallate papillae anteriorly, and contains the lingual tonsil of the posterior one-third of the tongue. Laterally, it is bounded by the pharyngeal tonsils, which are supported by the palatoglossus and palatopharyngeus muscles. The tonsillar capsule sits on the superior pharyngeal muscle, with the peritonsillar space between them. Together, the pharyngeal, lingual, and adenoidal tonsils form Waldeyer's ring. Just deep to the superior pharyngeal muscle sits the glossopharyngeal nerve, which can transmit the pain and odynophagia of inflammation during pharyngitis and tonsillitis.

The hypopharynx extends from the level of the hyoid bone to the inferior border of the cricoid cartilage, where it meets the cervical esophageal introitus, and contains the pyriform sinuses, postcricoid region, and posterior pharyngeal wall. The superior, middle, and inferior constrictor muscles form the open-tubed structure of the pharynx, and fuse in the posterior midline at the pharyngeal raphe. Due to this raphe, retropharyngeal abscesses form posterior to the constrictor muscles and tend to be bounded to one side of the retropharynx without crossing the midline. There are several important muscular/fascial layers and spaces between the pharyngeal wall and vertebrae. From anterior to posterior these are: the buccopharyngeal fascia (covering of pharyngeal constrictor muscles), retropharyngeal space, alar fascia, "danger space," prevertebral fascia, prevertebral space and musculature, and bony vertebral body. The deep spaces of the neck are covered in more detail elsewhere in this text.

Innervation of the pharyngeal musculature is via the vagus nerve through the pharyngeal plexus, except the stylopharyngeus muscle is innervated by the glossopharyngeal nerve. The arterial supply of the pharynx is mainly from the external carotid branches, including the ascending pharyngeal arteries, dorsal lingual arteries, tonsillar branches of the facial arteries, and palatine branches of the maxillary arteries. In the posterior pharyngeal submucosa, there is an extensive venous plexus, which drain inferiorly into the internal jugular veins. Lymphatic drainage from the pharynx is via the retropharyngeal, lateral pharyngeal, and deep jugular nodes.

INFECTIOUS CAUSES OF PHARYNGITIS IN THE CHILD

BACTERIAL

Streptococcal Pharyngitis

The most important distinction to make in a child with acute pharyngitis is to determine whether the etiologic agent is Group A Beta-Hemolytic Streptococcus (GABHS) a.k.a

Streptococcus pyogenes. This is the only common pathogen that necessitates the use of antibiotics (4). The overuse of antibiotics in pharyngitis from other pathogens, usually viral, should be avoided, with the exception of the rare bacterial infections. Treatment with antibiotics for GABHS will shorten the patient's symptoms by 24 to 48 hours and reduce infectivity as well as suppurative complications, but the most important reason to give antibiotics is to prevent late sequelae (rheumatic fever and rheumatic heart disease) (2–8). Because the symptoms of viral and bacterial pharyngitis are similar, and physicians using clinical judgment have been shown to overestimate the occurrence of GABHS, laboratory testing is required in pediatric patients (1,4,5,7).

GABHS infection is common in the 5- to 15-year-old age group, with a peak incidence during the early school years, and a decline in incidence in late adolescence and adulthood. In temperate climates, it is most common in the winter and early spring months (4,7). GABHS accounts for 20% to 30% of cases of pharyngitis in children, compared to 5% to 15% in adults, and is rare in patients less than 2 to 3 years (2). According to a 2008 study, the economic burden from pediatric streptococcal pharyngitis in the United States is estimated between $224 and $539 million per year, with most of the cost attributed to parent's time off from work (9). In addition to GABHS, infection with other serogroups of streptococcus is possible but much less common. These include Streptococcus C and G, which have been responsible for foodborne and waterborne outbreaks of pharyngitis, but with generally less severe symptoms than GABHS (8).

The incubation period for streptococcal pharyngitis is 1 to 4 days, after which patients will develop rapid onset of severe sore throat and odynophagia, with fevers, malaise, and possibly headache and gastrointestinal (GI) symptoms, such as abdominal pain and vomiting. In general, viral symptoms, such as cough, coryza, and nasal congestion are absent, and the presence of these symptoms makes the diagnosis of GABHS less likely. Tender, enlarged cervical lymph nodes are common. Pharyngeal examination shows erythematous oropharyngeal mucosa, including a beefy red uvula and possibly soft palate petechiae. Tonsils are also erythematous and inflamed, and may have a whitish, creamy exudate. Infants often have red, excoriated nares, with minimal rhinorrhea. Occasionally, patients will have a characteristic "scarlet fever" rash, consisting of fine, blanching, erythematous papules beginning on the trunk and spreading to the extremities, with sparing of the palms and soles (3). This rash has a texture like sandpaper, and will last 6 to 9 days. In addition to the rash, enlarged tongue papillae with erythema (strawberry tongue) may be present, with circumoral pallor. Infants and children less than three with GABHS tend to present predominately with irritability, fevers, and abdominal symptoms, such as vomiting.

Diagnosis of GABHS depends on clinical judgment and laboratory testing, and there are several different clinical guidelines available. A scoring system has been developed and validated, which assigns points for symptoms consistent with GABHS, and may help determine the risk of GABHS in each patient (10). All guidelines recommend against further testing if the patient does not have symptoms typical of GABHS. However, physicians have been shown to overestimate the incidence of GABHS, and overtreat with antibiotics (10). Therefore, in patients less than 15 years of age, with typical symptoms of sore throat, fever, adenopathy, and inflamed pharynx, laboratory testing should always be performed. The gold standard laboratory test is a pharyngeal swab, with culture on a blood-agar plate, which has a sensitivity of 90% to 95% (7,10). Throat swabs should be taken from bilateral tonsils and the posterior oropharyngeal wall, and not the oral cavity. However, culture results typically take greater than 24 hours to obtain, and a "rapid-strep" (rapid antigen detection test, RADT) has been developed. RADT results are available in 5 to 10 minutes, which allows for immediate antibiotic treatment of a positive result. Unfortunately, traditional RADT tests only have a sensitivity of 80% to 90%, making a false-negative result more likely (5,6,11). Newer RADT, which use optical immunoassays and chemiluminescent DNA probes, are 90% to 99% sensitive, but these are more expensive and may not be available. Therefore, a reasonable approach to the pediatric patient with sore throat is as follows: If the patient has symptoms typical of GABHS (fever, sore throat, lymphadenopathy), RADT should be performed in the office. If positive, the patient is started on antibiotic therapy immediately. If negative, a throat culture is obtained, and the patient is discharged home with a prescription for oral antibiotics. If the culture is positive, the patient is informed to fill the prescription and start therapy; if negative, they do not fill the prescription and are treated symptomatically. Practitioners should rely solely on the RADT if they have independently verified that their RADT has sensitivity greater than 90% (Fig. 52.1).

Penicillin or amoxicillin, which is more palatable for children, is an effective treatment for GABHS. First-generation cephalosporins, azithromycin, or clindamycin may be used in patients with penicillin allergy (1,6). Corticosteroids have not been proven to have benefit in acute streptococcal pharyngitis (12). Patients are not considered contagious after 24 hours of antibiotics, and should be allowed to return to school and regular activities at that time. If untreated, the GABHS pharyngitis is typically self-limited, with symptom resolution at 8 to 10 days, although throat cultures may be positive for up to 6 weeks in 50% of patients (8). Patients are considered contagious during the acute illness and 1 week thereafter if not treated (3). Testing or treatment of close contacts is generally not warranted, except in cases with recurrent pharyngitis between family members, or severely invasive strains of GABHS (e.g., necrotizing fasciitis). In children with recurrent strep throat and tonsillitis, tonsillectomy with or without adenoidectomy may be of benefit.

Approximately 10% of patients are considered carriers of GABHS, and will have positive strep testing without

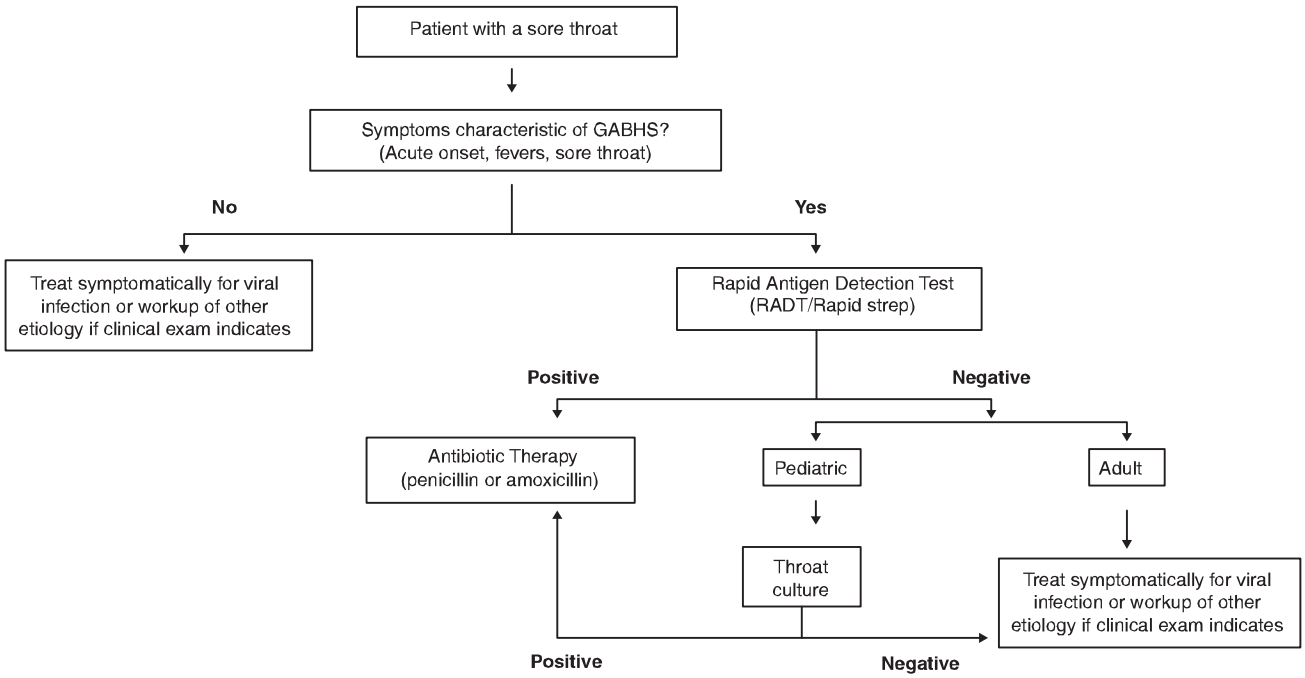


Figure 52.1 Algorithm for the diagnosis and management of sore throat and GABHS pharyngitis.

acute illness or immune response. Treatment of carrier patients, or their family members (and pets) has not been shown to be useful and should be avoided (13). However, antibiotic therapy may be appropriate with a personal history or close contact with someone who has had acute rheumatic fever or poststreptococcal glomerulonephritis, invasive strains of GABHS, or workers in health care facilities or nursing homes. Carrier patients can still develop pharyngitis from another serotype of GABHS or viral infection, and treatment should be started as appropriate.

Complications from streptococcal pharyngitis are rare but well described. These include rheumatic fever; rheumatic heart disease; poststreptococcal glomerulonephritis; suppurative complications such as peritonsillar, retropharyngeal, and parapharyngeal abscess; suppurative lymphadenopathy; mastoiditis; bacteremia; and sepsis. Rheumatic fever is diagnosed based on the Jones Criteria, which includes major and minor criteria such as carditis, polyarthritis, and chorea, and carries a mortality risk. Traditionally, the major role of antibiotic therapy is prevention of rheumatic fever, and rheumatic heart disease. It is estimated that 3% of patients with untreated GABHS infection will develop rheumatic fever, compared to 0.3% of patients treated with antibiotics. In the United States, rheumatic heart disease has largely been eliminated as a complication, but rates remain relatively high in undeveloped and underdeveloped countries, such as India. Antibiotics also decrease the rate of suppurative complications and associated abscess development.

Of special note is a relatively recently described but controversial entity, known as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal (PANDAS) infections. After streptococcal infection, including pharyngitis, these patients rapidly develop neuropsychiatric symptoms of obsessive-compulsive disorder (OCD) and tic disorders (14–17). The OCD and tics will last for several weeks before remitting, then abruptly return after the next streptococcal infection. In general, neuropsychiatric symptoms are from minimal to absent between episodes. It has been hypothesized that GABHS antineuronal antibodies cross-react with cells in the basal ganglia, giving rise to behavioral and motor disturbances (16). In several case series, tonsillectomy has been of benefit, with resolution of neuropsychiatric symptoms (17). The etiology of PANDAS is yet unknown, and its association with streptococcal infection has not been absolutely proven.

Corynebacterium Diphtheriae

Although now extremely rare, *Corynebacterium diphtheriae* historically claimed the lives of millions of children and adults. Death usually occurred from cardio- or neurotoxicity from the exotoxin, or from asphyxiation from membranous pharyngitis. Vaccine introduction began in the 1920s, and there has not been a confirmed case in the United States since 2003, although diphtheria remains endemic in developing countries with low vaccination coverage (18). *C. diphtheriae* is a gram-positive filamentous rod, which is transmitted via nasal, eye, or oral secretions, or from skin lesions.

In addition to the typical symptoms of sore throat and malaise, diphtheria is characteristically associated with a gray pharyngeal/tonsillar membrane, which is produced by the local tissue response and necrosis from the bacterial exotoxin

(present in approximately one-third of patients). This can extend to cover the oropharynx and larynx, and cause rapid death by asphyxiation, particularly in the young child. The pseudomembrane is firmly attached to the mucosa, and removal characteristically leads to bleeding of the underlying site with an edematous submucosa. Patients may also have a prominent reactive cervical adenopathy leading to a "bull-neck" appearance (1). Exotoxin-induced systemic cardiotoxicity and neurotoxicity are also possible and account for many of the adverse consequences of infection (19).

When strongly suspected based on clinical grounds, the diagnosis is confirmed with culture of the pseudomembrane on Loeffler or tellurite medium. Treatment consists of antibiotics and antitoxin, typically with penicillin or erythromycin, and the equine hyperimmune diphtheria antitoxin. Current recommendations for immunization include combined vaccination during childhood and booster injection every 10 years in adults (19).

Viral

In both children and adults, viral infection is the most common cause of pharyngitis, and is typically self-limited. Viruses that produce the common cold predominate, particularly the rhinovirus family followed by coronavirus and adenovirus (Table 52.1). The onset of viral pharyngitis may be more gradual than of bacterial pharyngitis, and symptoms typically include rhinorrhea, cough, and diarrhea. A viral etiology is suggested by the presence of conjunctivitis, coryza, hoarseness, and cough, and presence of these symptoms makes GABHS infection much less likely (1,7).

Preschool-aged children have an average of five to seven episodes of viral URI per year. This rate steadily decreases into adulthood, and plateaus at two to three episodes per year. Spread of viral pharyngitis is by direct contact and inhalation/ingestion of respiratory secretions, and is greatly increased by contact with other children at home or in daycare and school environments. Especially in the northern states, there is a seasonal incidence during the fall, winter, and early spring months, from September to April. Parainfluenza virus, the main etiologic agent of acute croup attacks, peaks in the late fall and late spring, whereas respiratory syncytial virus (RSV) and influenza viruses are highest between December and April (20).

Symptoms begin 1 to 3 days after transmission, and a sore, scratchy throat and inflamed pharynx is often the first sign. This is followed by the typical symptoms of URI, including nasal congestion and rhinorrhea. Influenza and RSV infections are more likely to produce fevers. The symptoms of URI last for approximately 1 week, then spontaneously resolve. Traditionally, patients were treated with over-the-counter medications such as saline rinses, decongestants, antipyretics, and antitussives, if necessary. However, recent evidence has shown that there is a high risk for overdose and serious adverse consequences in infants under 2 years of age; in addition, there is no conclusive evidence that these medications are effective for symptom resolution in pediatric patients. Therefore, over-the-counter cough and cold medications are no longer recommended for infants under 2 years of age, and caution should be used in recommending these medications to patients 2 to 11 years of age (21).

Treatment is symptomatic, and reassurance should be given. Parents may bring their child to the pediatrician or emergency room requesting antibiotics, but antibiotics should be avoided for viral pharyngitis. Aside from the cost of medication, development of antibiotic resistance is a concern when overused.

Coxsackie Virus

Herpangina, characterized by palatal vesicular enanthem and throat pain, is caused by the Coxsackie virus, and is often mistaken for acute bacterial tonsillitis. Coxsackie virus is in the enterovirus family, and was traditionally divided into Group A or Group B Coxsackie virus types, each of which has multiple strains. New molecular techniques have reclassified enteroviruses into five species, with the Coxsackie viruses coming under Human Enterovirus B and C groups (22). Herpangina usually occurs in children 3 to 10 years of age. Spread is by direct contact with infected saliva, fluids, or feces, commonly on unwashed hands in children, with a predilection for the summer months. Outbreaks in military barracks and other close quarter situations have been reported in older populations.

Symptoms begin suddenly, with fevers, myalgia, headache, and vomiting. Patients progress to severe sore throat and odynophagia, followed by the appearance of small vesicular lesions, typically on the soft palate and anterior tonsillar pillars, with sparing of the oral mucosa and gingiva. These lesions have characteristic appearance, starting as erythematous punctate lesions and developing quickly into small, 2 to 4 mm vesicles with central ulceration and erythematous base. These lesions may last for up to a week, although the fevers and other symptoms will resolve much more quickly in the first 3 to 4 days. Coxsackie A virus is also one of the causative agents in hand-foot-and-mouth (HFM) disease, which has a similar oropharyngeal presentation and the addition of vesiculopapular lesions on the palms and soles of the feet. Treatment of both herpangina and HFM is symptomatic, and both will spontaneously resolve in 1 week. Infection with Coxsackie virus or other enteroviruses in neonates is associated with significant morbidity and mortality, particularly when the infection occurs antenatally (23).

Inflammatory

PFAPA

A syndrome of periodic fever (>39°C), aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) was first described in 1987, and the exact etiology is yet unknown (24). PFAPA occurs sporadically in children less than 5 years of age, and is defined by the periodic high fevers

and oral/neck manifestations, which occur regularly every 2 to 8 weeks (average of 30 days) and last for 2 to 7 days (average of 4 days). These episodes have been described to occur like "clockwork," with a predictable and stable interval between symptomatic periods (25). Between episodes, patients return to complete health and are asymptomatic. In addition to the cardinal symptoms, headache, rash, arthralgia, and GI symptoms may be present (26). PFAPA is one of a spectrum of disorders with periodic fevers, and recent evidence points to an autoimmune or hyperactive immune response of Th1 cells to IL-1 cytokines (27). PFAPA is a diagnosis of exclusion, and other causes of pharyngitis, including GABHS, should be considered, and a thorough fever workup should be performed in every case. Cyclical neutropenia also needs to be evaluated and ruled out.

Steroids have been shown to be of benefit during acute episodes, and one or two doses of prednisone (1 mg/kg) aborts the fever episodes within a few hours, whereas the other symptoms will take longer to resolve. Cimetidine and colchicine have been used for prevention of episodes (28). Two well-designed randomized-controlled trials have concluded that tonsillectomy in PFAPA patients will lead to a decrease in episodes, longer interval between episodes, and in some cases complete resolution of PFAPA (29–31). However, given the tendency for spontaneous resolution and the possible efficacy of prophylactic treatment, the indications for tonsillectomy are still under investigation. PFAPA patients are often referred to the otolaryngologist with an established diagnosis of PFAPA for tonsillectomy evaluation, and clinical judgment should be exercised on a case-by-case basis (32).

Kawasaki Disease

The initial symptoms of Kawasaki disease (KD) may be mistaken for pharyngitis, and there are several case reports of KD presenting similarly to a retropharyngeal abscess or deep neck cellulitis (33,34). KD, also known as acute mucocutaneous lymph node syndrome, is a systemic vasculitis of unknown etiology which occurs in children less than 10 years of age. The classic symptoms of KD are high fever, adenopathy, mucositis (strawberry tongue), cheilitis (dry, cracked lips), conjunctivitis, erythematous rash, and erythema and desquamation of the palms and soles. Because of the initial high fevers and mucositis, patients may present for treatment of presumed pharyngitis. However, a high index of suspicion must be had for this syndrome, with examination of the eyes, trunk, and extremities as necessary, to avoid the long-term complications of coronary artery aneurysms and sudden death. Children with KD should be admitted to the hospital and started on IVIG and aspirin to prevent progression of large vessel disease.

Caustic Ingestion

Caustic ingestion is covered in depth in Chapter 93. Depending on the substance, ingestion of a variety of chemical agents may lead to necrosis or inflammation of the pharynx and upper GI tract. Visual inspection of the oral cavity and oropharynx, starting at the lips, may reveal ulceration, chemical burns, or exudative contact patches, and will help guide the treatment decision for endoscopy. In a patient with smoke and fire exposure, the pharynx needs to be closely examined for evidence of soot or burns, which would indicate smoke inhalation injury requiring close airway monitoring with a low threshold for intervention. In adolescents and adults, fumes from smoking tobacco and crack cocaine can cause acute pharyngeal mucosal inflammation and pain; edema of the supraglottis in these patients may lead to airway distress (35).

Posttransplant Lymphoproliferative Disorder

Posttransplant lymphoproliferative disorder (PTLD) is characterized by abnormal proliferation of lymphocytes (usually B cell) in chronically immunosuppressed patients, with a spectrum of lymphoid hyperplasia to non-Hodgkin lymphoma. Various risk factors for the development of PTLD have been identified, including young age, Epstein-Barr Virus (EBV)-seronegative status, high degree of immunosuppression, male gender, and Caucasian race (36). In the head and neck, PTLD can manifest at any site, including the paranasal sinuses, but the abundance of tonsillar tissue in the nasopharynx and oropharynx makes these sites particularly common. Patients present with hypertrophy of tonsillar tissue, including lingual, may also have mononucleosis-like symptoms including sore throat, muffled voice, and an increase in sleep-disordered breathing (37). Diagnosis requires biopsy via tonsillectomy, adenoidectomy, or lingual tonsillectomy, with histologic examination of tissue and flow cytometry. A correlation has been found between EBV viral load and the presence of PTLD and in some medical centers EBV levels are routinely monitored in stem cell transplant patients. Patients are treated with a reduction in immunosuppressive therapy, antivirals, and rituximab (anti-CD20) if EBV titers are high.

Oral Mucocutaneous Diseases: Epidermolysis Bullosa/Pemphigoid/Pemphigus/Stevens-Johnson Syndrome

Epidermolysis bullosa (EB) is an autoimmune disorder of skin and mucous membranes, which can be inherited or acquired, and is characterized by severe mechanical fragility of epithelial tissues, with blistering, erosions, and poorly healing ulcers (38). Similarly, mucous membrane pemphigoid is an autoimmune disorder of the basement membrane and presents with blistering and ulceration of mucosa and skin. Pemphigus is also an autoimmune disorder with several subtypes (including pemphigus vulgaris), and presents with cyclical vesicular and bullar eruption in the mucous membranes (39). Stevens-Johnson syndrome has numerous causes, most commonly drug reactions, and presents with large areas of ulceration and blistering on the skin and mucosal surfaces. Although these entities are pathologically

very different, the pharyngeal manifestations can be similar: mucosal blistering or ulceration, with sloughing of large patches of mucosa, usually with severe pain and dysphagia. Diagnosis is clinical and can be confirmed with biopsy of an oral or oropharyngeal lesion. These lesions can be quite extensive, with loss of mucosa over the lips, tongue, buccal mucosa, palate, and pharyngeal surfaces. The larynx and esophagus are susceptible, and great care must be taken in the examination of these patients in the operating room to prevent further skin and mucosal loss during instrumentation. In severe forms, laryngeal and mucosal sloughing leads to scar formation and stenosis, which may require a tracheostomy and/or G-tube. Further pathologic discussion is found in Chapter 51.

INFECTIOUS CAUSES OF PHARYNGITIS IN THE ADULT

Viral

Viral infection is the most common cause of pharyngitis in adults (30% to 60%), followed by inflammatory and bacterial (5% to 10%), and is typically self-limited. Rhinovirus, coronavirus, and other viral causes of the common cold, as described above, predominate. In adults, the typical disease course consists of 1 to 3 days without symptoms after transmission, followed by 3 to 5 days of sore throat, cough, headache, and nasal congestion. As in pediatric viral pharyngitis, fever is rare, and may point toward a bacterial etiology. Adults typically have two to four episodes of the common cold per year, compared to five to seven episodes in young children.

Epstein-Barr Virus

EBV is a common cause of acute sore throat, fever, and lymphadenopathy in adolescents and young adults. Any age group may be infected, but the clinical manifestations vary widely by age, and children may be asymptomatic or present with a cutaneous rash or neutropenia (40). EBV is a double-stranded DNA virus in the herpesviridae family, with a predilection for B lymphocytes. EBV has been associated with nasopharyngeal undifferentiated carcinoma, Burkitt lymphoma, and PTLD, but acute infectious mononucleosis (IM) remains the primary pathology from this virus.

In the classic form of IM, symptoms of pharyngotonsillitis predominate, with the addition of lymphadenopathy, splenomegaly (50%), and hepatomegaly (10% to 15%) (40). Transmission is via oral and respiratory secretions, with subsequent entry into the lymphoid tonsillar tissue of the pharynx. After an incubation period of 30 to 50 days, there is a prodromal period of fevers, chills, malaise, and anorexia, followed 10 to 14 days later by the classic triad of sore throat, fever, and lymphadenopathy (41). The onset of sore throat may be abrupt, and it is usually accompanied by severe odynophagia. Lymphadenopathy is variable, but usually involves the posterior cervical nodes and may involve the submandibular, jugular, and axillary nodes as well. More rare complaints are headaches, abdominal pain, and rash; the administration of amoxicillin will produce a pruritic, maculopapular rash in most patients with acute IM (42).

Patients may have muffled, "hot potato" voices, with or without increased work of breathing. Severe respiratory distress from tonsillar and lymphoid hypertrophy is extremely rare, and can usually be prevented with the use of steroids (42). Oropharyngeal examination shows symmetric tonsillar enlargement, which can be quite impressive, and all components of Waldeyer's ring may show enlargement and inflammation. Whitish exudates may be present on the tonsils and pharyngeal wall. The oropharyngeal mucosa is inflamed and erythematous, and may be difficult to examine due to tonsillar size. Petechiae at the junction of the hard and soft palate are seen in 25% to 60% of patients, and are typically 1 to 2 mm in diameter, although these are not diagnostic of IM. Hepatomegaly and splenomegaly may also be seen, and periorbital edema has been reported (41).

On laboratory testing, patients with acute IM have mononuclear lymphocytosis, with greater than 10% abnormal lymphocytes. Cold-agglutinins, usually of the IgM class, may be present, and are more common in patients who develop an autoimmune hemolytic anemia. Heterophile antibodies are associated with IM caused by EBV infection, are present in approximately 90% of adolescents with IM, and are the basis of the Monospot test (40). When the Monospot test is negative, but IM is highly suspected, EBV-specific antibody studies (to viral capsid antigen) can confirm the diagnosis. Although IM and peritonsillar abscess have similar symptoms of fever and pharyngitis, physical examination showing symmetric tonsillar enlargement with exudate makes IM much more likely. In adolescents and young adults, obtaining a Monospot test in the emergency room when IM is suspected can confirm the diagnosis, and spare the patient unnecessary procedures or imaging.

Patients with IM are treated symptomatically with rest, hydration, antipyretics, and analgesics. Respiratory support, including oxygen, sitting position, CPAP, or even intubation (rare), is given as needed. A single dose of dexamethasone during acute symptoms provides relief (42). Sore throat and dysphagia symptoms will peak at 3 to 5 days then resolve over the next week. Fevers may persist for 10 to 14 days, but improve over the late course of the illness. Most patients have resolution of symptoms by 2 to 3 weeks, but feelings of lethargy and malaise may linger for weeks or months.

Complications of IM include secondary bacterial infection, splenic rupture, hemolytic anemia, thrombocytopenia, and hepatic transaminase abnormalities. Bacterial infection is treated with antibiotics, but amoxicillin is avoided due to the rash, as mentioned above (42). Steroids

can be effective for hematologic complications. Patients should be informed to avoid contact sports to decrease the risk of splenic injury and hemorrhage, until splenomegaly is resolved on ultrasound examination.

Cytomegalovirus

Cytomegalovirus (CMV) is the pathogen responsible for 5% to 7% of IM (or IM-like illnesses), with clinical features similar to EBV-related IM (43). CMV is also in the herpesviridae family, and is present as an asymptomatic latent infection in a substantial portion of the population. CMV-related IM is more common in adolescents and adults who have had contact with children less than 2 years of age, such as daycare workers and teachers. CMV infection has similar symptoms of fatigue, malaise, and sore throat, but with less associated lymphadenopathy (44). Elevated transaminases are common (92%), but the heterophile-antibody test (Monospot) will be negative (43). Monoclonal antibodies against CMV can be tested to confirm the diagnosis, and treatment is symptomatic, similar to EBV-related IM. Other causes of non-EBV IM-like illness include human herpesvirus 6, HIV, herpes simplex virus (HSV), adenovirus, toxoplasmosis, and GABHS.

Human Immunodeficiency Virus

Acute retroviral syndrome (ARS) of early HIV infection has symptoms similar to IM, including sore throat, headaches, fevers, and malaise, in addition to myalgias, arthralgias, and nausea (45–47). ARS occurs abruptly after an incubation period of several days to 6 months, and affects up to 93% of patients with HIV. Twenty eight percent of patients will have oropharyngeal mucosal ulcerations, which may also be present in the cervical esophagus and genitalia (45). Nontender lymphadenopathy is present in the cervical, occipital, and axillary nodes, and a maculopapular skin rash involving the face and trunk is seen in up to 72% of patients. During this period of acute illness, patients have profound viremia, and are considered highly infectious (46). Diagnosis is based on enzyme-linked immunosorbent assay (ELISA) testing, with Western-blot confirmation. ARS is treated symptomatically and will resolve in 2 to 3 weeks; treatment for HIV infection is usually determined by an infectious-disease specialist.

Established HIV infection can have several manifestations of pharyngitis due to immunodeficiency and decreased host mucosal resistance. These include candidal infections (most common), CMV reactivation, HSV, human papillomavirus (HPV), among others. These are treated for the specific infection, concomitantly with treatment for HIV infection.

Herpes Simplex Virus

HSV, a double-stranded DNA virus with HSV-1 and HSV-2 strains, is an important cause of acute pharyngitis in the adolescents and adults. In the newborn and young child, primary HSV infection presents with gingivostomatitis, and the pharynx is usually spared (48). The virus is usually spread via sexual contact, with direct contact of infected oral salivary or genital secretions. HSV-1 is more common in the oral cavity, but HSV-2 can also occur and will present with the same clinical findings. An increased incidence of primary HSV infection in college students has been documented, but it is clinically difficult to distinguish primary HSV infection from other causes of acute pharyngitis including GABHS, and testing is required (49,50). In adolescents and young adults, HSV pharyngitis presents with fevers, pharyngeal erythema, and tonsillar exudates, with enlarged and tender cervical lymphadenopathy. One-third to one-half of patients will have characteristic painful herpetic ulcerations of the mouth or lips, which may also be present in the pharynx along the posterior wall and tonsillar pillars (48–50). Ulcers are characteristically shallow and covered with gray exudates. Vesicular lesions that bleed easily may be present, and covered with a blackened crust/clot. Gingival tenderness, erythema, and swelling are also characteristic (48). The disease is more severe in immunocompromised individuals, such as HIV. However, HSV infection can cause painful esophagitis even in the immunocompetent patient, which is typically rare, and if this is present, may help the clinician come to a diagnosis, particularly in an adolescent or college student.

Primary HSV symptoms resolve after 7 to 10 days, with the development of neutralizing antibodies. Reactivation of latent HSV infection presents with vesicular lesions of herpes labialis, and does not typically involve the pharynx. Diagnosis of primary HSV infection can be made by viral culture, which requires 12 to 48 hours. Cytologic examination may reveal multinucleated giant cells on a Tzanck smear, and other testing (ELISA, PCR) may be available. Patients are usually treated symptomatically for pain and dysphagia. Antiviral medications, including acyclovir, valacyclovir, and famciclovir, decrease the duration of disease and viral shedding, but is not standard and should be considered on a case basis (48). Immunocompromised patients should be started on antiviral medication immediately to prevent severe symptoms and systemic dissemination.

Human Papillomavirus

HPV infections of the oral cavity and oropharynx present with characteristic papillomatous growths on mucosal surfaces, which are typically asymptomatic. There are over 80 subtypes of HPV, with types 6 and 11 being the most common in the pharynx and upper respiratory tract. Pharyngeal infection is usually acquired through genital–oral sexual contact. In pediatric patients, HPV leads to recurrent respiratory papillomatosis, via transmission *in utero* or during birth. However, in a child with no history of RRP with new oral/oropharyngeal papillomas, sexual abuse needs to be considered. In the immunocompetent adolescent and adult, pharyngeal HPV infection leads to

papillomas, which are limited in size and can usually be easily removed in the office. However, removal does not eradicate the virus, which will still be present in the underlying mucosa and may lead to further papillomas. The infection can be more disseminated along mucosal surfaces in immunocompromised patients, including those with HIV. HPV infection has been implicated in the development of squamous cell carcinoma of the oropharynx, described elsewhere in this text.

Bacterial

Streptococcal Pharyngitis

GABHS infection is more rare in adults than in children, as stated above, and transmission is typically from close contacts or with children with GABHS. Presentation is similar to pediatric patients, with acute onset of sore throat, fevers, chills, malaise, with possible headaches or abdominal symptoms. Absence of tender cervical lymphadenopathy makes GABHS less likely in the adult (5). As in pediatric patients, the presence of typical viral symptoms of pharyngitis, including cough and coryza, also point away from GABHS infection. Because of the low incidence in adults, testing is usually not necessary (7). If GABHS is highly suspected, the rapid strep test can be performed. If the RADT is positive, patients are treated with penicillin V or amoxicillin; if the RADT is negative follow-up throat culture is NOT necessary in this age group.

Neisseria Gonorrhea

Oral gonorrhea is considered a sexually transmitted disease, and is a relatively uncommon cause of pharyngitis (<1%) (51,52). *N. gonorrhea*, a gram-negative diplococcus, typically affects the genital–anal region, and manifests as pain with urination, urethral discharge, and perianal inflammation and itching. Oropharyngeal gonorrhea is typically transmitted during oral sex, and rarely occurs as the only site of infection. It has been shown that the majority of patients (50% to 84%) will be asymptomatic, although culture positive (52,53,54). Symptomatic patients present with typical tonsillitis complaints, including sore throat, dysphagia, odynophagia, and throat itching. Examination may reveal evidence of oropharyngeal trauma, erythematous pharyngitis, and a whitish–yellow exudate from the tonsillar crypts. Cervical lymphadenopathy is only reported in 9% to 10% of patients (51). Severe oropharyngeal ulcerations have also been described (53). Pharyngeal swab with gram stain may reveal the diagnosis, but this is considered unreliable, and a culture on chocolate agar should be performed. Some laboratories have PCR testing available. Although the pharyngeal symptoms may be self-limited, antibiotics should be given in all cases in order to treat the likely infection of the genital site, and prevent further transmission. All patients should be treated concomitantly for *Chlamydia trachomatis*, as the two have a high incidence of coinfection (54,55). Typical antibiotic treatment is a single dose of intramuscular ceftriaxone for the gonorrhea and a single oral dose of azithromycin for the chlamydia.

Arcanobacterium Haemolyticum

Arcanobacterium haemolyticum is a rare cause of bacterial pharyngitis, implicated in 0.5% to 2.5% of patients, with similar symptoms of acute streptococcal pharyngitis (8,56,57). In addition to sore throat and inflammation, 20% to 25% of patients develop a scarlatiniform rash on the trunk and extremities, but with the face, palms, and soles spared. Infection tends to occur in adolescents and young adults, and should be suspected in this age group when the rapid strep test or culture is negative (57). *A. haemolyticum* is not part of the normal respiratory flora, and may become invasive after acute pharyngitis or tonsillitis, and lead to a peritonsillar abscess, other deep neck abscess, endocarditis, meningitis, or sepsis (58). Erythromycin is the standard antibiotic therapy, although a more broad-spectrum antibiotic regimen may be used.

Syphilis

Syphilis is caused by the spirochete *Treponema pallidum*, which has primary, secondary, and tertiary clinical stages of infection. Involvement of the pharynx is usually during the primary or secondary stages, and is generally acquired through oral sex (59,60). Oral sites are the most common, including the lips and tongue, and 4% to 12% of patients with primary syphilis will have oral or oropharyngeal manifestations (59,61–63). Primary syphilis in the pharynx presents as a painless ulcer on the tonsil or pharyngeal wall after an incubation period of 3 to 90 days (average 3 weeks). This may be unnoticed and therefore untreated. The primary chancre lasts from 2 to 8 weeks, and may be associated with lymphadenopathy during the first few weeks (60). Painless ulceration of the tonsil with lymphadenopathy has been mistaken for neoplasm, and a thorough social history should be emphasized (62). The secondary stage of syphilis represents systemic dissemination, and will present 2 to 12 weeks after primary infection. During the secondary stage, lymphadenopathy and skin lesions (maculopapular scaly, nonpruritic rash) are the most common findings. The features of secondary syphilis in the pharynx are highly variable, but the most characteristic are mucous patches, which are slightly raised, with silvery-gray pseudomembranes surrounded by erythema (59,62). Typical sites are soft palate, tonsillar pillars, buccal mucosa, and tongue. Confluent oral lesions may become painful, and these lesions are highly contagious. The symptoms of primary and secondary syphilis may be more pronounced and severe in patients with HIV, and the incidence of syphilis is increasing in this population (60). The gumma lesions of tertiary syphilis may present anywhere in the body, including the oral cavity and oropharynx. Further information concerning diagnosis and treatment of syphilis is found in Chapter 17.

Fungal

Candidal Infections

Fungal infections generally do not lead to acute pharyngitis in the immunocompetent patient. However, in chronically debilitated or immunosuppressed patients, including those with HIV, transplant patients on antirejection medications, chronic systemic or inhaled steroid use, broad-spectrum antibiotics, radiation therapy, and diabetes mellitus (DM), fungal infection can occur and may lead to severe systemic disease (64–66). *Candida albicans* is by far the most common isolated organism, leading to "thrush"—a pseudomembranous candidiasis infection of the oral cavity, oropharynx, and possibly larynx and cervical esophagus. *C. albicans* is a normal commensal organism of the oral cavity and does not typically cause symptoms. With immune compromise, the fungus will invade into mucosal surfaces, and is considered an opportunistic infection—the most common type in patients with HIV (67).

C. albicans infection presents with oral and pharyngeal pain, dysphagia, and burning sensation. With hypopharyngeal and cervical esophageal involvement, the dysphagia and odynophagia can be quite severe, and candidal infection should always be considered in immune-compromised patients with these symptoms (64). Examination shows the characteristic white, cheesy mucosal plaques, which can be scraped off to reveal an erythematous underlying mucosa. KOH preparation and microscopic evaluation is performed of the exudate, and budding yeasts with pseudohyphae can be seen to confirm the diagnosis.

Candidal infection can occur in any age group with immunocompromise. Two to five percent of normal newborns exhibit signs of oral/oropharyngeal thrush, which is self-limited and may not require treatment. Neonatal invasive disease is well described, and risk factors include: very low birthweight (less than 1,500 g), broad-spectrum antibiotic administration, prolonged ventilatory support, parenteral alimentation or IV catheterization, and abdominal surgery (65,68). Infection may be isolated to the oropharynx and mucosal surfaces, or become disseminated and severe. In children and adolescents, candidal infection is usually due to immunodeficiency from transplants or malignancy. Isolated patches on the pharyngeal mucosa and larynx may be due to inhaled steroids from asthma treatment. Oropharyngeal candidal infection is much more common in adults, where HIV and DM play a larger role (68).

Candidal infection, which is isolated to the oral cavity and pharynx, is treated with topical nystatin or fluconazole, in isolation or as part of a "stomatitis cocktail." Recurrent infections should be treated with systemic antifungal therapy (69). Prophylactic fluconazole is generally not recommended due to concerns of antimicrobial resistance, but may be helpful in patients at high risk for invasive fungal infections.

Other species of *Candida*, including *Candida krusei*, *Candida glabrata*, and *Candida tropicalis*, are much more rare, but may be increasing as the population with HIV increases. These will present with similar symptoms and exam findings as *C. albicans* (65).

Infection by other mycoses in the pharynx, including *Cryptococcosis*, Histoplasmosis, Rhinosporidiosis, and Blastomycosis, are rare and associated with involvement at other sites.

Inflammatory

Reflux Pharyngitis

Gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux (LPR), in addition to hiatal hernia and *Helicobacter pylori*-positive gastritis, commonly present with symptoms of pharyngeal and laryngeal inflammation. This may include chronic sore throat, burning sensation in the throat, sour taste in the mouth, frequent dry cough, hoarseness, and globus sensation with throat clearing (70–73). Sleep may be disturbed by coughing, and morning halitosis is a common complaint (73,74). As shown on experimental histologic examination, gastric acid has an inflammatory effect on the pharyngolaryngeal mucosa including submucous gland hyperplasia, edema, and vascular engorgement (75,76). Both the inflammatory changes as a direct effect of stomach acid contacting mucosa and a vagal-mediated signaling leads to cough and other symptoms. It should be noted that many patients (especially children) with reflux of gastric contents that reaches the pharynx (LPR) do not have typical symptoms of GERD, including heartburn or indigestion. Therefore, patients may falsely believe that acid reflux is not the cause of their symptoms.

Examination findings are nonspecific, and may include erythema and edema. Oropharyngeal "cobblestoning," a granular, bumpy appearance to the posterior oropharyngeal wall, is a classic description, but is not found in all patients and its absence does not exclude reflux disease. Laryngeal findings of edema and pachydermia on the interarytenoid mucosa are more revealing, although the only test which can definitively confirm the diagnosis is a pH probe (74). Dual probe pH testing, with a proximal pharyngeal sensor and a distal esophageal sensor, can be performed to specifically assess for LPR. However, most practitioners will start empiric treatment with lifestyle modifications and proton-pump inhibitors, with improvement of patient's symptoms to confirm the diagnosis (72–74).

Postnasal Drip

Postnasal drip (PND) is associated with nasal inflammation with increased mucous production and drainage into the pharynx, most commonly from allergic rhinitis. PND is a common cause of globus pharyngeus and chronic cough, but may also cause a chronically irritated and sore throat (irritative pharyngitis) (77). In addition, nasal congestion with obstruction, seen with inflammatory processes that produce increased edema and nasal secretions, can lead to chronic mouth breathing, particularly at night. Mouth

breathing provides less humidification, and leads to a dry and irritated posterior pharyngeal wall with a sore throat. After a thorough history, patients are treated for rhinitis with nasal saline, nasal steroids, and possibly humidification, which improves the pharyngeal symptoms.

Granulomatous Disease

Granulomatous diseases are characterized by the presence of granulomas, containing macrophages, giant cells, fibroblasts, and other inflammatory cells. These are manifest in a wide variety of infectious, inflammatory, autoimmune, and neoplastic disorders. In the pharynx and tonsils, caseating granulomas due to *Mycobacterium tuberculosis* (TB), accompanied by sore throat and nasal obstruction, are possible as a primary infection or after expectoration of infected sputum (78). Although rare in the United States, this diagnosis should be considered in a patient with fevers, lymphadenopathy, tonsillitis, as well as typical pulmonary symptoms (cough, hemoptysis) and night sweats of TB. After diagnosis, patients are treated with systemic antimycobacterial medications, with examination and treatment of close contacts.

Crohn's disease is a granulomatous inflammatory bowel disease of unknown etiology, with a classic histologic triad of noncaseating granuloma formation, fissures, and transmural inflammation with lymphoid aggregates. The distal ileum and colon are the most commonly affected sites, but any portion of the GI tract, including the oral cavity and pharynx, can be involved (0.5% to 20%) (79). Oral and pharyngeal manifestations include hypertrophic gingivitis, aphthous ulcers, lip swelling, and cobblestoning of the buccal or pharyngeal mucosa. These lesions can occur any time during the course of the disease, and multiple recurrences are common. Diagnosis is confirmed by biopsy and colonoscopy, and patients are treated with systemic steroids with variable response.

Foreign body reaction and granuloma as a response to exogenous materials in the pharynx are also possible, including traumatic (e.g., fish bone), iatrogenic (e.g., suture), or by abnormal deposition of hair or keratin debris. Foreign body granulomas can mimic an infectious process, which is unresponsive to antimicrobial therapy. Biopsy and removal will reveal the granuloma surrounding the foreign substance.

Radiation Pharyngitis

Ionizing radiation for the treatment of head and neck malignancies has both acute and long-term effects on the pharynx. These side effects are generally dose-dependent, starting at 20 Gy of standard fractionated radiotherapy, and prevention is impossible (80). Acutely, radiation exposure can cause pharyngeal edema and erythema, with a patchy fibrinous exudate, and is a result of cell damage and high cell turnover rates. If a high dose of radiation is given over a short time, ulceration may develop. Mucositis symptoms are worse with concomitant chemoradiation therapy, and may be treatment-limiting. Spontaneous healing takes 3 to 4 weeks, and is inhibited by tobacco smoking and high-dose radiotherapy (80). Chronically, radiation treatment leads to atrophy of the submucous glands in the oral cavity and pharynx, with decreased salivary production. In addition to symptoms of dry, sore throat and dysphagia, a decrease in saliva can lead to an increase in local and systemic infection. Treatment of mucositis consists of oral hygiene and topical anesthetics, analgesics, antibiotics, and antifungals, which may be given separately or as part of a "stomatitis cocktail" (81). Systemic analgesics are commonly used for pain management.

HIGHLIGHTS

- Pharyngitis is a common disorder of the head and neck.
- Symptoms of pharyngitis include: sore throat, dysphagia, odynophagia, and voice changes.
- Viral infection is the most common cause of pharyngitis in children and adults.
- Children have a higher rate of bacterial infection, especially GABHS, than adults.
- Children should undergo strep testing (RADT or culture), with penicillin or amoxicillin for a positive result.
- Adults with a negative RADT do not need to be cultured or treated for GABHS.
- EBV causing mononucleosis is a common cause of pharyngitis in adolescents and young adults.
- Sexually transmitted diseases, including *N. gonorrhea*, HSV, syphilis, and HPV, can present with pharyngitis.
- Candidal pharyngitis is common in immunocompromised patients.
- LPR disease and PND can lead to an irritative pharyngitis.

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53 Odontogenic Infections

Timothy D. Doerr

Odontogenic infections are common infections primarily treated by dental professionals. These infections are usually associated with dental caries or periodontal disease and are seen more often in underserved populations where regular dental care is lacking. In most cases, odontogenic infections are successfully treated in the early stages by the dental professional with a minor dental procedure and oral antibiotics. The initial treatment commonly consists of drainage of infectious tissue with extraction or endodontic treatment of the diseased tooth.

In some cases, the infection will spread from the dental alveolar structures into the adjacent soft tissue spaces. This can lead to serious infections of the fascial spaces of the face and neck. When these infections are not promptly managed, serious, even life-threatening complications can arise. It is often in the setting of an advanced odontogenic infection that the otolaryngologist first becomes involved. Patients will have local anatomy that can be distorted by infection and are at risk for airway obstruction. The otolaryngologist needs an understanding of the progression of odontogenic infections to properly treat these patients.

This chapter focuses on the microbiology, pathways of spread, and appropriate management of odontogenic infections. This knowledge will allow the surgeon to successfully treat these infections and help prevent major complications. The chapter also highlights the importance of the dental anatomy and fascial spaces in predicting and treating the spread of an odontogenic infection.

DEMOGRAPHICS

The incidence of an odontogenic infection will vary with the population studied. Those individuals with poor dental hygiene and those who are immunosuppressed are most susceptible. The peak incidence of odontogenic infections is in the third and fourth decades with a larger percentage of the complicated infections occurring in diabetic patients (1–4). There is nearly equal distribution between male and female patients although this has varied in some studies (2,3,5).

Although any tooth can produce an odontogenic infection, most infections involve the mandibular first, second, and third molars (2). In the pediatric population, odontogenic infections are less common overall, but are more likely to occur in maxillary teeth (1).

MICROBIOLOGY

Normal flora in the oral cavity contains over 1,000,000 organisms per cubic centimeter of which 10% are aerobic cocci and 90% anaerobic bacteria. The bacterial flora varies among the different oral cavity sites and with the health of the individual. The flora is also influenced by patient age, immune status, diet, environment, and host factors (6). Streptococci are the most common aerobic bacteria found in the oral cavity with the *viridans* species most prevalent. Staph is relatively infrequent in the oral cavity but becomes more prevalent in the setting of a mixed flora infection. Anaerobes increase in number in the setting of chronic infections like periodontitis (7).

An odontogenic infection is primarily caused by bacteria that colonize the mouth. These bacteria, when given the appropriate circumstances, can become pathogens. As a general rule, odontogenic infections are polymicrobial with a large percentage being primarily anaerobic infections (6,8).

Prior studies have shown that approximately one quarter of the infections were caused by aerobic or facultative anaerobic bacteria while about three-fourths were caused by strict anaerobes (9). Studies have also shown that when anaerobes predominate, the clinical infection is more severe. Based on these published culture data, appropriate empiric antibiotic therapy for odontogenic infections requires antimicrobial agents able to treat streptococcus and oral anaerobes species.

SPREAD OF LOCALIZED INFECTIONS

Most odontogenic infections begin with necrosis in the dental pulp from deep caries. Pulp necrosis is then followed by the spread of bacteria through the pulp chamber into the adjacent bone and soft tissues (Fig. 53.1).

Infected teeth are usually tender to percussion and may show a diminished or absent response to electrical tooth vitality testing. With the initial onset of pain, there may be no changes seen on the initial radiograph, but later periapical bony changes can be seen. With a chronic infection, a periapical cyst will be visible on imaging. Typically, treatment during this initial period with either endodontic treatment or extraction should alleviate the tooth pain and can also effectively drain the infection.

It is important to recognize that the initial steps in the development of a severe odontogenic infection may progress very slowly. It may take several months and even years for an infection from dental decay to reach the dental pulp and produce pulp necrosis and periapical abscess. The vast majority of patients will have had several signs and symptoms alerting them to an impending infection. In fact, 100% of patients experienced pain before presentation. In many cases, that pain was intermittent, but the patient did not seek a dental evaluation until severe pain or acute swelling with trismus ensued (10).

Once the infection is in the bone, it will usually follow a path of least resistance until reaching a plate of cortical bone. An infection can remain contained in the medullary bone space or erode through the cortical bone into the soft tissues (Fig. 53.2).

If the infection involves the adjacent soft tissue, it can cause a diffuse inflammatory response with cellulitis or form an abscess. A walled-off abscess in the labial or buccal gingiva is termed a parulis while an infection extending into the alveolar mucosa forms a vestibular space abscess.

The direction of spread of odontogenic infection is in part predicted by the location of the diseased tooth. Maxillary tooth roots are in closer proximity to the labial and buccal bone plates. The root position combined with the thick alveolar bone in the hard palate usually results in extension of infection to the labial or buccal side. This direction of spread produces swelling of the upper lip (Fig. 53.3).

On the rare occasions when an infection travels medially (lingually), a tender unilateral mass can form on the palate. By comparison, the mandibular tooth roots are closer to the lingual cortex posteriorly, and infections of these teeth can spread through the thinner plate of bone into the floor of the mouth. Despite this anatomic relationship, the vast majority of mandibular tooth infections (both anterior and posterior) will also spread through the buccal cortex.

As a rule, an odontogenic infection produces pain when the necrotic pupal contents are under pressure and also when the soft tissues and periosteum over the cortical bone are distended. The pain associated with a localized infection can decrease significantly as the tissue pressure drops when infection spreads through the bone and periosteum into the soft tissues. The position and root anatomy of an infected tooth are generally predictive of the location of the associated dentoalveolar abscess (Table 53.1).

The treatment of a dental infection at this stage involves a thorough drainage of the infected soft tissues combined with extraction of the offending tooth and administration of systemic antibiotics (Fig. 53.4).

SPREAD OF LOCALIZED INFECTIONS

When the infection of a diseased tooth spreads more deeply into the soft tissue instead of exiting superficially through an oral or cutaneous path, the spread is greatly influenced by the tooth position and the adjacent fascia

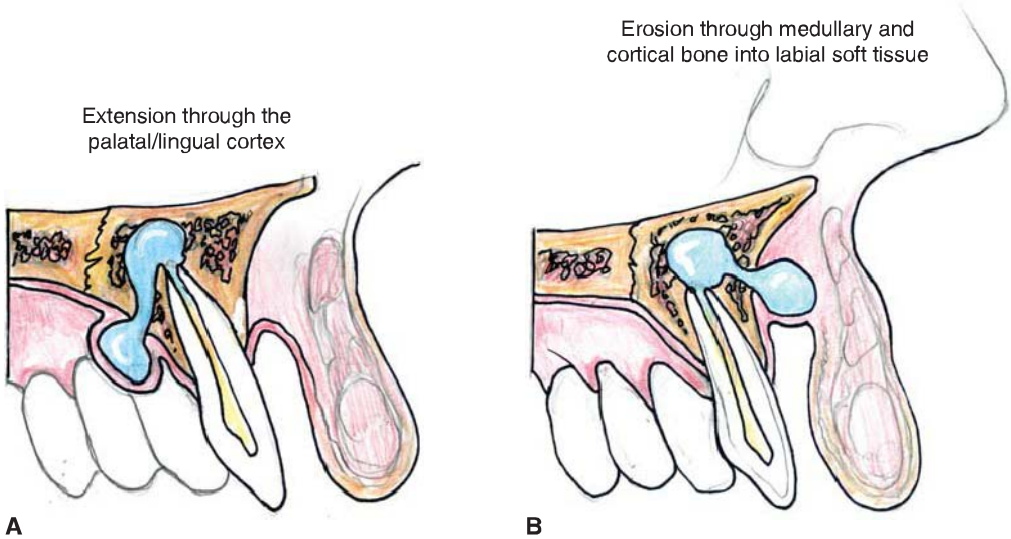


Figure 53.1 Spread of infection from an infected tooth root through the palatal/lingual cortex (**A**) and labial/buccal cortex (**B**).

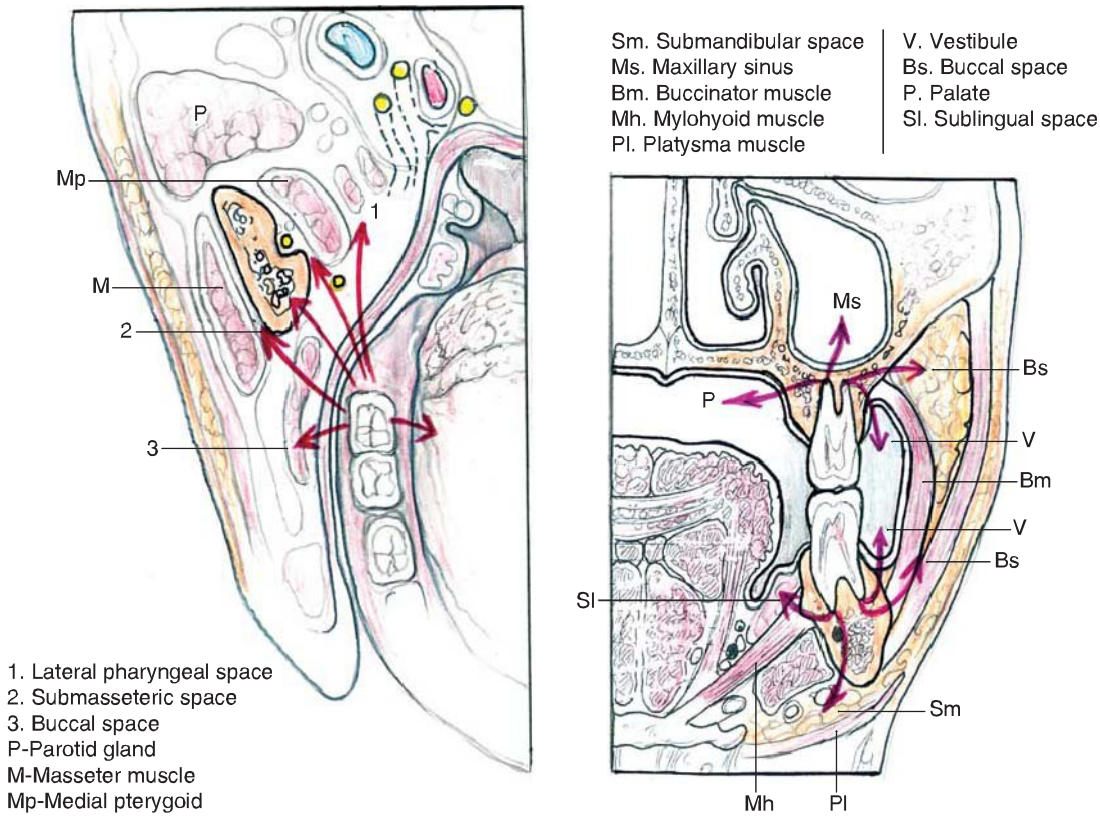


Figure 53.2 Various routes of spread for odontogenic infections.

attachments. Maxillary and mandibular teeth thus have distinctly different patterns of spread based on these anatomic relationships.

In general, dental infections of the anterior maxilla will spread superiorly into potential spaces bounded by the mimetic muscles. Maxillary tooth infections occasionally can also spread via the dental roots into the maxillary sinus.



Figure 53.3 Lip cellulitis in a child secondary to a fractured maxillary incisor tooth with pulpal exposure.

The masticator spaces are in close proximity to the roots of the maxillary molars, and they may be involved directly by odontogenic infections from these teeth. Once an infection reaches the masticator and cervicofacial spaces, it can spread into the deeper parapharyngeal space.

TABLE 53.1 PRESENTATION AND LOCATION OF DENTAL ABSCESSES

Tooth		Common Abscess Location	Less Common Abscess Location
Mandible	Central incisors	Labial	Lingual
	Lateral incisors	Lingual	Labial
	Canine	Labial	Lingual
	Premolar	Buccal	Lingual
	Molars	Buccal	Lingual
Maxilla	Central incisors	Labial	Palatal
	Lateral incisors	Labial	Palatal
	Canine	Labial	Palatal
	First premolar	Labial (buccal roots) Palatal (palatal roots)	—
	Second premolar	Buccal	Palatal
	Molars	Buccal (buccal roots) Palatal (palatal roots)	—

Modified from Goldberg MH, Topazian RG, Hupp JR. *Oral and Maxillofacial Infections*. 4th ed. Philadelphia, PA: WB Saunders, 2002.



Figure 53.4 New clinical picture of facial/neck abscess from a left premolar dental infection.

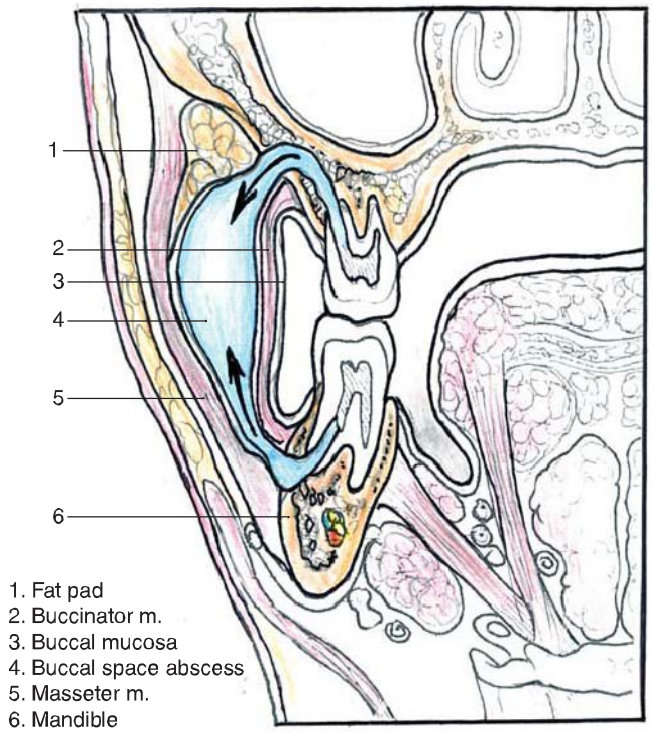


Figure 53.5 Formation of a buccal space abscess.

CANINE SPACE INFECTIONS

The canine space represents a potential space bounded by the muscle heads of the upper lip levators. These lip elevator muscles originate high on the maxilla and insert at the upper lip at the angle of the mouth. Although this space is infrequently involved with dental infections, it becomes involved if an infection from a maxillary cuspid tooth perforates the lateral cortex superior to the attachment of those upper lip elevators. Such an infection usually produces a firm swelling of the medial cheek and lateral surface of the nose that blunts the nasal labial crease. Rarely, this infection can spread from canine space through the valveless facial veins to involve the orbit. Most canine space infections are successfully treated by drainage with an intraoral incision placed high in the maxillary vestibule combined with extraction or root canal therapy of the diseased tooth.

BUCCAL SPACE INFECTIONS

The buccal space is located between the buccal muscle and buccopharyngeal fascia medially and the cheek skin laterally. Its anterior limit is the lip, and its posterior boundary is the pterygomandibular raphe. Superiorly the space is bounded by the zygomatic arch, and inferiorly it extends to the lower aspect of the mandible. As noted previously, infections from mandible and maxillary bicuspids and molars tend to drain in a lateral direction through the buccal cortex. Infection perforating the bone above the attachment of the buccinator muscle on the maxilla or below the attachments of the buccinator muscle on the mandible leads to a buccal space infection or abscess (Fig. 53.5).

Clinically, a buccal space infection produces tender swelling of the cheek that can extend to the mid upper lip. Here the space is limited by orbicularis oris muscle fibers at the philtrum. The buccal space extends posteriorly over the ramus of the mandible and to the border of the parotid. Superior spread of a buccal infection leads to swelling of the soft tissues of the orbit that "closes the eye" (Fig. 53.6).

Usually a buccal infection will be superficial to the orbital septum and not involve the orbital contents. However, the swollen eye needs to be carefully examined to ensure that the infection has remained preseptal and does not put the vision at risk. An infection that becomes postseptal will involve the orbital contents including the extraocular muscle and may extend to the orbital apex and cavernous sinus.

Because of its lax lateral soft tissue boundary, the buccal space has an ability to expand to a surprisingly large volume with purulent secretions. Despite the impressive swelling, a patient may not have much trismus. Although these buccal infections may be approached intraorally, most advocate draining these infection pockets through well-placed skin incisions. Incisions placed at the angle of the mandible allow complete drainage of the space and are cosmetically acceptable. The space should be opened with careful blunt spreading to avoid injuring branches of the facial nerve.



Figure 53.6 Submandibular space abscess from a pulpally involved mandibular molar tooth. The swelling over the mandible is ill defined and prevents palpation of its inferior border.

MASTICATOR SPACE INFECTIONS

The masticator spaces include the masseteric space, the pterygoid space, and the temporal spaces. These constituents of the masticator space are distinct anatomic entities that communicate with each other as well as with the more lateral buccal space. Additionally, these spaces communicate with the submandibular space inferiorly and the parapharyngeal space medially (Fig. 53.7).

The most superior of the masticator spaces is the temporal space. This space is divided into a superficial and a deep portion. The superficial temporal space exists between the temporalis fascia and the lateral surface of the temporalis muscle, while the deep temporal space rests between the medial surface of the temporalis muscle and the skull. Inferiorly the temporal space merges into an infratemporal space. The lateral extent of the infratemporal space is the temporalis muscle, and the medial limit is the skull base.

The second of the masticator spaces is the masseteric space. Its boundary is the masseter muscle laterally and the surface of the mandible medially. The third masticator space is the pterygoid or pterygomandibular space. This space extends from the pterygoid muscles to the mandible. Both the masticator and pterygoid compartments communicate freely with each other and with the temporal space above. The largest communication exists between the deep temporal and pterygoid/pterygomandibular space such that infections can spread easily from one to the next.

Infections of the temporal space can usually be drained either intraorally or externally but are probably best drained with an external incision along the zygomatic arch paralleling the course of the facial nerve. Infections that involve the masseteric space are most commonly associated with infection of the molar teeth. The source is usually the mandibular molars but can also be a maxillary molar. Chronic infections including pericoronitis of the molar gingival flap can also cause masseteric space infections.

The clinical hallmark of masticator space infections is trismus. Without trismus, the examiner may assume that masticator spaces are not involved. A notable exception to this rule is the immunocompromised patient in whom the presentation may lack the inflammation and signs of a deep space infection. With masseteric space infections, there can be some fullness over the muscle from myositis, but swelling is not seen initially because the infection is deep to a large muscle. The absence of swelling with the presence of trismus allows the clinician to differentiate a buccal from a masseteric space infection. As infection of the masseteric and pterygoid spaces spreads to involve the temporal space, swelling will increase with continued trismus.

Infections of the masseteric and the pterygoid spaces are potentially accessible from both an intraoral and external approach depending on the clinical circumstances. However, trismus can limit intraoral access and cause potential difficulty if an airway is needed. In these cases, the abscess should be drained through an external incision placed at the angle of the mandible so that all the masticator spaces can be entered.

MANDIBULAR SPACES

Although the submandibular and sublingual spaces represent distinct anatomic spaces, they can be viewed as a unit in terms of their surgical management. The mylohyoid is the critical structure in understanding sublingual and submandibular space infections. The mylohyoid forms the floor of the oral cavity and separates the sublingual space above from the submandibular space below. The muscle attaches to the lingual surface of the mandible along an oblique downward line from posterior to anterior. The tooth roots of the premolars and first molars are usually above the mylohyoid line, while the second and third molar roots are often below this line (Fig. 53.8).

Sublingual Space

The sublingual space is bounded anteriorly and laterally by the mandible. Superiorly its boundary is the sublingual mucosa, and inferiorly it is the mylohyoid muscle. The posterior boundary of the space is the hyoid, while the medial border is the genioglossus, styloglossus, and geniohyoid muscles. Only loose connective tissue separates the two sides of the floor of the mouth.

Infections of the sublingual space typically start out as tender brawny swellings of the lateral floor of the mouth near the mandible. As the infection progresses, it spreads towards midline and often to the opposite sublingual space. There may be some elevation of the tongue with more

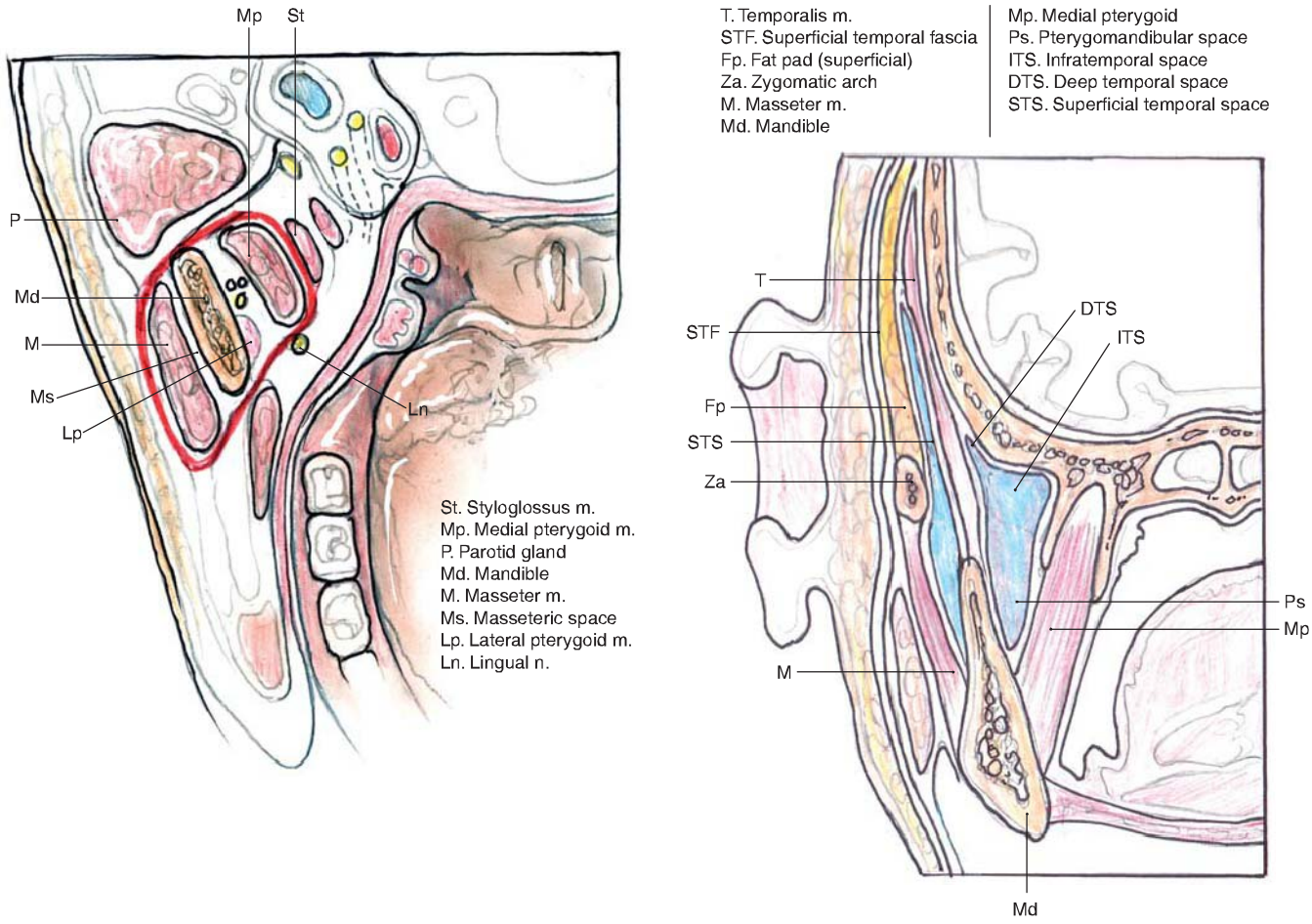


Figure 53.7 Masticator space infections.

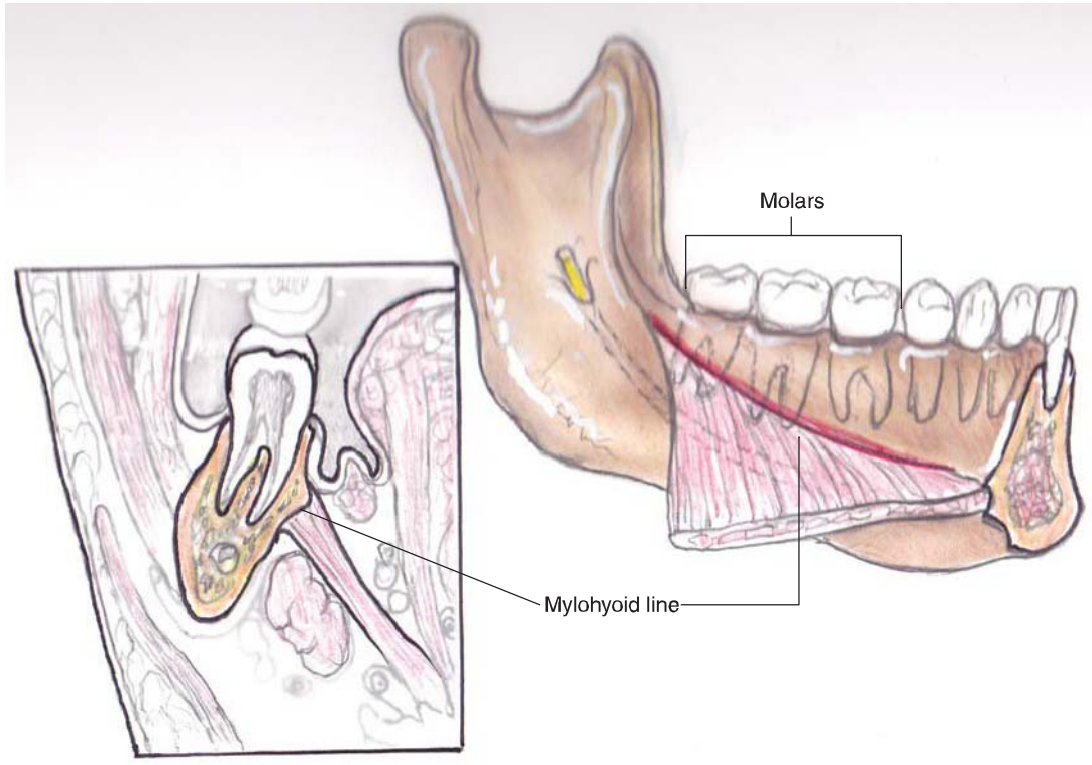


Figure 53.8 Mylohyoid line on mandible.

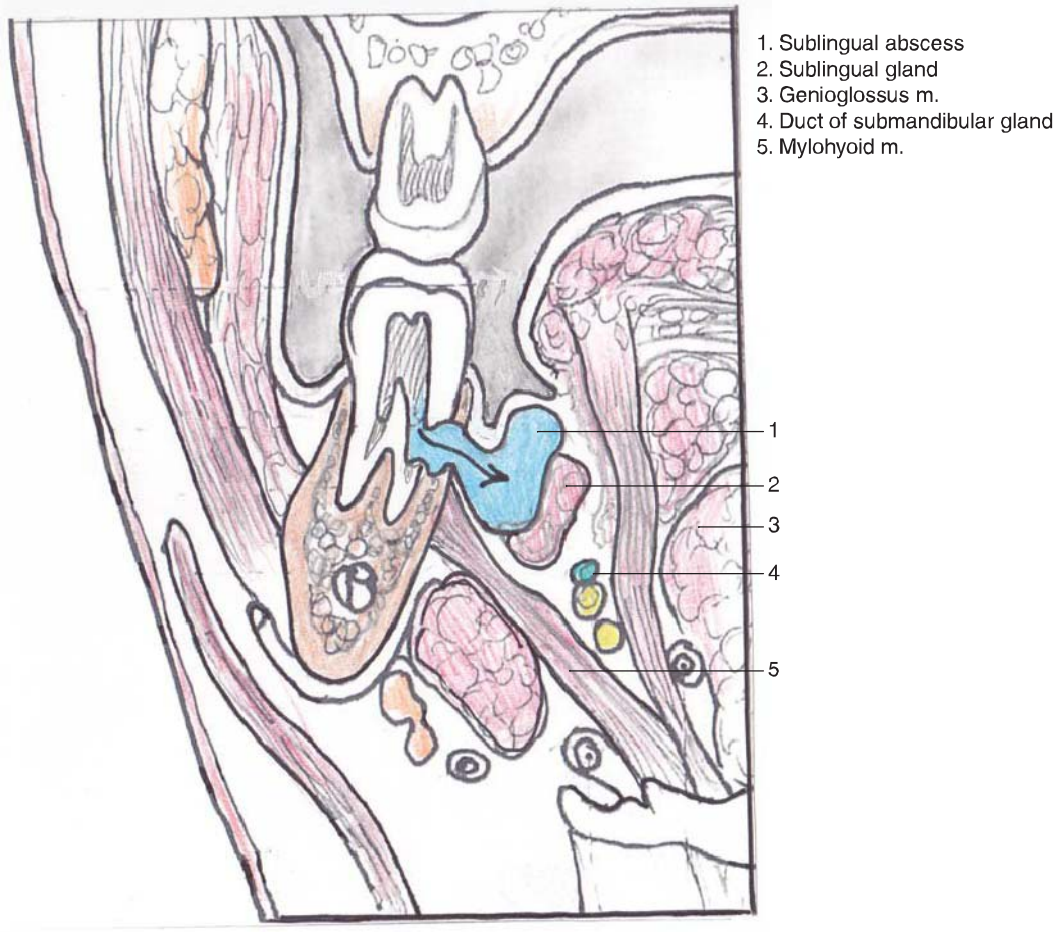


Figure 53.9 Sublingual abscess.

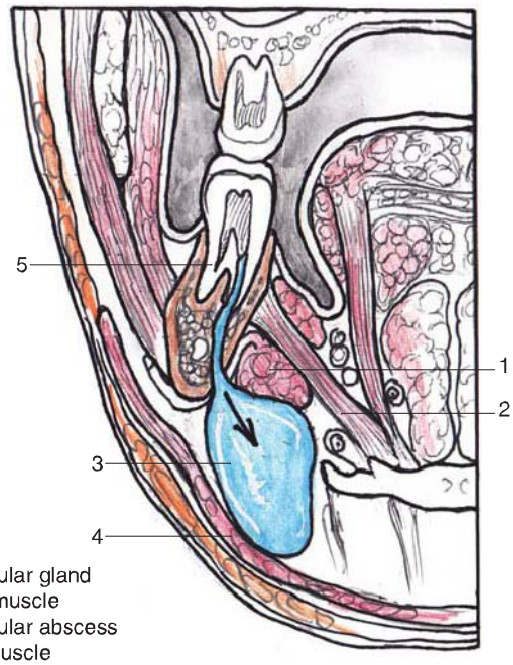
advanced cases. Infections of the sublingual space can extend anteriorly where the space communicates with the submental space. The treatment of sublingual space infections is with surgical drainage using an intraoral incision that parallels the submandibular duct to avoid its injury (Fig. 53.9).

Submandibular Space

The submandibular space is separated from the overlying sublingual space by the mylohyoid muscle. The lateral extent of the submandibular space is the skin, superficial fascial, and platysma muscle. The medial limits of the space are the mylohyoid, hypoglossus, and styloglossus muscles, while the inferior border is the anterior and posterior digastric muscles. The anterior portion of the submandibular space communicates freely with the submental space, while the posterior portion communicates with the sublingual space and deeper neck spaces (Fig. 53.10).

Submental Space

The submental space represents a midline space beneath the anterior aspect of the lower jaw. Its boundaries are



1. Submandibular gland
2. Mylohyoid muscle
3. Submandibular abscess
4. Platysma muscle
5. 2nd /3rd molar

Figure 53.10 Submandibular abscess.

both anterior digastric muscles, while the roof consists of the mylohyoid muscle and the floor of the mouth mucosa. The anterior and lateral borders are formed by the anterior mandible arch, while the hyoid is the posterior border. Rarely the space may be involved by infection directly from the lower central incisors. Far more frequently, the submental space is involved by the extension of infections from the submandibular and submental spaces originating in the second and third and rarely first mandibular molars.

LUDWIG ANGINA

Ludwig angina is a distinct pattern of infection that usually originates in the submandibular or sublingual space and then disseminates to all the floor of the mouth spaces by way of the posterior border of the mylohyoid to involve the submandibular and sublingual spaces bilaterally as well as the submental space. The infection begins as a cellulitis, advances to a fasciitis, and then becomes a true suppurative infection. Over 90% of cases of Ludwig angina are odontogenic, usually arising from infected second and third mandibular molars (5,11). Ludwig infections tend to spread quickly from one space to another, resulting in progressive brawny edema of the anterior and lateral neck skin with the floor of the mouth swelling and elevation of the tongue. As the tongue becomes more posteriorly and superiorly displaced, it leads to odynophagia, dysphagia and drooling. The tongue displacement can lead to supraglottic airway obstruction and asphyxiation if the airway is not secured. In the era before antibiotic and surgical therapy, the progression of the Ludwig infections was steady and unrelenting with death from airway obstruction occurring at 10 to 12 days (12).

Effective treatment of Ludwig angina involves three critical elements. These are (a) securing a safe airway, (b) administering appropriate antibiotics, and (c) surgical drainage of the infected spaces. The surgeon has to also be aware of secondary issues of sepsis. Because the potential for rapid spread and precipitous airway obstruction, the physician must ensure that the airway is secure. The decision of when and how to secure the airway is based on careful patient evaluation. The surgeon must look for signs and symptoms of respiratory distress and intervene before there is critical airway compromise. Patients who have significant tongue swelling, posterior tongue displacement, dyspnea, or stridor need to have the airway secured. Likewise, patients with airway edema on fiberoptic laryngoscopy, or significant swelling of radiographic exam, need to have a secure airway.

If a patient is seen in the early stages of an odontogenic infection before the airway shows signs of compromise, close airway monitoring with supplemental oxygen can be considered. However, these patients should be observed closely in an intensive care unit setting where the necessary resources to establish a difficult airway are readily at hand. When choosing to closely observe a patient without an established airway, the otolaryngologist must be aware of the danger of precipitating airway obstruction that can occur by placing a patient supine for diagnostic studies.

When the diagnosis of Ludwig angina is made and the disease puts the airway at risk, all authors agree that establishing a secure airway is critical. There is, however, no consensus on the best means of establishing the airway. Considerable debate exists in the recent literature over the need for a surgical airway. The historical standard had called for an awake tracheostomy prior to surgical drainage of the infection. These recommendations were based on studies reporting that up to 75% of cases of Ludwig's required a surgical airway (11). Dependence on this surgical approach is not without risks including the inherent difficulties of performing a tracheotomy in the setting of neck swelling and distorted anatomy.

Other authors have suggested alternative strategies for airway management (13–15). A number of recent studies support the use of fiberoptic oral or nasal intubation. Ovassapian et al. were successful in intubating 25 of 26 patients with deep neck abscess including 17 patients with Ludwig angina. Although fiberoptic techniques are feasible, it must be recognized that fiberoptic intubation can be much more difficult by infections that distort anatomy, produce immobile soft tissues, and cause trismus. A fiberoptic intubation does offer the potential advantage of more rapid control of the airway and avoids the risks and complications of a surgical airway. Intubation, however, is a less secure airway, and patients are at increased risk for accidental extubation. In the scenario of severe infection, re-intubation may not be possible.

The assessments of both the surgical and anesthesia teams are critical in deciding how to secure the airway. As a general rule, fiberoptic endotracheal intubation can be attempted in most cases of advanced odontogenic infection. It must be done by an experienced team member working in concert with a surgeon who is ready and capable of establishing an emergent surgical airway. The fiberoptic intubation is best performed in the semi-seated position with the instruments for a surgical airway immediately on hand. Newer devices including the intubating fiberoptic laryngoscope (Glidescope) have not yet been established for these cases but show clinical promise. Under no circumstances should induction of general anesthesia be followed by attempts at blind nasal or oral intubation. This approach is likely to precipitate loss of the airway and the associated potential lethal complications.

Those patients with Ludwig or other deep neck infection who have potential for respiratory embarrassment require the airway be secured and maintained or at least very closely monitored for at least 48 hours after surgical drainage because of the potential for postoperative swelling.

Simultaneous with securing the airway, patients with Ludwig angina must be started promptly on parenteral antibiotics targeting the expected pathogens. Empiric treatment directed against mixed aerobic and anaerobic flora has proven successful. It is rare that culture results will have a significant influence on patient management. After starting antibiotic therapy, patients should be kept on the appropriate coverage until swelling resolves. In a severe infection, this could take several days. There is considerable controversy concerning the use of systemic steroid in the setting of severe odontogenic infections. Those patients with airway swelling may derive some benefit from the use of steroids, but they are not to be relied on for airway management. Certainly for patients with diabetes the use of systemic steroids will impact control of blood glucose.

Surgery for Ludwig Angina

Surgical drainage is clearly indicated for patients with an abscess, patients with impending complications, and those showing no improvement after 24 to 48 hours of appropriate parenteral antibiotics. Many authors contend that earlier surgical intervention improves clinical outcomes (16,17). Often, in patients with Ludwig's, the surgeon does not encounter a discrete abscess but rather a malodorous "dirty dishwater" fluid.

Traditional surgical management of Ludwig angina called for a horizontal incision placed superior to the hyoid and extending laterally to a few centimeters below each angle of the mandible. Recent studies reported early surgical drainage using multiple small incisions as equally effective in treating the infection (5). Bross-Soriano et al. drained the infection with a 1.5- to 2.0-cm incision placed 2 cm below the lower border of the mandible dissecting in a subplatysmal plane into the submandibular and sublingual spaces. A similar incision and dissection below the symphysis of the mandible is used to open the submental space. Posteriorly all of the spaces are joined together by the dissection. When other spaces are involved, additional incisions are necessary to get to the parapharyngeal and the retropharyngeal spaces to drain fluid collections.

Needle aspiration is an accepted method for obtaining material for culture but is inadequate to sufficiently drain the infection. Aspiration can remove infected fluid but can delay recovery because dependent drainage is not established and irrigation of the wound is not performed. Aspiration with placement of indwelling catheters that allow repeat aspirations and irrigation can serve as an alternative to surgical incision and drainage in carefully selected cases.

GENERAL TREATMENT GUIDELINES

The appropriate management of an odontogenic infection can involve medical, surgical, or dental treatment or some combination of all of these. The dental management is probably least familiar to the otolaryngologist. The controversies in the management of the infected tooth are beyond the scope of this chapter. However, it is imperative that the source of the infection be eliminated. Generally, for more extensive infections, tooth extraction is required. However some infected teeth may be salvaged with endodontics. This management decision is a matter of clinical judgment for the dentist, but generally, extraction is the most rapid way to alleviate an infection while simultaneously providing egress for the infectious materials. Any associated dentoalveolar abscess need to be drained at the time of tooth extraction (18,19).

Prior studies have demonstrated improved outcomes with early surgical drainage of odontogenic infections. The mechanism by which early surgical drainage speeds resolution of odontogenic infections is unknown. A number of factors including improved local perfusion, decreased hydrostatic pressure, and the introduction of superficial mucosal flora all may have a role in halting spread of infection and speeding recovery (11). Anaerobic bacteria can cause significant tissue destruction, and this debris is far better cleared with an open wound. Trismus also resolves more quickly and allows earlier return to function (12).

The surgical approaches to drain the various spaces involved in odontogenic infections is detailed within the various subsections of this chapter. The use of drains in treating infections has not been studied specifically. Some surgeons prefer suction drains, while others favor passive dependent drainage. Drains that provide the ability to irrigate the wound cavity will offer a theoretical advantage in treating complex infections. Regardless of the type of drain used, the key is making sure that all the involved spaces are entered and that all loculations are opened. This can usually be accomplished with blunt digital dissection using any preoperative imaging as a guide.

Imaging

The use of diagnostic imaging has become routine in the management of an odontogenic infection. When seen in the initial stages of a suspected dental infection, dental imaging including dental films and an orthopantogram is usually sufficient to manage a patient. Dental films often will reveal a radiolucency, and orthopantograms may show some thinning of the cortical bone. In more advanced infection where there is involvement of adjacent soft tissue, computerized tomography (CT) with contrast is the most commonly ordered study. The CT scan can show the presence or absence of a fluid collection as well as involvement of the various anatomic spaces. Involvement of the masticator spaces and the parapharyngeal spaces is better revealed (20). The use of intravenous contrast better delineates the relationship of the great vessels of the neck. The presence of subcutaneous

air is an ominous sign and mandates the surgeon to drain the area quickly. When there is involvement in the lower neck or when there are findings of gangrene in the neck, the scan should be extended down into the mediastinum and chest. It is important to recognize that with many odontogenic infections, especially Ludwig angina, a true abscess may not be appreciated on CT scan. A decision to operate should be based on a careful clinical assessment and not on imaging alone. Regardless of imaging results, patients who do not improve on therapy deserve exploration.

Magnetic resonance imaging (MRI) has a limited role in the management of odontogenic infections. Although it provides excellent soft tissue resolution, in most cases, an MRI provides limited information beyond that gained from a contrast-enhanced CT scan. In addition, the additional time required for MRI image acquisition is potentially problematic when there are airway concerns. Ultrasound also has only a limited role in managing odontogenic infections. It is good at examining superficial spaces for involvement but is not able to clearly define the deeper spaces of the neck (21).

Treatment with Antibiotics

The initial treatment of odontogenic infections requires the administration of appropriate antibiotics. Given the prevailing microorganism found in these infections, gram-positive anaerobic cocci and gram-negative anaerobic rods. Empiric therapy directed against these pathogens is necessary and appropriate. Penicillins continue to be effective against most of the microorganisms present in these infections. It is inexpensive and presents minimal side effects. There are, however, reports of varying levels of resistance against this group of antibiotics. Given the increasing resistance seen, most would recommend beta-lactam stable antibiotics or those used in combination with beta-lactamase inhibitors (6,11,18,19,22). Clindamycin is also appropriate for patients with a possible allergic reaction to penicillin. It has excellent action against aerobic and anaerobic bacteria, and is not susceptible to the action of beta-lactamases. Clindamycin has been shown to have similar efficacy in a number of clinical studies to amoxicillin–clavulanate (23).

Previous studies have reported that culture and sensitivity data did not result in changes in antibiotic or other treatments (1). In many cases, the patient had already received antibiotics, which could further limit the utility of culture results. Clinical improvement with antibiotic treatment is the desired end point. Nonetheless, obtaining culture data at the time of incision and drainage may provide some information for those few patients who do not improve sufficiently on empiric therapy. Appropriate antibiotic treatment should be continued until there is resolution of symptoms and findings of inflammation. In severe cases, this may require extended periods of treatment (Table 53.2).

COMPLICATIONS OF ODONTOGENIC INFECTIONS

Dental infections may produce a virulent local infection that spreads to the adjacent deep neck spaces. These infections can then progress to life-threatening conditions including systemic sepsis, necrotizing fasciitis, and descending mediastinitis.

Deep Neck Space Infections

It is well recognized that the majority of deep neck spaces are of odontogenic origin. It is therefore mandatory to look for a potential dental source in any patient with a deep neck space abscess. As previously noted, the mandible teeth, particularly the molars, are statistically the most likely source of infections. Maxillary teeth are more likely to serve as the dental source in the pediatric population (1,2,11,17). The deep neck space infections associated with odontogenic sources include infections involving the retropharyngeal space and the parapharyngeal space. These generally require treatment with incision and drainage and administration of systemic antibiotics (2,11,18,19).

While the current chapter focuses on the issues unique to odontogenic infections of the head and neck, it does not comprehensively examine deep neck space infections. For a review of the management of deep neck space infections, the reader is referred to Chapter 55 of this text.

Cervical Necrotizing Fasciitis

Necrotizing fasciitis is a rare but severe bacterial infection of the soft tissues of the neck and its fascia. A necrotizing infection can arise from any head and neck source, but dental sources are most common. When the diagnosis is missed or when treatment is delayed, the infection can spread rapidly to involve the subcutaneous fat, deep fascia, and muscles. These polymicrobial infections produce tissue necrosis with subcutaneous emphysema. The infection requires emergent surgical debridement of all nonviable tissue at which time cultures can be obtained. These patients may require serial surgical procedures to treat the disease. Early, aggressive surgical management with appropriate medical therapy can preserve more of the overlying skin and reduce morbidity and mortality (24,25).

Mediastinitis

Infections that reach the deep neck spaces as well as those that extend in the soft tissues of the lower neck can extend to involve the mediastinum. There are a number of factors that promote the spread of odontogenic deep neck infections towards the mediastinum. These include the enclosed cervical fascial spaces of the neck that communicate with the chest. The negative intrathoracic pressures with respiration that combine with gravity to channel infection

TABLE 53.2 ANTIBIOTICS FOR ODONTOGENIC INFECTIONS

	Oral	Parenteral
Very effective	amoxicillin/clavulanic acid penicillin clindamycin metronidazole (anaerobes only)	ampicillin/clavulanic acid penicillin clindamycin metronidazole (anaerobes only)
Effective	erythromycin cephalexin tetracycline	cefazolin cefoxitin carbapenems
Not effective	sulfa quinolone	gentamicin tobramycin amikacin Third generation cephalosporins

inferiorly into the mediastinum is another factor. These infections are potentially lethal and must be treated aggressively. Surgical drainage of both the neck and mediastinum, eradication of the odontogenic source, and broad-spectrum intravenous antibiotic therapy are all required. Wide exploration of the neck and mediastinum with debridement of all nonvital tissue is needed (26,27). Again, in these circumstances appropriate airway management is critical.

HIGHLIGHTS

- Odontogenic infections are caused by the microorganisms of the oral cavity. These infections are usually polymicrobial and frequently involve aerobic streptococci as well as anaerobic peptostreptococci, *Prevotella*, and *Fusobacterium*.
- The infections usually begin in a carious tooth where the infection enters the bone through the pulp chamber. Although any tooth can be involved, mandibular molars are the most common.
- Amoxicillin/clavulanic acid and clindamycin represent effective oral antibiotic therapy for odontogenic infections while ampicillin/clavulanic acid and clindamycin are effective parenteral therapy.
- A buccal space abscess usually presents with significant facial swelling and pain but no significant trismus. In contrast, infections of the masticator spaces are recognized by pain and limitations on mouth opening.
- The mylohyoid attachment to the mandible is important in understanding the spread of infections to the submandibular and sublingual spaces. Infected teeth whose roots reside below the mylohyoid usually produce an infection of the submandibular space while those whose roots are above the line infect the sublingual space.
- Ludwig angina is an infection of the floor of the mouth and submandibular spaces. With progression, the infection can produce airway obstruction. Proper management of Ludwig's requires securing of the airway, appropriate intravenous antibiotics, and surgical drainage.
- Localized odontogenic infections usually require extraction of the infected tooth, drainage of any fluid collection, and the administration of antibiotics. Untreated odontogenic infections can spread and lead to severe, life-threatening complications including airway obstruction, mediastinitis, systemic sepsis, and death.

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54 Management of Temporomandibular Joint Pain and Dysfunction

Joseph J. Fantuzzo *Sveta Karelsky*

Temporomandibular disorders (TMDs) are conditions affecting or arising from the temporomandibular joint (TMJ), muscles of mastication, or both. TMD typically manifests as pain in the head and neck region and there is often an effect on neighboring structures. The pain can mimic other painful disorders of the head and neck as well. TMDs may be interpreted as facial pain, headaches, earaches, aural fullness, clicking or popping of the ears, mild hearing loss, tinnitus, dizziness, difficulty with mouth opening, chewing or speech, closed or open lock of the TMJ, wear of the occlusal (biting) surfaces of the teeth, joint noises (clicking or popping), and other complaints. TMDs occur in an estimated 5% to 15% of the general population, peaking in young adults age 20 to 40 years. Signs of TMD occur equally in males and females, but symptoms occur and are reported more frequently in women of childbearing age. Approximately 2% of the general population seeks treatment for TMJ-related symptoms (1,2).

Patients with complaints of TMJ-related pain often have parafunctional oral habits or a history of trauma, as well as concomitant medical or psychological conditions. TMJ disorders TMDs may be divided into nonarticular muscle disorders and articular (intracapsular) disorders. Nonarticular disorders include masticatory muscle (myofascial) pain and dysfunction and can commonly be associated with fibromyalgia or other chronic pain states and irritable bowel syndrome (3). Trauma can affect the TMJ itself and associated structures. Articular disorders include osteoarthrosis, inflammatory joint diseases, infections, and benign and malignant lesions.

The role of the otolaryngologist is both to differentiate temporomandibular from other regional pathology and to initiate a treatment plan for the disease. Because of the variety of symptomatic presentations of TMDs patient perceptions of the origin of symptoms vary widely. Patients may be referred to the otolaryngologist for presumed pathology of the ear, sinuses, or parotid gland. It is not uncommon for patients to have been treated for infectious disorders of these structures prior to referral. An appropriate explanation of the anatomic basis of pain must be provided for the patient if trust is to be gained and recommendations are to be carried out. Symptoms and their severity must be accepted as reported and treated accordingly. Accurate diagnosis is important in the development of an effective treatment plan.

Patients should be reassured that TMD is generally a benign condition and clinical improvement is expected in time and with appropriate therapy. Complete elimination of symptoms is difficult and at times impossible. The goals of therapy include patient education, alleviation of pain, and improvement in jaw function.

Pain and jaw dysfunction are the hallmarks of TMD, and the pathophysiology, differential diagnosis, and management of the problems behind pain and limited jaw function are the primary focus of this chapter.

ANATOMY AND PHYSIOLOGY OF THE TMJ

The TMJ exists between the base of the skull (temporal bone) and the mandible (condylar process). The articulating bony surfaces, the articular disk, several ligaments, and numerous associated muscles make up the joint (Fig. 54.1). The purpose of the temporomandibular (or craniomandibular) articulation is to provide range of motion and to allow for the functional aspects of the mouth and jaws during breathing, speech articulation, mastication, and swallowing.

Of the bones of the head, only the TMJ and the ossicles of the ear have articulations. The secondary TMJ in humans develops by the 10th week of gestation, from mesenchymal condensations of two separate blastemas for the condyle and temporal bone. The TMJ and ear ossicles are derived from membranous bone (4,5). Superior to the condylar blastema, a band of mesenchymal tissue differentiates into

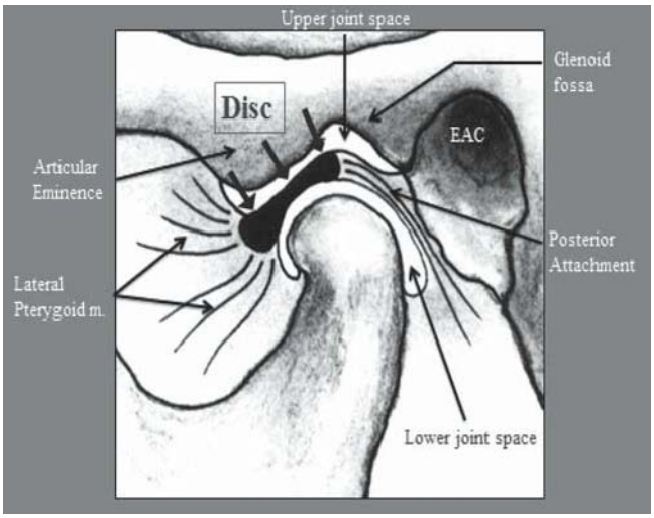


Figure 54.1 TMJ—Normal anatomy.

the disc as an extension of the lateral pterygoid muscle (4–6). Embryologic studies suggest an intimate relationship between the fetal TMJ and the middle ear through the petrotympanic fissure. This relationship may contribute to referred pain patterns or the spread of infection (7).

The articular disc is a biconcave structure that prevents bone on bone contact of the articulating surfaces and more evenly distributes articular forces. It has an anterior and posterior band and intermediate, thinner avascular zone. The disc is also attached at the medial and lateral condylar poles. The disc divides the articular space of the TMJ into a superior and inferior joint space. Posteriorly, the retrodiscal attachment is bilaminar and has significant neurovascularity. This retrodiscal tissue is intracapsular, and pain within the joint itself may be due to retrodiscal injury or inflammation. Theories of intracapsular pain are discussed later in the chapter (4,5).

The development of the primary and adult dentition influences the shape of the fossa, eminence, and condylar head. The glenoid fossa represents a concavity within the temporal bone that fits the mandibular condyle. The anterior wall of the fossa is the articular eminence. The posterior wall, made up of the tympanic plate of the temporal bone, is also the anterior wall of the external acoustic meatus. An early periosteal lining becomes the dense, avascular, fibrous connective tissue cover for the articular surfaces. The articulating surfaces are different from hyaline cartilage surfaces of other synovial joints. Edentulism leads to secondary change within the fossa and eminence (8).

The TMJ is thinly encapsulated anteriorly, medially, and posteriorly, with a thick capsule laterally forming the temporomandibular ligament. The ligament has a narrow deep portion and wider fan-shaped lateral portion. The fibrous capsule and ligament provide support and limit jaw range of motion.

The sensory innervation of the TMJ is from the auriculotemporal, deep temporal, and masseteric nerves. The blood supply to the capsule and disc is from the branches of the maxillary artery.

The motor activity of the joint results from motor innervation of the masticatory musculature, through the third division of the trigeminal nerve. The various muscle groups of the face, tongue, palate, and hyoid are also involved in functions that include the TMJ: The masticatory muscles (masseter, temporalis, medial pterygoid, and lateral pterygoid) and other important muscles (digastrics and supra- and infrahyoid muscle groups) play a significant role in the functioning of the TMJ. The actions of the muscles together on the hyoid, mandible, and related structures are important during jaw function. This interrelationship is important to consider when arriving at a differential diagnosis. A thorough review of anatomy including the actions of this musculature is beyond the scope of this chapter.

Movements of the mandible include opening and closing, protrusion, retrusion, and lateral excursions. The motion of the mandible at the TMJ is hinge-like occurring primarily within the lower compartment and gliding or translatory within the upper compartment. Unlike other joints, the left and the right side disc, condyle, and associated musculature function simultaneously. Maximum mandibular opening (between incisors) is 40 to 55 mm, is generally less in women, and decreases with advancing age (4,5,9).

PATHOPHYSIOLOGY

TMDs typically present with pain with mandibular function, limitation of mandibular movement, and joint sounds. Muscle-related pain is more common than internal joint–related pain, but they often occur together. Muscle pain may adversely affect internal joint function and vice versa, over time. Differentiating muscle pain from internal derangement is important to successful treatment. Myalgias generally present regionally with muscle weakness or fatigue and limited passive range of motion. Palpation reveals muscle tenderness. Typical problems include myalgia and myositis due to parafunction, trauma, or infection. The involved musculature may be tender, swollen, and warm. Chronic masticatory muscle contraction may be seen, with myofibrosis limiting range of motion. Previous trauma, surgery, and planned restricted range of motion (maxillomandibular fixation) will result in limited range of motion that may or may not return to normal over time.

The literature suggests that patients with myofascial TMD pain may be hypersensitive to pain, or have altered pain perception pathways. Some have features of brain morphology consistent with other chronic pain states, such as fibromyalgia. In such patients, studies of CNS regions involved in pain processing indicate changes to areas processing pain signals from the trigeminal system (10,11).

An intracapsular disorder implies a disc–condylar fossa abnormality and is associated with joint noise, and abnormal, often limited condylar movement. Intracapsular disorders are referred to as internal derangements and represent anterior disc displacement with or without reduction. The anterior displacement is thought to represent adaptive change

Wilkes Classification of Internal Derangement

Stage I	Early reducing disk displacement No pain or limitation, early opening click
Stage II	Late reducing disk displacement One or more episodes of pain, mid to late opening click, transient catch & lock
Stage III	Nonreducing disk displacement: acute/subacute Multiple painful episodes, locking, restricted mobility
Stage IV	Nonreducing disk displacement: chronic Increasing functional disturbance
Stage V	Nonreducing disk displacement: chronic with osteoarthritis, crepitus, scraping, grating, grinding symptoms; pain, restricted motion, difficult funtion

Figure 54.2 Wilkes classification of internal derangement.

within the joint to functional demand. Disc displacement with reduction is associated with joint noise, and may or may not progress to disc displacement without reduction. Anterior displacement without reduction is present when the disc remains displaced throughout mandibular motion. The disc may interfere with condylar movement. Typically there is an absence of joint noise. A nonreducing disc is thought to represent a more chronic problem (12) (Fig. 54.2).

Mouth opening is typically limited to less than 25 mm with a nonreducing disc displacement (closed lock). The mandible will deviate to the affected side upon opening, as the unaffected side translates normally. Lateral excursion (toward the unaffected side) is limited on the affected side as well. Degenerative changes of the bone may or may not be present with disc displacement. Intracapsular adhesions may be present. These fibrous adhesions are thought to occur with stretching and bleeding within the superior joint space.

Psychosocial Comorbidity

TMD patients often present with a level of pain, stress, and depression beyond that expected by the clinician. It is not clear whether these occur as a result of chronic pain, or whether they contribute to the parafunctional habits that can generate TMJ-related disorders. A large Finnish study found that patient-reported TMD symptoms are significantly associated with stress, depression, overload at work, life satisfaction, and work satisfaction. Pain perception and predisposition to TMD may be significantly affected by psychosocial stressors (13). When evaluating patients with TMD stress must be addressed by the treating clinician.

Molecular Biologic Mechanism of Injury

Both mechanical functional limitation and inflammation contribute to pain. Inflammation may lead to intracapsular swelling and pain. There can be inflammation of the joint capsule (capsulitis) and of the synovial lining (synovitis) resulting in pain and limitation in movement.

Trauma to the vascular and richly innervated retrodiscal tissues can also cause effusion, pain, and limited range of motion. The inflammation within the joint can cause secondary muscle splinting leading to more limitation in range of motion and more discomfort.

Milan described a theory of direct mechanical stress leading to the creation of free radicals contributing to a degenerative process within the joint. Direct mechanical injury from excessive load leads to increased levels of IL-8 and production of nitric oxide synthetase with NO release and free radical formation causing direct tissue damage and induction of arachidonic acid, inflammation, and tissue breakdown within the joint (14).

Other causes of free radical formation include the theories of hypoxia–reperfusion and that of neurogenic inflammation. The theory of hypoxia–reperfusion proposes that clenching increases pressure within the joint, which overwhelms capillary perfusion pressure, leading to hypoxia. Reperfusion leads to free radical formation. Neurogenic inflammation occurs with the release of neuropeptides (substance P, calcitonin) released from activated nerve terminals within the capsular ligament and retrodiscal tissue contributing to the inflammatory response.

Another hypothesis for closed lock of the TMJ is that of adhesion of the disc to the articular eminence secondary to insufficient lubrication of the joint from overloading. Nitzan described impairment of joint lubrication due to free radical formation. Inflammation secondary to macro- or microtrauma causes free radical formation and increased oxidative stress within the joint leading to the loss of lubricating hyaluronic acid (HA) and chondroitin sulfate within synovial fluid. Increased hyaluronidase leads to breakdown of HA, the major lubricant within the joint. Loss of lubrication causes capsular fibrosis and immobility of the TMJ disc. Arthrocentesis has been proposed by Nitzan and colleagues to allow for immediate release of the disc. Decreased lubrication increases viscosity and contributes to disc dislocation as the disc adheres to the glenoid fossa during motion. Adhesions vascularize and add to restriction. Increasing laxity of the lateral disc attachment occurs and the disk is gradually displaced (15,16).

Synovial fluid analysis attempts to identify the underlying pathogenesis of TMDs. The synovial membrane provides nutrients to cartilage. Diminished synovial fluid quality and quantity is thought to compromise nutrition of the articular surfaces and diminish protection and lubrication of the joints (15).

Inflammatory mediators within the injured joint worsen and prolong pain and dysfunction. Cytokines, proteases, and other substances have been implicated in internal derangement and degenerative joint disease (17). Osteoarthritis may be an imbalance between protease and protease inhibitor. Specific cytokines and growth factors have been implicated. Cytokines (IL-1, IL-6, IL-8, interferon, and TNF) may

induce proteases. Growth factors induce tissue inhibitor of metalloproteinase. Matrix metalloproteinase has been identified as a mediator of cartilage degradation (18). PGE2 synthesized by synovial cells, mediated by IL-1, plays a role in bone resorption. LTB4, synthesized by synovial cells, is elevated in painful joints and is chemoattractant for inflammatory cells. Synovial fluid analysis demonstrates increased IL-B and IL-6 in osteoarthritis (19–24).

Surgical procedures have been developed, based on the above theories. The goal of arthrocentesis or arthroscopy as the initial surgical intervention for internal derangement and osteoarthritis is to reduce the presence of inflammatory mediators as well as to lyse adhesions.

Hypomobility Disorders

Causes of TMJ hypomobility may be trismus or anatomical obstruction such as bony or fibrous ankylosis. Pain and limited range of motion may also be secondary to internal derangement of the joint. Imaging is helpful in arriving at a diagnosis. A screening panoramic radiograph may be helpful to rule out fracture, unusual anatomy (coronoid hyperplasia), or pathology. Computerized tomography (CT) imaging may be necessary to identify a fracture, degenerative disease, ankylosis, or neoplasia. Magnetic resonance imaging (MRI) is helpful when evaluating the location of the articular disc, presence of joint effusion (inflammation), and in revealing the presence of fibrous ankylosis. Hypomobility due to trismus is most frequently caused by infection, inflammation, neoplasm, radiation, or trauma. If painless, trismus may be associated with the presence of a tumor. Rarely temporal arteritis can cause trismus (25–27).

Ankylosis can be due to fibrous scar formation, bone formation, or a combination of both. Trauma is the most frequent cause in developed nations. Children who are unable to translate with opening the jaw are at increased risk of developing ankylosis. TMJ infections are rare but are reported as the cause of TMJ ankylosis in 10% to 49% of cases (28). Inflammatory arthritis such as rheumatoid and psoriatic arthritis contributes to another 10%. Juvenile idiopathic arthritis can affect the TMJ often with absence of symptoms in 50% of children (29–31). Clinical examination findings of limited opening or deviation with opening without pain should prompt the clinician to evaluate further with MRI. Intra-articular steroid injections may be beneficial (32).

The ankylotic joint requires surgical management to release fibrous tissue or resect heterotopic bone. Reankylosis is a common complication. Gap arthroplasty has a low (50%) success rate and TMJ reconstruction is often indicated with autogenous or alloplastic materials (28).

Hypermobility Disorders

Hypermobility leading to subluxation or dislocation of the TMJ can occur with yawning, prolonged opening, during a seizure, or due to trauma. A subluxed condyle becomes temporarily trapped anterior to the articular eminence. Typically, the patient will spontaneously self-reduce the mandible. Treatment is often necessary with dislocation. Dislocation implies the need for manually assisted mandibular reduction. Immediate manual reduction is essential as manipulation becomes more difficult with time. If the patient experiences repetitive dislocations with pain interfering with daily function, surgical intervention is considered. Surgical options include plication with wires, osteotomy of the zygomatic arch (Le Clerc procedure) to create an obstruction and eminectomy to remove obstruction and allow spontaneous reduction of the subluxed mandible. With eminectomy, subluxation will continue to occur, but without risk of dislocation. Lateral pterygoid myotomy is described by some authors as beneficial therapy (33–36).

Posttraumatic TMDs

Maxillofacial trauma may be the initiating event in certain cases of TMD. Many types of traumatic events are associated with temporomandibular dysfunction, including accidental, assault-related, or surgical trauma. Fractures of the mandible and surrounding structures often require treatment by the otolaryngologist, and awareness of their effect on the temporomandibular articulation is helpful.

Mandibular fractures often cause pain, malocclusion, restricted opening, loss of mandibular height, muscle spasm, or deviation of the mandible to one side. If not properly addressed, any of these features may cause disabling TMD. Normal TMJ function requires a complex mechanism of intact bone and balanced muscular forces, and traumatic disruption of any of these elements can lead to joint pathology. Anatomic reduction and rigid fixation, when indicated, are important for a good functional outcome.

Fracture of the mandibular condyle, in particular, tends to predispose to pathology of the TMJ. Condylar fractures comprise around 30% of mandible fractures, and may involve the condylar neck or, more rarely, be intracapsular. The position of the articular disc relative to the fracture site is thought to have prognostic significance. Disk displacement from the fracture appears to strongly predispose to posttraumatic joint ankylosis, as the insulating role of the disk between the articulating surfaces is lost. Joint ankylosis, or fusion, is perhaps the most severe form of TMD and produces complete joint immobility on the affected side. This is not frequently encountered in the industrialized world, but in developing countries it is quite a common consequence of mandibular trauma. Up to 98% of ankylosis cases have been estimated to originate from trauma to the mandibular condyle (37). This may be particularly common in sagittal fractures, especially when a bone fragment with a raw edge is displaced laterally or there is another, associated mandible fracture (38–40) (Fig. 54.3).

The treatment of mandible fractures involving the condylar process has long been controversial. Generally, anatomic reduction and fixation of condylar fractures in

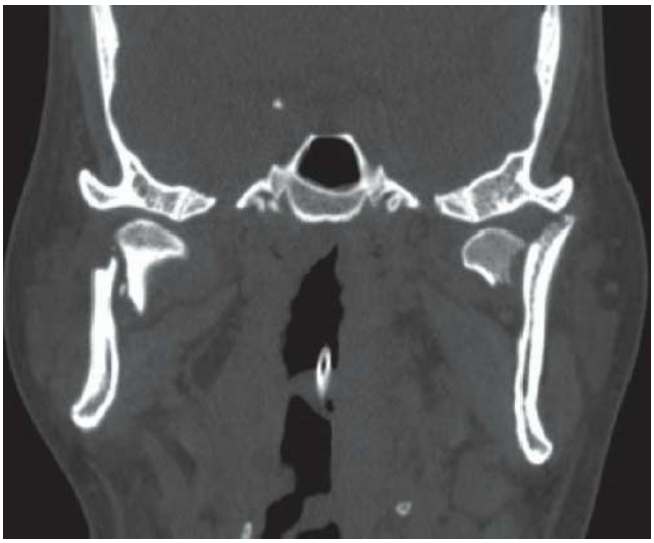


Figure 54.3 CT—bilateral mandibular condyle fracture.

adults is recommended when there is loss of mandibular height or gross comminution or dislocation of fractured segments. Anatomic fracture reduction along with postoperative rehabilitation seems to generate good results (41). However, there is a lack of studies directly comparing different treatment modalities for fracture with regard to TMJ function in adults. In children and adolescents, nonsurgical management yields excellent functional TMJ results (42).

Fractures of the skull base may affect the TMJ by involving the glenoid fossa or the adjacent external auditory meatus. Such trauma may directly disrupt the joint or cause bleeding and inflammation in the joint space, resulting in pain and dysfunction. Often these fractures are the result of life-threatening multitrauma and the involvement of the TMJ is not noticed or is not a priority. When evaluating fractures through the temporal bone, which are covered in detail elsewhere, the otolaryngologist is well-served to note their relationship to the TMJ. These fractures are generally not addressed surgically, but diagnosis and institution of TMJ rehabilitation may be helpful.

FOCUSED HISTORY AND PHYSICAL EXAM

When obtaining a history, trauma is occasionally discovered as a precipitating event. As previously mentioned, other contributing physical, emotional, and psychological factors need to be identified. It is important to define the duration of symptoms, any history of trauma or other inciting factors, the nature of pain including its onset, location, quality, timing, associations (with motion, with mastication, with awakening, or after the day's work), modifying factors that make symptoms better or worse and the presence or absence of joint sounds, limitation in range of motion, and presence of parafunctional habits. It is helpful to inquire about whom the patient has seen for the presenting problem and what studies and/or treatments (medical, surgical, appliances, physical therapy, occlusal adjustments, or counseling) have been attempted.

As part of the head and neck examination, evaluation of the TMJ generally includes an assessment of the jaw range of motion, auscultation for joint sounds and palpation, with the goal of reproducing the patient's chief complaint.

The head and neck should be inspected for symmetry and alignment of the face, jaws, and teeth. The muscles of mastication, specifically the temporalis and masseter muscles, should be palpated for point tenderness.

When assessing mandibular range of motion, the maximum comfortable opening, maximum opening with pain (active range of motion) and maximum assisted opening (passive range of motion), should be measured. Measurements are made from maxillary to mandibular incisal edges and recorded in millimeters. Normal opening should be smooth, pain free, and without noise or deviation. The location of pain with opening and the presence and location of joint sounds should be noted along with the presence and direction of deviation.

With internal derangement, deviation is toward the side of obstruction (disc displacement) as the normal side functions appropriately. An early deviation with return to smooth midline opening and closing implies early disc displacement with reduction. Deviation toward the affected side along the entire, yet limited range of motion, with no joint sounds, is a sign of disc displacement without reduction. As disc displacement becomes more chronic in nature, the range of motion follows a similar pattern but is generally greater.

Lateral excursive movements are measured from the midline incisal edge at starting, to end lateral excursive movement—recorded in millimeters. Lateral excursions are diminished in a direction away from the involved joint when a nonreducing disc displacement is present. Limited range of motion with consistent deviation on opening but equal lateral excursive movements implies a muscular disorder.

Joint sounds are common in the general population. Nonpainful joint noises without restriction in range of motion do not require intervention. Clicks are described as early, middle, or late, occurring during opening or closing. Crepitus can also be auscultated and/or palpable and may be present with disc perforation, osteophytes, or bone on bone articulation.

The TMJ should be palpated bilaterally evaluating condylar movement, pain, swelling, and crepitus. The patient can be examined for tenderness over the joint capsule or retrodiscal tissue. Preauricular and endaural palpation should be performed.

Intraoral inspection and palpation for odontogenic or other sources of pain and inflammation should be carried out. The clinician should evaluate for signs of parafunction such as bruxism (e.g., wear patterns on teeth inappropriate for age or normal function, excessive tooth mobility, buccal mucosal ridging, or lateral tongue scalloping) (43–45).

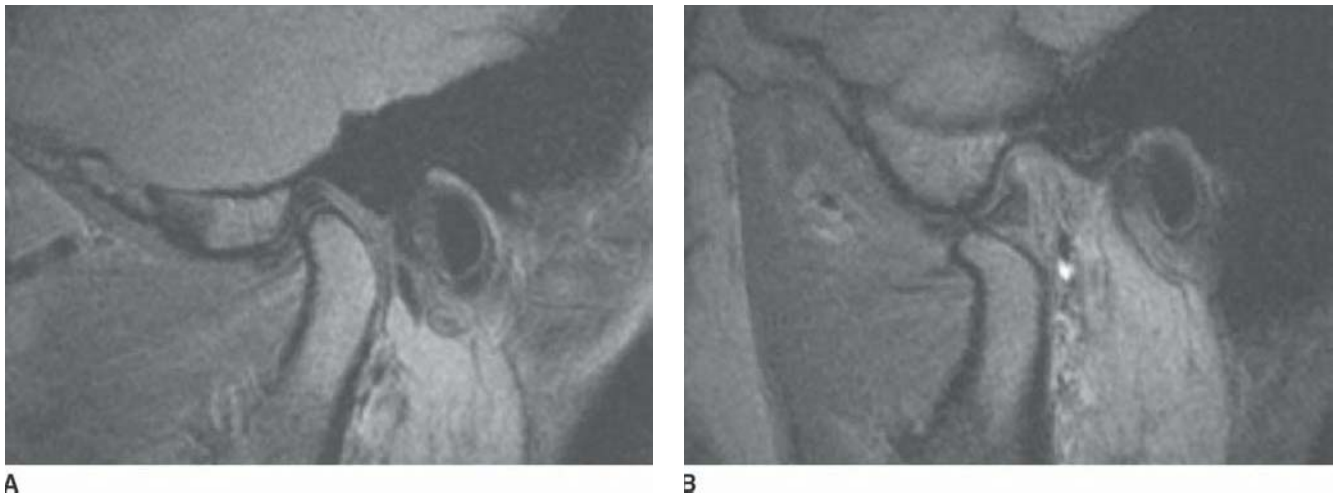


Figure 54.4 **A:** MRI—normal TMJ closed mouth view. **B:** MRI—normal TMJ open mouth view.

IMAGING

Imaging often begins with the panoramic radiograph. The panorex is an excellent screening tool. It is readily available, and quickly and easily rules out fracture, gross arthritic changes, tumors, cysts, or malformations. As with other evaluations of the head and neck, CT is helpful for evaluating bony abnormalities and gives information about the soft tissue structures as well. MRI gives greater soft tissue detail and is considered the imaging modality of choice for suspected disc–condylar abnormality (internal derangement) (Fig. 54.4A and B). Radiographic findings need to be interpreted with caution, however. Disc displacement and degenerative joint disease is frequently seen in asymptomatic "normal subjects" (46,47).

DIFFERENTIAL DIAGNOSIS

TMD pain frequently mimics other diseases seen by the otolaryngologist. Ear complaints are the most common such presentation of TMD and often consist of otalgia, aural fullness, tinnitus, and crackling or popping sounds of the ear on the affected side. Less commonly, patients report hearing loss or hearing described as "in a tunnel" on the affected side. Feelings of imbalance and dizziness are occasionally reported.

In 996 patients referred by an otolaryngology practice to a TMD treatment center, 85% complained of ear symptoms, including otalgia (64%), dizziness (42%), and muffled hearing (30%). Sixty percent complained of throat symptoms, while headaches were reported by 81% (48). In all comers with TMD, the reported prevalence of otologic complaints varies widely, but it is well established that they are an important part of the symptom complex of TMD. Ear symptomatology as a whole may be more prevalent in patients with myofascial disorders than in those with internal joint derangements, and overall pain perception referable to TMD tends to be worse in those with ear symptoms than those without. One group reports a statistically significant association between pain on palpation of the condyle and otalgia derived from TMD. Ear symptoms do tend to improve with treatment of TMD, as seen in studies comparing symptoms before and after conservative treatment with dental occlusal appliances and nonsteroidal anti-inflammatory drugs (NSAIDs) (49,50).

A comprehensive otologic workup must be carried out by the otolaryngologist to rule out ear disease before aural symptoms are attributed to TMD. In the presence of an ear exam that does not correspond with the presenting complaint, preauricular tenderness to palpation, as well as pain on palpation of the lateral anterior wall of the external auditory canal (EAC), indicates temporomandibular involvement. Occasionally, the degree of inflammation of the TMJ is such that it creates pain and edema of the shared anterior wall of the EAC, which may be mistaken for otitis externa. The dentition should be examined for signs of wear and the appropriate history elicited with regard to bruxism and other TMD risk factors.

TMJ dysfunction may masquerade as many other complaints in the head and neck, or be associated with these complaints. Occasionally, the patient with severe TMD that produces facial pain, tenderness to palpation, and edema will be diagnosed with and treated for parotitis. The proximity of the parotid gland to the TMJ contributes to this confusion, and the gland must be examined with care to rule out pathology.

Perhaps not surprisingly, emerging evidence suggests a link between TMD and headache. Certainly the two disorders appear to share psychosocial predisposing factors. Tension type, chronic daily headaches, and temporal headaches are most closely associated with TMD, and TMD severity appears to be correlated with frequency in some headache types (51–53). Neck pain or stiffness may also be present, as has been reported in up to a third of TMD patients (54).

MANAGEMENT

Management of TMDs is divided into surgical and nonsurgical options. The majority of TMDs are self-limiting. No consensus exists across the practicing community regarding when and how to treat various TMDs and even which TMD problems should be treated. Since no good long-term studies exist, data does not as yet support the superiority of any method of management. The efficacy of most treatment approaches is unknown. Noninvasive, reversible therapies that include educational, dietary, medical (nonsteroidal anti-inflammatory pain medications and muscle relaxants), prosthetic (occlusal appliance), physical therapy (heat, ice, exercise) or behavioral approaches (eliminating parafunctional habits—such as clenching or grinding—that may be harmful), and psychotherapy are therefore preferred for the majority of TMJ-related issues. The goal of therapy is to do what is least invasive and reversible if at all possible while attempting to decrease pain and improve function. Clinical studies indicate that when conservative, reversible, noninvasive therapy is emphasized, the presenting signs and symptoms improve in the vast majority of patients.

No evidence exists to say that restorative dentistry, orthodontic treatment, or orthognathic (jaw-straightening) surgery predisposes to, prevents, or causes TMD. Extensive restorative dental procedures should be avoided. No treatment is necessary when there is absence of pain and/or no loss of function.

Excessive over jet (a smaller lower jaw relative to the upper jaw in the anteroposterior plane) is the only jaw deformity that correlates with an increased risk of TMD (55). TMDs such as condylar resorption may contribute to anterior open bite malocclusion. No evidence exists to suggest that anterior open bite causes TMJ pain. Overall, with the exception of mandibular deficiency with associated Angle Class II malocclusion, the current literature does not support the role of dental malocclusion as an etiologic factor in disorders of the TMJ (56).

Treatment planning for TMDs may be based on medical and dental history, physical exam, audiology testing, speech and swallowing evaluation, psychosocial assessments related to quality of life, and imaging. A multidisciplinary approach is favored. Consultation with pain specialists, physical therapists and behavioral therapists and/or psychiatrists is often requested. Depression is associated with TMJ complaints and chronic pain (57–60).

The role of surgery to address TMJ disc abnormalities is controversial. Nonsurgical, conservative therapies are undertaken with good success in most cases. A small percentage of patients who have persistent, significant pain and disabling dysfunction with pathology directly involving the TMJ proper (degenerative disc and intracapsular disease), and for whom conservative treatment has failed, may be considered candidates for surgical intervention. Temporomandibular arthrocentesis (joint lavage), arthroscopy, or open joint surgeries are all options, but randomized controlled trials to support the efficacy of individual surgical procedures have not been performed. Additional TMJ problems that may require surgery include trauma, arthritis and disc disease, ankylosis, growth disorders, recurrent dislocation, neoplasia, and fractures.

Whatever the problem or treatment approach entails, the patient and clinician should share a common understanding of the scientific basis, indications, goals, risks and benefits, and prior history of the proposed intervention before moving ahead.

Supportive patient education, nonsteroidal anti-inflammatory agents, a diet limited to what is comfortable and physical therapy are attempted prior to irreversible interventions such as surgery. Occlusal appliance therapy and psychological assessments and behavioral therapy are often employed as nonsurgical means of treatment with good success. Surgery is considered a last resort, for those who fail conservative treatment, or for those with severe pain and loss of function.

Occlusal Appliance (Splint) Therapy

Parafunction (bruxism) is related to the development of myofascial pain (61,62). Multiple, various TMJ splints have been used over the past century. They differ in design, rationale for use, and manner of use. Occlusal appliances include repositioning devices meant to "unload" the joint, position the lower jaw anteriorly, or increase the vertical dimension of occlusion. Studies have shown TMJ splints to be effective for myofascial pain and for protection of the dentition in patients with parafunctional habits, but the type of splint has little consequence. Splint therapy has not been shown to be efficacious in treatment of intracapsular TMDs other than to possibly "unload" the joint and reduce inflammation. Reduction in inflammation may result in an improvement in jaw range of motion (63–65). Posttreatment imaging (MRI) studies have not shown an effect on disc position (66). Splint therapy does not alter the course of degenerative or inflammatory joint disease (67,68).

Each type of splint has its proponents. Soft splints are thought to encourage bruxism (69,70). Repositioning appliances have shown a high rate of recurring joint noise and progressive pain (71,72). Bite plane splints cover the anterior teeth with no posterior contact and are used with the hope of disrupting mandibular proprioception to decrease muscle activity (73). Prolonged use can cause changes in the occlusion.

The authors prefer an appliance that does not introduce irreversible change in either the occlusion or disk/condylar morphology. The indication is primarily for management of myofascial pain (74–76), effective in approximately 70% of cases (77). It is not known why splint therapy is effective, but electromyographic studies have shown a short-term decrease in temporalis and masseter muscle activity (78–80). A flat plane occlusal appliance fabricated in centric relation and adjusted to maintain posterior and



Figure 54.5 Maxillary flat plane occlusal appliance with ball clasps.

anterior even contacts with canine guidance or group function in protrusive and lateral excursions, serves this purpose. The flat plane occlusal appliance is made of a hard acrylic and covers the occlusal surface of the teeth and is worn on the maxillary or mandibular arch. Ball clasps may be used to aid retention (Fig. 54.5).

The Cochrane Database states that there is insufficient evidence to either support or discourage use of TMJ splint therapy (81,82). Further studies are necessary to validate the use of TMJ splints. Cognitive awareness and positive patient expectations may have more to do with the success of splint therapy than the biomechanical impact of occlusal appliances (83–86). In a patient with a significant parafunctional habit, at the very least, occlusal appliances may provide protection for the dentition.

Pharmacotherapy

Medical management is used to reduce pain and inflammation. NSAIDs are effective in myofascial pain, synovitis, osteoarthritis, and symptomatic disc displacement (87). Corticosteroids are useful in acute hypomobility disorders associated with pain. Prolonged use is not indicated due to the negative effects of long-term steroid use. The decision to use narcotic analgesics is a difficult one. The clinician should realize that TMDs often represent a chronic pain condition and opioid analgesics are therefore only indicated for short durations and used with caution. Many clinicians prescribe muscle relaxants for patients with TMDs. Patients report little benefit and the authors therefore do not routinely use muscle relaxants. Muscle relaxants may play a role in myofascial pain, bruxism, and hyperactivity of the masticatory musculature in parafunction. There is no benefit in patients with intracapsular TMDs. Botulinum toxin A is effective in treatment of a hyperactive masticatory system and in patients with dystonia (88–91). Anxiolytics and antidepressants also play a role in the management of chronic pain conditions. A full discussion of pharmacologic agents used in the management of facial pain is beyond the scope of this chapter.

Physical Therapy

Physical therapy includes range of motion exercises, massage, thermal treatments, ultrasound, and electrical stimulation. At home physical therapy prescribed by the treating clinician or provided by a trained physical therapist is beneficial and directed toward reducing pain and inflammation and improving range of motion.

TMJ SURGERY—CLOSED

Arthrocentesis

Joint effusion seen on MRI is an indicator of inflammation associated with hypertrophy of the synovial lining and production of exudates. Arthrocentesis is an effective initial procedure used to dilute inflammatory mediators with the hope of reducing pain in patients who have not responded to nonoperative therapy (92). Arthrocentesis is also indicated for patients with increased negative pressure within the joint causing the disc to be adherent to the fossa during motion. This may be secondary to a dysfunction of the natural lubrication system within the joint secondary due to cellular injury caused by hypoxia and reperfusion as discussed earlier in the chapter. Reactive oxygen species lead to degradation of surface-active phospholipids. Hyaluronic acid serves to protect these phospholipids from phospholipase A2, and helps maintain mobility of the joint. Degradation leads to a reduction in synovial fluid viscosity (93) and restricted mobility. Proinflammatory cytokines (IL-1B, TNF-α, IL-6, IL-10) induced by inflammation are associated with pain and dysfunction within the joints. Arthrocentesis reduces proinflammatory mediators within the joint to decrease pain and improve range of motion.

Arthrocentesis is performed using an 18 gauge needle as an inflow track positioned at a 10:2 point along the tragal–canthal (Holmlund-Hellsing) line. A second 18 gauge needle is placed just anterior, as an outflow track, and 100 mL normal saline is used to lavage the joint. After completion, the jaw is manipulated with a goal of achieving 40 mm interincisal opening. Steroids or sodium hyaluronate can be injected to reduce inflammation or improve the lubrication of the joint. Nitzan et al. (94) demonstrated the rationale and effectiveness of arthrocentesis in relieving closed lock with improvement in function and pain reduction. Laskin reported an 88% success rate in 39 joints.

Arthroscopy

In 1975, Ohnishi (95) was the first to use a Watanabe small-joint arthroscope to enter the TMJ. TMJ arthroscopy was initially developed as a diagnostic procedure.

As techniques have evolved, arthroscopy has become more than a diagnostic tool and is most often employed to improve range of motion and decrease pain through removing scar tissue, stretching the capsular ligament, resurfacing the joint surfaces, disc repositioning, lysis of adhesions, and lavage (to wash out inflammatory mediators) with or without direct injection of therapeutic agents. The success rate approximates that of arthrocentesis (96,97). Dolwick and Nitzan showed that arthrocentesis with lysis and lavage without placement of a scope gives similar results (92). Potential complications of both arthrocentesis and arthroscopy are rare, although risk is greater with arthroscopy. For the majority of TMJ surgeons, arthroscopic lysis and lavage have been replaced by arthrocentesis alone (98).

Open TMJ Surgery for Internal Derangement

The goal of open surgery is to allow the patient to return to normal daily function through reduction in pain, improved range of motion, and the ability to tolerate a regular diet by addressing the anatomical limitation and restoring a near normal anatomy of the joint. More often than not, open surgery is employed after attempts at nonoperative management, arthrocentesis, and/or arthroscopic lysis and lavage have failed. Occasionally, with significant pain and functional impairment, surgery is attempted early on.

Open surgery attempts to repair or reposition the disc or remove the disc with or without replacement. Arthrotomy is reserved for ankylosis, tumor resection, trauma, growth disturbances, and severe degenerative joint disease. Preauricular, postauricular, or endaural skin incision approaches allow access to the joint.

Complications of open joint surgery include persistent pain, hemorrhage, infection, auriculotemporal nerve and facial nerve injury, formation of fibrous adhesions, occlusal change, and ankylosis (more commonly with discectomy alone) (99).

After surgery, the author recommends the following TMJ surgery–specific postoperative instructions: Patients are asked to apply ice for the first 24 hours after surgery and then heat. The occlusal appliance is worn continuously after surgery and adjusted as necessary to maintain even occlusal contacts.

Patients need to understand that mouth opening will be limited during the first week to 10 days after surgery. Postoperative jaw opening exercises are prescribed.

After the initial 2 weeks analgesics are taken only as needed, and exercises can be performed on a less formal basis. In addition, patients are asked to continue oral appliance wear, and to remove the oral appliance only for routine oral hygiene. The postoperative diet is initially full liquid and advanced to mechanical soft over 2 weeks, and to regular as tolerated. Patients are asked to avoid hard, chewy foods such as pizza crusts, bagels, and submarine sandwiches indefinitely.



Figure 54.6 Prosthetic joint TMJ concepts, Inc., Ventura, CA.

TMJ Reconstruction

TMJ reconstruction is indicated for congenital or developmental deformity, after tumor resection, in severe degenerative joint disease, and for treatment of bony ankylosis. Reconstruction is currently performed using autografts (costochondral) or alloplastic joint replacements (Fig. 54.6). The preauricular approach is combined with a submandibular incision in most cases, although transparotid/transfacial approaches are also of value. TMJ alloplasts have strong supporters and opponents. TMJ alloplasts have resulted in significant past failures (100,101). A few FDA approved joint replacements have shown success (102).

CONCLUSION

TMJ dysfunction is common in the general population and often will be diagnosed by the otolaryngologist when investigating complaints related to the ear or other head and neck structures. TMD can be broadly divided into intracapsular and myofascial pathology and the distinction is an important one to make if the correct treatment is to be instituted. Parafunctional habits, chronic pain states, psychosocial comorbidity, or a history of trauma is often elicited from patients with TMD. Treatment should begin

with patient education and proceed conservatively with reversible pharmacologic measures, lifestyle modifications, and occlusal appliance therapy. Surgery is generally reserved for those failing conservative measures or experiencing unrelenting symptoms, and no surgical approach has been shown to be superior to others. TMD therapy remains a highly individualized process, with long-term participation required of both the patient and clinician.

HIGHLIGHTS

- TMDs refer to conditions affecting the TMJ, muscles of mastication, or both and often has an effect on neighboring structures.
- Patients with complaints of TMJ-related pain often have parafunctional oral habits or a history of trauma, as well as concomitant medical or psychological conditions.
- The TMJ exists between the base of the skull (temporal bone) and the mandible. The articulating bony surfaces, the articular disk, several ligaments, and numerous associated muscles make up the joint.
- TMDs typically present with pain with mandibular function, limitation of mandibular movement and joint sounds.
- Intracapsular disorders imply a concrete disc–condylar fossa abnormality and are associated with joint noise, and abnormal, often limited condylar movement.
- TMD pain frequently mimics other diseases seen by the otolaryngologist.
- Supportive patient education, nonsteroidal anti-inflammatory agents, a diet limited to what is comfortable, occlusal appliance, behavioral and physical therapy are attempted prior to irreversible interventions such as surgery.
- Open surgery attempts to repair or reposition the disc or remove the disc with or without replacement.
- Arthrotomy is reserved for ankylosis, tumor resection, trauma, growth disturbances, and severe degenerative joint disease.
- TMJ reconstruction is indicated for congenital or developmental deformity, after tumor resection, in severe degenerative joint disease, and for treatment of bony ankylosis.

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55 Deep Neck Infections

Behrad B. Aynehchi *Gady Har-El*

Deep neck space infections (DNSIs) are a relatively infrequent entity in the postpenicillin era. Their occurrence, however, poses considerable challenges in diagnosis and treatment and they may result in potentially serious or even fatal complications in the absence of timely recognition. The advent of antibiotics has led to a continuing evolution in etiology, presentation, clinical course, and antimicrobial resistance patterns. These trends combined with the complex anatomy of the head and neck underscore the importance of clinical suspicion and thorough diagnostic evaluation. Proper management of a recognized DNSI begins with securing the airway. Despite recent advances in imaging and conservative medical management, surgical drainage remains a mainstay in the treatment in many cases.

ETIOLOGY

Knowledge of the portal of entry enables the surgeon to anticipate the pathway of extension within the neck, potential complications, and sites for drainage. In the preantibiotic era, the majority of deep neck infections in adults and children originated from the tonsils and pharynx, most commonly leading to parapharyngeal space infections (1). Acute rhinosinusitis in children may also cause retropharyngeal lymphadenitis. Suppuration of these inflamed nodes can eventually culminate in abscess formation. Early administration of antimicrobials in adult patients has led to a decreased incidence of upper respiratory tract infections and consequently significantly fewer DNSIs originating from this site. This trend has given way to infections of odontogenic sources becoming the primary source of deep neck infection in adults, recognizing a strong association with poor oral hygiene and lower socioeconomic status (2). Additional but less common origins of deep neck infections include salivary gland infections, penetrating trauma, surgical instrument trauma, spread from superficial infections, necrotic malignant nodes, mastoiditis with resultant Bezold's abscess, and unknown causes (3–5). In inner cities, where intravenous drug abuse (IVDA) is more common, there is a higher prevalence of infections of the jugular vein and carotid sheath from contaminated needles (6–8). The emerging practice of "shotgunning" crack cocaine has been associated with retropharyngeal abscesses as well (9). These purulent collections from direct inoculation, however, seem to have a more benign clinical course compared to those spreading from inflamed tissue (10). Congenital anomalies including thyroglossal duct cysts and branchial cleft anomalies must also be considered, particularly in cases where no apparent source can be readily identified. Regardless of the etiology, infection and inflammation can spread throughout the various regions via arteries, veins, lymphatics, or direct extension along fascial planes. When confined to a certain area or space, this inflammatory process will eventually form a phlegmon or abscess.

FASCIAL ORGANIZATION OF THE DEEP NECK

An understanding of the applied anatomy of the neck includes a consideration of the layers of the deep cervical fascia and the compartments or spaces formed by the arrangement and attachments of these layers. This knowledge is crucial for planning treatment strategies and anticipating potential complications. The cervical fascia is divided into the superficial and deep fascia. The deep fascia is further subdivided into three layers or components: the superficial, middle, and deep. A summary of the organization of the cervical fascia is presented in Table 55.1. Figure 55.1 features a midsagittal visualization of the fascia and deep neck spaces.

TABLE 55.1 CLASSIFICATION OF FASCIA IN THE NECK

- Superficial cervical fascia
- Deep cervical fascia
  - Superficial layer of the deep cervical fascia
  - Middle layer of the deep cervical fascia
    - Muscular layer
    - Visceral layer
  - Deep layer of the deep cervical fascia
    - Alar fascia
    - Prevertebral fascia
  - Carotid sheath formed by contributions of superficial, middle, and deep layers of deep cervical fascia

Superficial Cervical Fascia

The superficial cervical fascia lies beneath the skin of the head and neck, extending from the top of the head down to the shoulders, axilla, and thorax. This layer covers adipose tissue, sensory nerves, superficial vessels, lymphatics, the platysma muscle, and the muscles of facial expression. The platysma is absent in the midline. In contrast to the deep cervical fascia, which is composed of mainly fibrous connective tissue, the superficial cervical fascia is a layer of fibrofatty tissue connecting the overlying skin to the deeper fascial layers. Infections of this superficial space should be managed with appropriate antibiotic therapy in the case of cellulitis or extended to incision and drainage in the presence of an abscess (11).

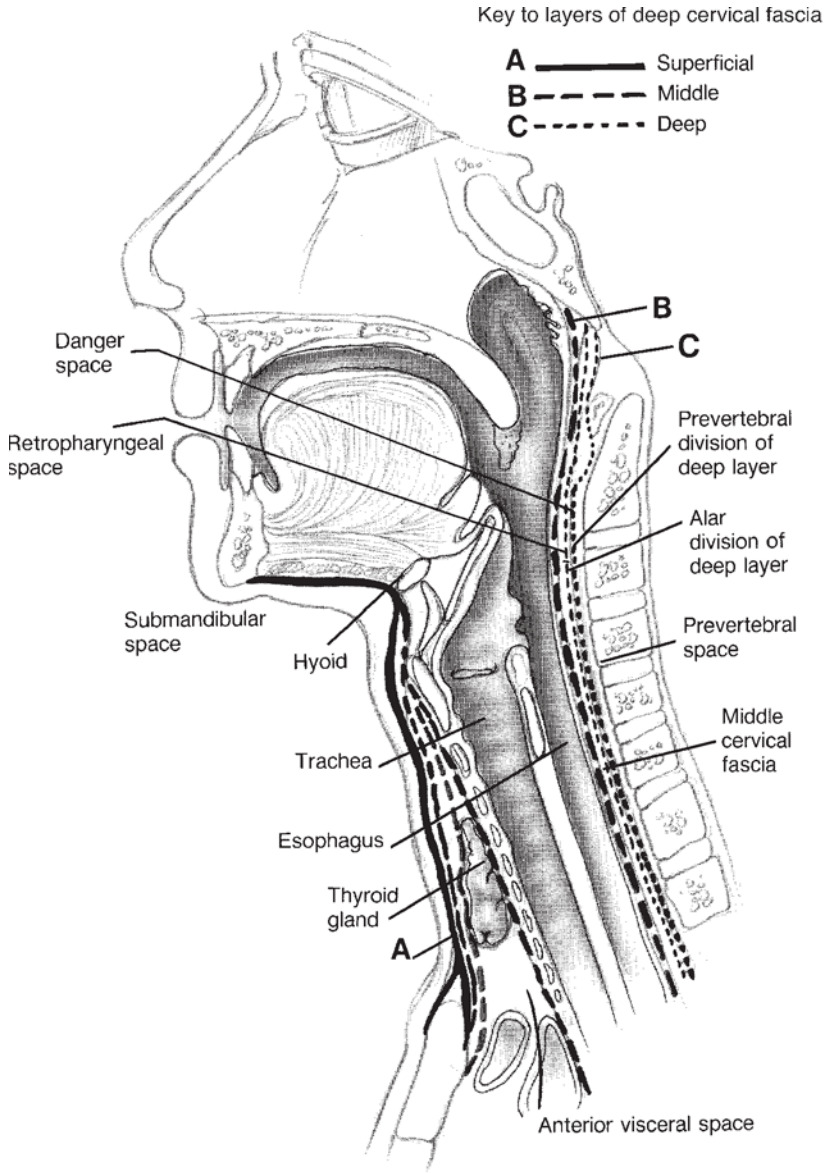


Figure 55.1 Midsagittal section of the neck shows the fascia and spaces of the neck.

Deep Cervical Fascia

As noted earlier, the deep cervical fascia is a fibrous connective tissue layer that is, for surgical purposes, subdivided into the superficial, middle, and deep components. The appropriate designation for each layer is as follows: the superficial layer of the deep cervical fascia, the middle layer of the deep cervical fascia, and the deep layer of the deep cervical fascia. A practical observation is that layers overlying nonexpansile components such as the sternocleidomastoid muscle (SCM) are well-developed membranes that can be sutured. On the other hand, fascia surrounding expansile visceral organs such as the pharynx and cheeks is a loose areolar tissue, not amenable to suture retention. Additionally, muscles and organs within these layers are generally free to glide upon contraction and relaxation.

The superficial layer of the deep cervical fascia, also referred to as the investing layer, completely surrounds the neck. The superior nuchal line, ligamentum nuchae of the cervical vertebrae, and the mastoid process are the posterior attachments. The fascia splits to envelope the sternocleidomastoid and trapezius muscles as it courses anteriorly. In the anterosuperior direction, an attachment is made to the inferior zygomatic arch. Moving inferiorly, the parotid gland is enveloped superficially, while the deep extent involves the carotid canal of the temporal bone. The stylomandibular ligament, which separates the parotid and submandibular glands, is formed as this investing fascia tracks anteriorly to cover the submandibular gland and muscles of mastication. The inferior extent includes attachments to the hyoid, acromion, clavicle, and scapular spine. The suprasternal space of Burns is formed as the fascia surrounds the intermediate tendon of the omohyoid muscle. This space may contain a lymph node along with a vessel bridging the two anterior jugular veins (12). A useful tool in understanding the contents of this plane is the "rule of two's," referring to the two muscles above the hyoid bone (masseter and anterior belly of the digastrics), two muscles that cross the neck (trapezius and SCM), two salivary glands (parotid and submandibular), and two fascial compartments (parotid and masticator spaces) (11).

The middle layer of the deep cervical fascia, also called the visceral fascia, is divided into a muscular and visceral division. The muscular division of the middle layer of the deep cervical fascia surrounds the sternohyoid, sternothyroid, thyrohyoid, and omohyoid strap muscles. Contents of the visceral division include the parathyroid glands, thyroid gland, esophagus, trachea, larynx, pharyngeal constrictor muscles, and buccinator muscle. This visceral division further contributes to two additional planes: the pretracheal fascia and buccopharyngeal fascia. The pretracheal fascia overlies the trachea. The buccopharyngeal fascia lies posterior to and separates the esophagus from the deep layer of the deep cervical fascia. This plane also marks the anterior border of the retropharyngeal space. The buccinators, pharyngeal constrictor muscles, and esophagus lie between the pharyngobasilar fascia anteriorly and the buccopharyngeal fascia posteriorly (12). The two raphes formed by the buccopharyngeal fascia include the posterior midline raphe, which attaches to the alar layer of the deep layer of the deep cervical fascia, and the pterygomandibular raphe within the lateral pharynx (11). Portions of the middle layer of the deep cervical fascia that surround the trachea and esophagus merge with the fibrous pericardium in the superior mediastinum, representing a possible portal of spread of infection.

The deep layer of the deep cervical fascia, also known as the prevertebral fascia, is composed of two divisions as well: the prevertebral and alar divisions. The prevertebral division contains the cervical vertebra, phrenic nerve, and paraspinous muscles. This fascia runs from the skull base to the coccyx, forming the anterior wall of the prevertebral space, with lateral and posterior attachments to the transverse spinous processes, respectively. The clinical significance of this boundary is the confinement of primary vertebral infections to the prevertebral space with very limited spread to the danger space. The alar division is situated between the prevertebral division posteriorly and the buccopharyngeal fascia of the visceral division of the middle layer of the deep cervical fascia anteriorly, separating the retropharyngeal and danger spaces. This layer extends from the skull base to the second thoracic vertebra. The notable structure within this plane is the cervical sympathetic trunk. In reviewing the deep fascial and special relationships within the neck, the following structures are encountered as one goes from anterior to posterior: the pharyngobasilar fascia, the esophageal or constrictor musculature, the buccopharyngeal fascia of the visceral division of the middle layer of the deep cervical fascia, the retropharyngeal space, the alar division of the deep layer of the deep cervical fascia, the danger space, the prevertebral division of the deep layer of the deep cervical fascia, the prevertebral space, and finally the vertebral body (12).

The carotid sheath is formed by contributions of all three layers of the deep cervical fascia, extending from the skull base to the thorax. Contents of this sheath include the common carotid artery, internal jugular vein (IJV), vagus nerve, and ansa cervicalis (11).

DEEP NECK SPACE ANATOMY

The above-mentioned planes of the deep cervical fascia form various real and potential spaces within the neck. These spaces though are not completely impermeable often communicate with each other in generally predictable routes. Strong fascial connections to the hyoid bone anteriorly that may function as a barrier to the inferior spread of infection have led to the classification of these spaces based on their relationship to this landmark. The spaces will be described as those involving the entire neck (retropharyngeal space, danger space, prevertebral space, and carotid space), those that lie above the hyoid bone (parapharyngeal space,

TABLE 55.2 DEEP NECK SPACES

- Spaces involving the entire length of the neck
  - Retropharyngeal space
  - Danger space
  - Prevertebral space
  - Carotid space
- Spaces limited to above the hyoid bone
  - Parapharyngeal space
  - Submandibular space
  - Parotid space
  - Masticator space
  - Peritonsillar space
  - Temporal space
- Spaces limited to below the hyoid bone
  - Anterior visceral space
  - Suprasternal space

submandibular space, sublingual space, parotid space, masticator space, peritonsillar space, and temporal space), and those that lie below the hyoid bone (anterior visceral space and suprasternal space). Table 55.2 outlines the classification of the aforementioned spaces.

Spaces Involving the Entire Neck

Retropharyngeal Space

The retropharyngeal space extends from the skull base to the tracheal bifurcation in the superior mediastinum (Figs. 55.2–55.4). The space is medial to the carotid sheath, anterior to the danger space, and posterior to the buccopharyngeal fascia of the visceral division of the middle layer of the deep cervical fascia. The nodes of Rouviere reside within this space and may cause abscess formation upon drainage from the paranasal sinuses or nasopharynx, especially in children. A midline raphe connecting the alar division of the deep layer of the deep cervical fascia to the buccopharyngeal fascia accounts the off-midline presentation of infections within this space, facilitating distinction from disease processes originating within the danger and prevertebral spaces, which generally lie in the midline. Routes of direct spread are mainly from the parapharyngeal space (12).

Danger Space

The danger space is flanked by the prevertebral and retropharyngeal spaces, extending from the skull base to the level of the diaphragm with minimal resistance (hence the name). It is bordered laterally by the transverse processes of the vertebrae (Fig. 55.4). The most noteworthy structure within this space is the cervical sympathetic trunk. Common sources of infectious spread are from the retropharyngeal, parapharyngeal, and prevertebral spaces (12).

Prevertebral Space

This space runs from the skull base to down to the coccyx, bordered by the vertebral bodies posteriorly, danger space anteriorly, and transverse processes laterally (Fig. 55.4). The dense areolar tissue within this space is in contrast to the loose counterpart found within the danger space. The main neurovascular constituents include the vertebral

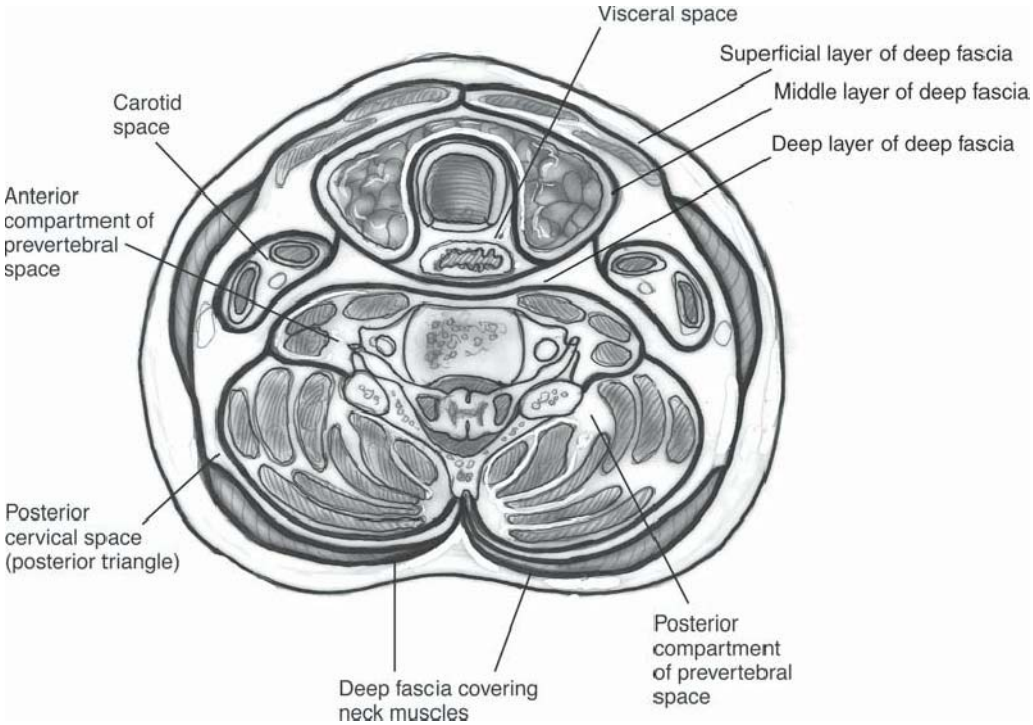


Figure 55.2 Cross section of the neck at the thyroid level.

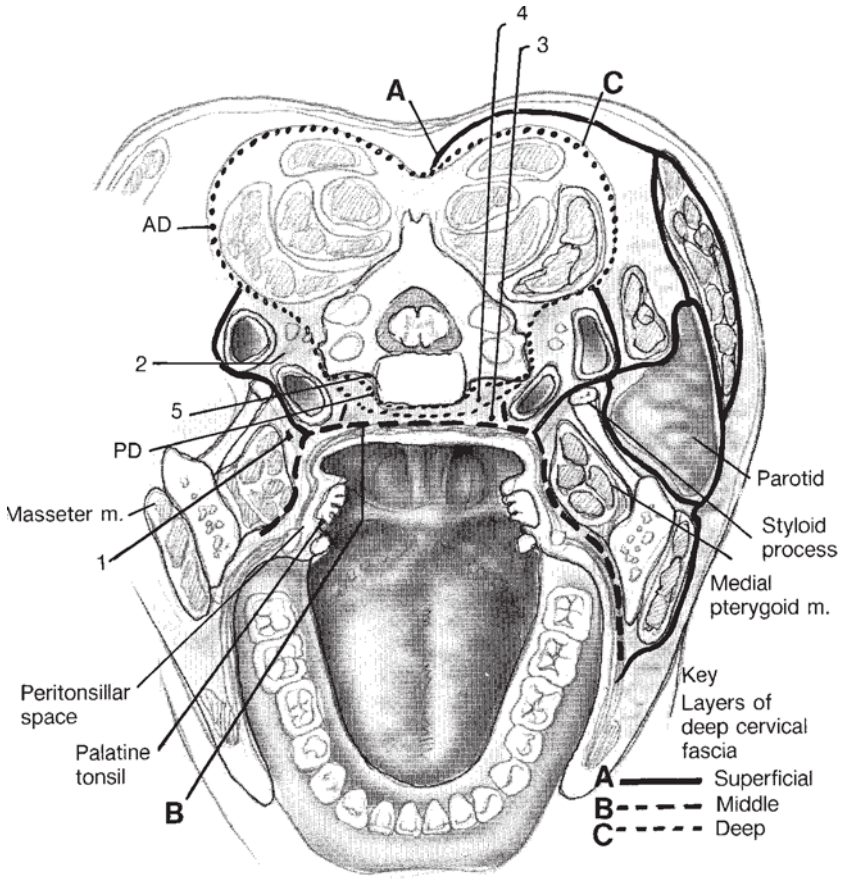


Figure 55.3 Cross section of the neck at the level of the oropharynx shows the anatomic relations of the deep neck spaces. *1*, parapharyngeal space; *2*, carotid space; *3*, retropharyngeal space; *4*, danger space; *5*, prevertebral space; AD, alar division of deep layer; PD, prevertebral division of deep layer.

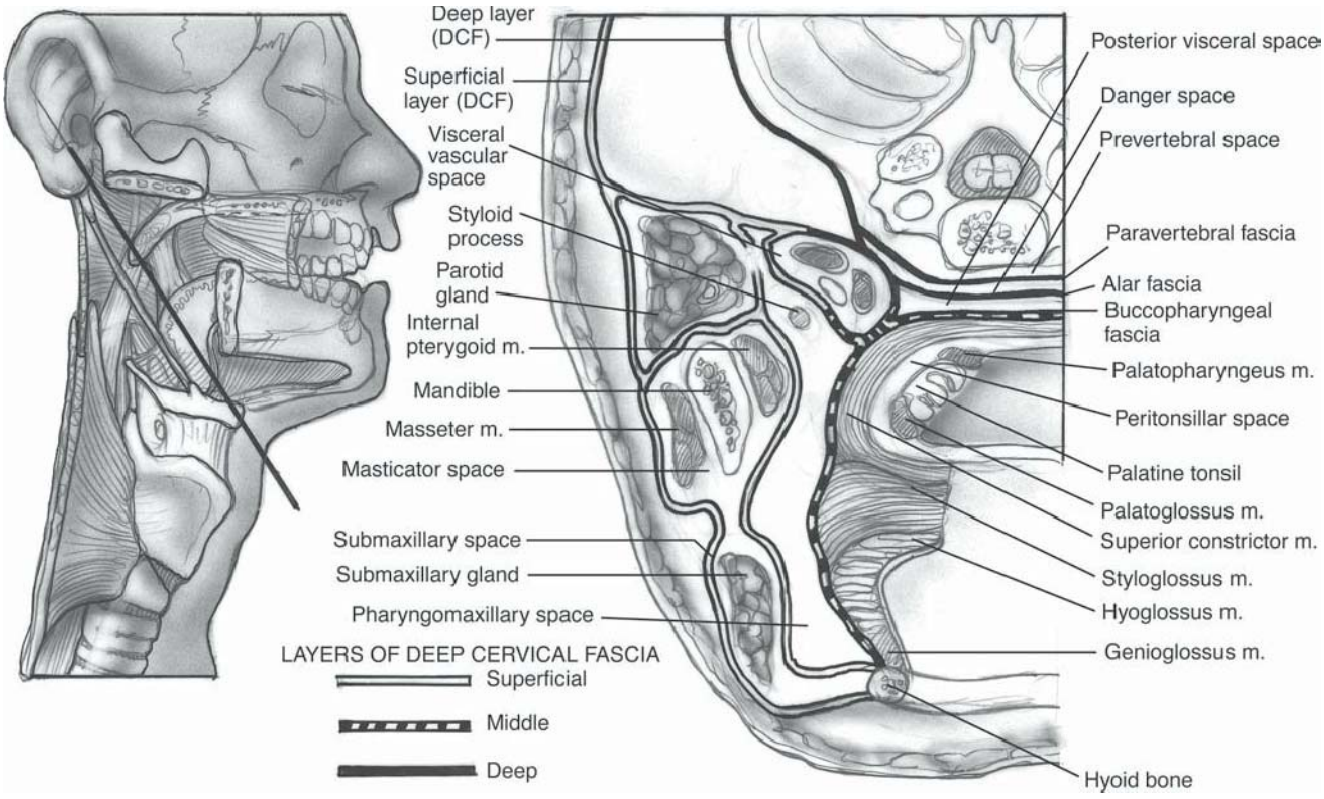


Figure 55.4 Oblique section through the neck shows the anatomic relations of the spaces limited to above the hyoid bone to the spaces that transverse the entire neck. The important relation between the parapharyngeal (pharyngomaxillary) space and the other spaces is evident.

vessels, phrenic nerve, and brachial plexus. The paraspinous, prevertebral, and scalene muscles are located within this space as well. Direct extensions of infection are from the vertebrae (e.g., Pott's abscess) or penetrating injuries (12).

Carotid Space

Also referred to as the visceral vascular space, this is a potential space enclosed by the carotid sheath extending from the skull base to the thorax (Fig. 55.4). Its contents include the carotid artery, IJV, vagus nerve (cranial nerve X), and sympathetic plexus. Spread is generally from the adjacent parapharyngeal space, penetrating trauma, or IVDA (12).

Spaces above the Hyoid Bone

Parapharyngeal Space

Also known as the lateral pharyngeal, peripharyngeal, or pharyngomaxillary space (Figs. 55.3–55.5). This has classically been described as an inverted pyramid with the base at the skull base superiorly, and the apex at the greater cornu of the hyoid bone inferiorly. The lateral borders are the lateral pterygoid muscle, mandible, and parotid gland. The medial boundaries include the superior constrictor and levator and tensor veli palatini muscles, all enveloped by the middle layer of the deep cervical fascia. It lies posterior to the medial pterygoid muscle (where involvement will result in trismus) and pterygomandibular raphe, and anterior to the prevertebral fascia. This space is further split into the prestyloid and poststyloid compartments by the styloid process, which are anterior and posterior to this landmark, respectively. The poststyloid compartment houses neurovascular structures including: cranial nerves IX, X, XI, XII, the sympathetic chain, the carotid artery, and the IJV. The prestyloid compartment contains fatty tissue, the styloglossus and stylopharyngeus muscles, the deep lobe of the parotid gland, and lymph nodes. Several notable neurovascular structures course through this compartment as well: the internal maxillary artery; and the auriculotemporal, lingual, and inferior alveolar nerves. The parapharyngeal space serves as a hub for infectious spread from several deep neck spaces. The carotid space travels through the parapharyngeal space en route to the mediastinum. Lateral spread of infection will communicate with the masticator space, inferior spread will reach the submandibular space, and posteromedial extension appears in the retropharyngeal space (12).

Submandibular and Sublingual Spaces

These two spaces communicate freely, and are hence presented together. It should be noted though that the terms submandibular or submaxillary space are commonly utilized in describing the combined submandibular and sublingual spaces. The superior border of these spaces is the mucosa of the floor of the mouth. They are limited by the hyoid bone posteroinferiorly, the mandible anteriorly and laterally, and the base of tongue posteriorly. The submandibular and sublingual spaces themselves are separated by the mylohyoid muscle, with the prior lying below and the latter lying above this landmark. Both spaces, however, communicate around the posterior edge of this muscle. It is for this reason that Ludwig's angina will result in a generalized swelling of the submandibular area along with elevation of the floor of the mouth. While underlying the mylohyoid, the submandibular space is further separated

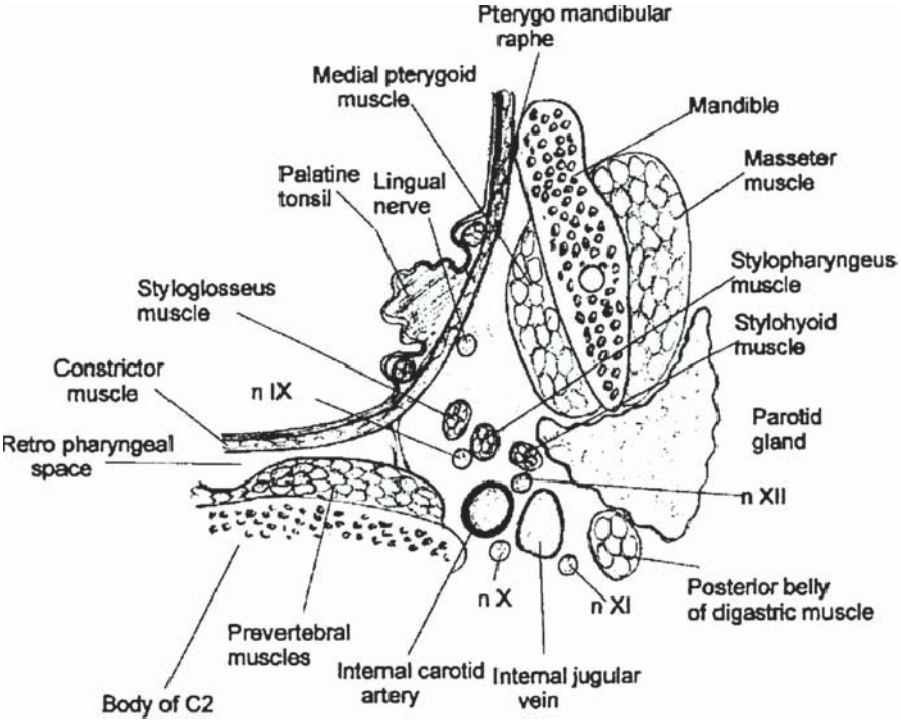


Figure 55.5 Schematic representation of the parapharyngeal space in an axial view at the C2 level.

from (but also freely communicates with) the submental space by the anterior belly of the digastric muscle. The sublingual space houses the hypoglossal nerve, the sublingual salivary gland, and Wharton duct. The submandibular gland sits in both the sublingual and submandibular spaces as it straddles the posterior edge of the mylohyoid muscle. The mylohyoid line is an oblique line along the mandible that aids in the evaluation of submandibular or sublingual space infections from odontogenic sources. The incisors to first molars lie above this line. Infections originating in the roots of these teeth generally present initially in the sublingual space. On the other hand, the second and third molars are situated below the mylohyoid line, with infectious processes of these tooth roots draining primarily to the submandibular or parapharyngeal space (12).

Parotid Space

This space, also known as the parotidomasseteric space, is created as the superficial layer of the deep cervical fascia envelopes the parotid gland, periparotid lymph nodes, facial nerve, posterior facial veins, and external carotid artery (Fig. 55.4). The fascia adheres tightly to the gland laterally. The resultant firm capsule deems differentiation of an abscess versus cellulitis within this space virtually impossible on physical examination, despite the relatively superficial location. In contrast, deficiency of the fascia along the medial border allows for communication of the gland with the prestyloid parapharyngeal space (12).

Masticator Space

This space is also formed by an investment of the superficial layer of the deep cervical fascia (Fig. 55.4). Its contents include the masseter, medial and lateral pterygoid muscles, body and ramus of the mandible, inferior alveolar vessels and nerves, buccal fat pad, and temporalis tendon. The masticator space may be divided into the masseteric space, between the mandibular ramus and masseter muscle; and the pterygoid space, between the mandibular ramus and pterygoid muscles. The masticator space is situated anterolateral to the parapharyngeal space and deep to the temporal space. Infections of this space are primarily from the third mandibular molar (12).

Peritonsillar Space

The peritonsillar space is sandwiched between the palatine tonsillar capsule medially, and the superior pharyngeal constrictor muscle laterally (Fig. 55.4). The anterior and posterior limits are formed by the palatoglossus and palatopharyngeus muscles or anterior and posterior pillars, respectively. The posterior third of the tongue serves as the inferior boundary. Delayed drainage of purulent collections from this space may result in parapharyngeal space extension (12).

Temporal Space

The temporal space is enclosed by the squamous temporal bone medially and the superficial temporalis fascia laterally. This space is further split into superficial and deep components by the temporalis muscle. Notable contents include the internal maxillary artery and the third division of the trigeminal nerve (V3) (12).

Spaces below the Hyoid Bone

Anterior Visceral Space

This space runs from the thyroid cartilage down to the level of the fourth thoracic vertebra (Fig. 55.2). The pharynx, esophagus, trachea, thyroid and parathyroid glands are the most notable components, all enclosed by the visceral division of the middle layer of the deep cervical fascia and nested behind the strap muscles. The most common portals of infection into this space include perforation of the anterior esophageal wall by trauma, foreign bodies, and endoscopic instrumentation (12).

Suprasternal Space

This is a potential space that sits just above the sternal notch, enveloped by the superficial layer of the deep cervical fascia. The suprasternal space of Burns features a small lymph node and bridging vessels between the anterior jugular veins (12).

BACTERIOLOGY

During the preantibiotic era, the organism most often isolated from deep neck space abscesses was *Staphylococcus aureus*. Since the introduction of antibiotics, aerobic Streptococcal species and non-Streptococcal anaerobes have become the chief offending agents in DNSIs. Most infections, however, are polymicrobial (13,14). These organisms generally represent members of oral flora, reflecting the most common site of origin: odontogenic infections. Practically speaking though, the organisms isolated will vary with the initial portal of entry. Notable aerobic species include *Streptococcus viridans, Streptococcus pyogenes, Staphylococcus epidermis*, and *S. aureus* (14,15). Two important relationships are that of *S. viridans, S. pyogenes*, and *S. aureus* with IVDA and *S. aureus* with infants. Methicillin-resistant *Staphylococcus aureus* (MRSA) has been increasingly associated with IVDA, infants, and immunocompromised patients as well (16–22). Currently, the most frequently isolated anaerobes include *Peptostreptococcus, Fusobacterium*, and *Bacteriodes* (6,14,19,23), though their overall prevalence is likely underestimated in most reports due to difficulty in culture growth. Production of beta-lactamase has led to the growing resistance of anaerobic agents to penicillin (23,24). *Eikenella corrodens* is increasingly found in head and neck infections, bringing with it a very clinically relevant resistance to clindamycin and metronidazole.

Gram-negative rods, such as *Haemophilus, Escherichia, Pseudomonas*, and *Neisseria*, are usually only seen in hospitalized, debilitated, or immunocompromised patients (3). *Klebsiella pneumoniae* is found to have a predilection for poorly controlled diabetics. Atypical and granulomatous

organisms, including *Actinomyces*, tuberculous and nontuberculous mycobacteria, cat scratch or *Bartonella henselae*, and tularemia (25,26), are seen far less frequently.

DIAGNOSIS

History, physical examination, laboratory tests, and diagnostic imaging yield vital information in diagnosing and managing patients with DNSIs. The first priority, however, is expedient and aggressive management of potential respiratory compromise. Upon confirmation or achievement of a secure airway, a comprehensive and careful evaluation is necessary in elucidating possible sources of infection in order to direct optimal therapeutic approaches. It is also important to note that many patients presenting to an otolaryngologist with a possible DNSI have already been placed on an outpatient antibiotic regimen, possibly altering the typical presenting symptoms and findings, underscoring the importance of a thorough evaluation (1,27).

History and Physical Examination

As with any disease process, a thorough history of the present illness must be solicited. This starts with a survey of symptom onset, intensity, duration, and any systemic inflammatory symptoms and signs such as pain, fever, swelling, malaise, fatigue, or redness. Localizing complaints of dyspnea, odynophagia, dysphagia, voice changes, drooling, trismus, and otalgia direct the clinician toward a possible site of infection (13,28–31). Potential instigating events including recent dental infection or procedures, sinusitis, pharyngitis, otitis, upper aerodigestive tract surgery, intubation, IVDA, blunt or penetrating trauma, or skin infection should be inquired about as well. Immunocompromised patients, most commonly those with diabetes, human immunodeficiency virus (HIV), acquired immunodeficiency syndrome, autoimmune diseases, malignancy, chemoradiotherapy treatment, or steroid use must be identified and attended to with a higher level of vigilance, as they tend to be susceptible to more virulent and atypical organisms in addition to a much more aggressive disease process (7,32,33).

The physical examination of any patient with a potentially life-threatening diagnosis must be accomplished in a systematic and complete manner. A general overview of the patient may reveal respiratory distress, labored breathing, anxiety, signs of dehydration, weakness, photophobia, limited neck motion, lethargy, altered voice, track marks from IVDA (6), or cognitive deficits. Deficiencies on cranial nerve examination can assist in localizing the source of the infectious process. The facial skin and scalp must be inspected for any signs of superficial infection, inflammation, or swelling. The presence of purulence, inflammation, or tenderness on otoscopic examination may direct the physician toward the presence of a Bezold's abscess (Fig. 55.6) or the rare occurrence of spread of a DNSI from an odontogenic source into the external auditory canal (34). While evaluation of the oral cavity will mainly focus on possible odontogenic sources of

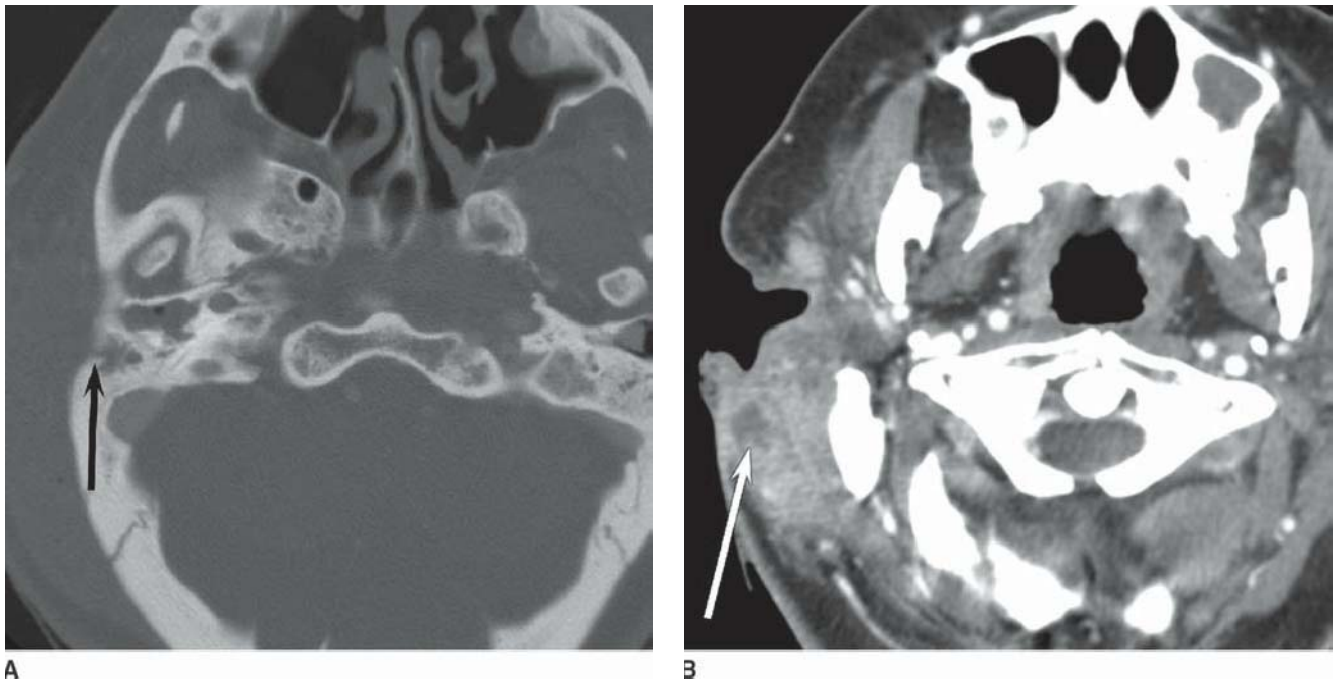


Figure 55.6 Coalescent mastoiditis with Bezold abscess. **A:** Axial contrast-enhanced CT on bone window shows complete opacification of underpneumatized right mastoid air cells with a lateral cortical breakthrough (*arrow*). The external auditory canal is also nearly completely opacified. **B:** More inferior image, on soft tissue windows, shows abscess (*arrow*) alongside the mastoid tip, involving the SCM (Bezold abscess).

infection, a survey for trismus, floor of mouth swelling, and salivary flow from Stensen's and Wharton's ducts is just as crucial. The oropharynx must be examined for signs of asymmetry, bulges, uvular deviation, inflammation, or swelling. The neck should be palpated for any crepitus, swelling, tenderness, or lymphadenopathy. The final component of the physical examination, awake fiberoptic laryngoscopy, is compulsory in any patient with signs of potential airway compromise such as dyspnea, dysphagia, stridor, odynophagia, hoarseness, and limited range of neck motion. The presence of deviation, swelling, or inflammation in the airway will obviously raise the level of urgency and shift the immediate priority from treatment of a potential DNSI to securing the airway. The most common symptoms and physical examination findings encountered in patients with specific DNSIs are elaborated on the following sections.

Laboratory Tests

Laboratory tests should be obtained concurrently with the history and physical examination. In anticipation of a possible trip to the operating room (OR), routine preoperative labs along with a complete blood count with differential, and complete metabolic panel must be drawn. When past or current medical history indicates, HIV screening, blood glucose levels, and tuberculin skin testing should be obtained. Additionally, blood cultures and available aspirate cultures are recommended. Cultures with positive gram stain but without growth raise the suspicion for an anaerobic organism (11). Given the relatively increased frequency of atypical and aggressive organisms associated with immunocompromised patients, it would be prudent to obtain acid-fast and fungal cultures in this population (35). While the majority of patients with a DNSI demonstrate an elevated white blood cell (WBC) count, patients with HIV and tuberculosis who had drainable abscesses often exhibit persistent leukopenia (WBC count < 8000 per milliliter) (6). It is also important to note the presence of leukocytosis in the background of steroid administration, potentially confounding the clinical picture when attempting to follow the response to medical or surgical therapy with serial WBC counts.

Imaging

Computed Tomography

The ability to identify the specific spaces involved, early or potential complications, and the nature of DNSIs has designated contrast-enhanced computed tomography (CECT) scanning as a critical component of the diagnostic work up (28). The scan itself is excellent for delineating both bony and soft tissue structures. The addition of intravenous contrast further assists in differentiating a well-formed abscess from a phlegmon or cellulitis and visualizing the great vessels. An abscess on CECT scan will demonstrate a central area of low attenuation or hypodensity with ring enhancement of its wall, surrounded by soft tissue edema. The presence of air on CECT scanning is also strongly predictive of an abscess (36). This modality does have certain noteworthy limitations however. Miller et al. (37) noted an improvement in accuracy from 77% to 89% when CECT scan was combined with a clinical examination, with similar findings in the pediatric population noted by Vural et al. (38). The quality of certain images can also be compromised by the presence of metal materials within the head and neck causing streak artifacts. Another drawback relates to the risk of radiation exposure, particularly in pediatric patients facing serial scans. Finally, intravenous contrast may be contraindicated in patients with allergies to these agents or with compromised renal function. Occasionally, with retropharyngeal abscesses, differentiation between a well-formed abscess and phlegmonous soft tissue edema may be difficult with CECT. In addition, although needle aspiration may be helpful with diagnosis in a questionable radiologic diagnosis, this procedure carries a false-positive rate of up to 25% (39).

Plain Film Radiography

While plain films have generally limited utility relative to other imaging modalities, they may be useful in the detection of certain types of DNSIs. Panorex jaw films may reveal an odontogenic source for certain DNSIs (11). Findings of tracheal deviation, subcutaneous emphysema, mediastinal widening, and pneumomediastinum on chest films are associated with possible thoracic collections or mediastinitis (29). In contrast, the usefulness of anteroposterior and lateral neck films in diagnosing retropharyngeal, prevertebral, and parapharyngeal abscesses has been questioned following the findings by Nagy and Backstrom (40) of a sensitivity of 83% for plain films versus 100% sensitivity with CECT scanning.

Magnetic Resonance Imaging

Relative to CECT scanning, magnetic resonance imaging (MRI) yields superior soft tissue differentiation, particularly in infections involving the prevertebral or parotid spaces, and intracranial cavity. Limitations of CECT scanning, including radiation exposure risk, streak artifacts, and intravenous dye allergies, are all circumvented with MRI (11). Additionally, magnetic resonance angiography is useful in the evaluation of potential vascular complications of DNSIs including thrombi, vessel narrowing, aneurysm, rupture, and pseudoaneurysm (41). While this modality may complement CECT scanning in select cases, the vast majority of patients do not undergo MRI due to the high cost, contraindication with metal or electrical implants, and lengthy time requirement posing considerable discomfort and risk in patients with dyspnea, dysphagia, and children who require sedation (39).

Ultrasonography

Frequently used in Europe for the evaluation of DNSIs, ultrasound is a less expensive and noninvasive alternative to CECT scanning that is gaining popularity in the United States.

Portability and the avoidance of radiation exposure in the pediatric population are additional advantages. Its major utility lies in guiding diagnostic or therapeutic needle aspirations in the setting of a stable airway (42,43). Due to the lack of anatomic detail needed for surgical planning, difficulty in interpretation and visualization of deeper lesions (39), the recommended role for ultrasound appears to be as an adjunct to CECT scanning or MRI (35).

MANAGEMENT

Successful management of DNSIs can be achieved by prompt and adequate treatment, emphasizing control of the airway, effective antibiotic therapy, and timely aspiration or surgical intervention when indicated. In addition, a thorough search for the initial infectious source must be carried out in order to prevent a recurrence.

Airway

Safe and secure airway maintenance is the most important initial therapeutic objective in the management of DNSIs (44). Hypoxia and asphyxia remain the most common causes of mortality rather than uncontrollable sepsis (45). Clear indications for watchful waiting versus intubation or tracheotomy do not always exist; therefore, each patient must be assessed individually. Keeping in mind the potential for rapid deterioration without warning, admission into a monitored unit with close and frequent observation by medical staff is critical. Signs of progressing stridor, dyspnea, or increased work of breathing are valuable clues of potential airway compromise. In the setting of clinical deterioration, early intubation or tracheotomy circumvents the performance of these procedures in more dire circumstances.

Options for managing the airway include conventional endotracheal intubation, awake fiberoptic intubation, and tracheotomy (46). Airway instrumentation during endotracheal intubation in an awake patient carries the risks of laryngospasm and possible abscess rupture with subsequent aspiration. Therefore, only an anesthesiologist or otolaryngologist with extensive experience should perform this procedure. The addition of nebulized epinephrine is helpful in reducing mucosal edema. Awake fiberoptic intubation, most commonly nasotracheal, has gained significant popularity as the availability of flexible fiberoptic scopes and subsequent experience level of operators have grown. The procedure requires the patient to sit in an upright position, preventing backward collapse of the tongue and pharyngeal walls. Inhaled nebulized lidocaine and nasopharyngeal "trumpets" coated with lidocaine jelly are generally effective in facilitating comfortable intubation in an awake patient. A tracheotomy set must be available should a surgical airway become necessary. It has been suggested that many retropharyngeal and true Ludwig's abscesses be managed surgically from the outset in the interest of avoiding emergent "slash" tracheotomies in suboptimal settings (6,14,47). In patients with significant airway edema, sepsis, or extensive collections where extubation within 48 to 72 hours is questionable or not expected, elective tracheotomy following successful intubation or tracheotomy under monitored anesthesia care and local anesthetics should be performed in favor of shorter hospital and intensive care unit (ICU) stays (47).

Medical Management

The species of pathogens that cause the overwhelming majority of DNSIs in immunologically sound or compromised individuals have been mentioned earlier in this chapter. This predictability in clinical circumstances allows for reasonable knowledge in administering appropriate empiric agents until cultures and sensitivities from aspirates or surgical drainage become available. Most cases involve mixed flora of gram-positive cocci and gram-negative rods along with beta-lactam–resistant anaerobes. Optimal coverage for these organisms is supplied by a penicillin in combination with a beta-lactamase–resistant antibiotic along with a drug effective against anaerobes (such as metronidazole or clindamycin). Patients susceptible to *Pseudomonas* should receive an anti-Pseudomonal penicillin (such as ticarcillin–clavulanate, piperacillin–tazobactam, or imipenem–cilastin), a quinolone (such as ciprofloxacin, or levofloxacin), or an aminoglycoside. Clindamycin or vancomycin should be administered to those at risk of a MRSA infection (7,23,48,49). Recent evidence (31,50) has shown that an uncomplicated abscess, particularly in a pediatric patient, contained within a lymph node (as seen on imaging) can be treated effectively with a 48- to 72-hour trial of antibiotics and close observation without surgical intervention. Concurrent treatment of predisposing comorbidities in adults and children will improve immune function as well. In cases where surgical drainage is required, parenteral antibiotics will be continued postoperatively until the patient is afebrile for 48 hours, and then switched to an oral agent for an additional 2 weeks. Supplemental intravenous hydration is also a vital component in supporting the host response to infection.

Surgical Drainage

The decision to institute surgical drainage is based on several factors. In questionable cases, a 48-hour period of careful observation and monitoring along with intravenous antibiotic therapy and hydration may be indicated prior to considering a trip to the operative suite. Progression of symptoms indicating surgical drainage can be manifest by persistent fevers, tenderness, swelling, and elevated WBC counts. This trial period must involve frequent examinations in order to accurately gauge the overall clinical status of the patient. Additional indications for drainage include potential airway compromise, critical condition from

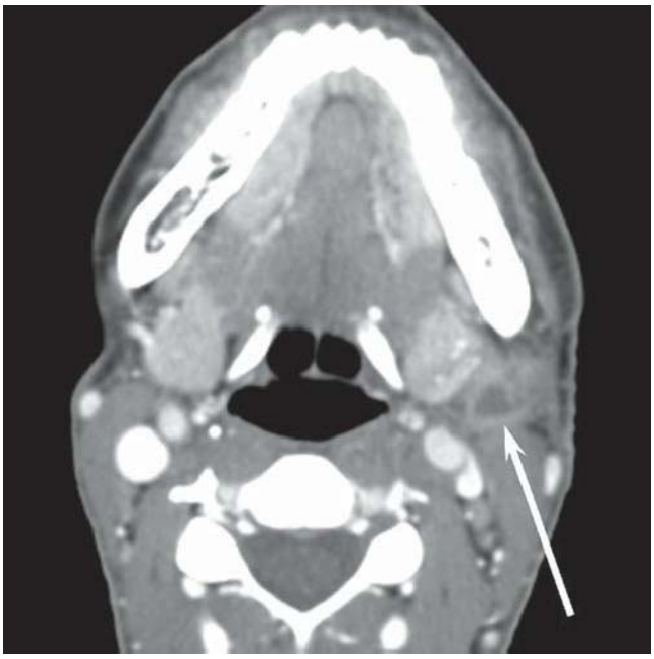


Figure 55.7 Tuberculous adenitis. Axial contrast-enhanced CT shows an abscessed lymph node (*arrow*) at the tail of the left parotid. TB-infected nodes may be of low density, or may become frankly abscessed.

complications or septicemia, and evidence of collections larger than 3 cm or involving multiple spaces (28,51). Surgical drainage can involve various approaches including transoral drainage, external cervical drainage, and less invasive methods such as needle aspiration or indwelling catheter placement (11). Upon accessing the cavity, a sample of purulent fluid or debrided tissue must be collected and submitted for culture and sensitivity. With regard to granulomatous diseases such as tuberculosis and atypical mycobacterial infections (Fig. 55.7), medical management, excisional biopsy, or needle aspiration is generally favored over incisional drainage in the interest of avoiding the potential for a persistently draining sinus tract.

Transoral and Intraoral Drainage

Peritonsillar space abscesses are approached transorally. Uncomplicated retropharyngeal abscesses are usually drained in this manner as well. Select parapharyngeal space infections lying immediately beneath the lateral pharyngeal wall may also be accessed transorally. Odontogenic collections limited to the alveolus can be addressed with simple tooth extraction and subsequent root drainage. Buccal space and shallow sublingual abscesses are entered through the intraoral mucosa. Finally, incision and dissection through the retromolar trigone and masseter muscle yields access to the masticator space (11). While spaces approached intraorally are amenable to drain placement, this practice is discouraged in more distal transoral routes (retropharyngeal, peritonsillar, or parapharyngeal) due to the risk of aspiration.

External Drainage

Collections within the anterior visceral, submandibular, parapharyngeal, prevertebral, and carotid spaces are generally drained with an external cervical approach. All involved spaces must be incised and drained with care taken to avoid injury to vital structures while utilizing the shortest route from the outside (35). Following access to the abscess cavity, loculations are broken and the space is thoroughly irrigated. Larger wounds undergoing considerable debridement will remain open and be packed with antimicrobial iodoform, eventually healing by secondary intention. Smaller cavities can be closed loosely with sutures and Penrose drain placement.

Needle Aspiration and Catheter Placement

Simple, unilocular collections in stable patients may be amendable to less invasive techniques. Palpable abscesses can be directly aspirated with a needle. Alternatively, introduction of an intravenous catheter permits irrigation within the cavity. Pigtail catheter placement with the Seldinger technique affords continued drainage and flushing (52). CECT or ultrasound guidance is usually necessary in localizing deeper collections (53,54). The main advantage of this modality is the avoidance of the potential morbidity associated with open surgical approaches including scarring, contamination with spread of infection, and neurovascular injury.

COMPLICATIONS

Despite expedient diagnosis, antibiotic administration, and surgical drainage, complications may occur. An important predisposing factor for a complicated DNSI is an immunocompromised host. Spread of infection to adjacent vital anatomic structures also occurs more commonly in the background of delayed presentation or diagnosis (30). Aggressive and vigilant management is vital in avoiding the potentially catastrophic outcomes associated with a complicated disease course.

Neurovascular Complications

Carotid artery pseudoaneurysm and rupture can occur with infectious spread to the carotid space. Patients most frequently present with a pulsatile neck mass (55). Additional findings include recurrent sentinel hemoptysis or bloody otorrhea, hematoma within the soft tissues of the neck, and hemodynamic collapse (11,56,57). Once recognized, the standard intervention is surgical ligation of the common carotid artery (56). If time permits, less invasive endovascular stenting or vessel occlusion in an interventional radiology suite may also be attempted (58,59).

Lemierre's syndrome, or IJV thrombophlebitis (Fig. 55.8), is a rare but serious complication of DNSIs (60,61). The anaerobe, *Fusobacterium necrophorum*, is the most common causative organism, with clinical manifestations of spiking fevers, neck stiffness, pulmonary and systemic

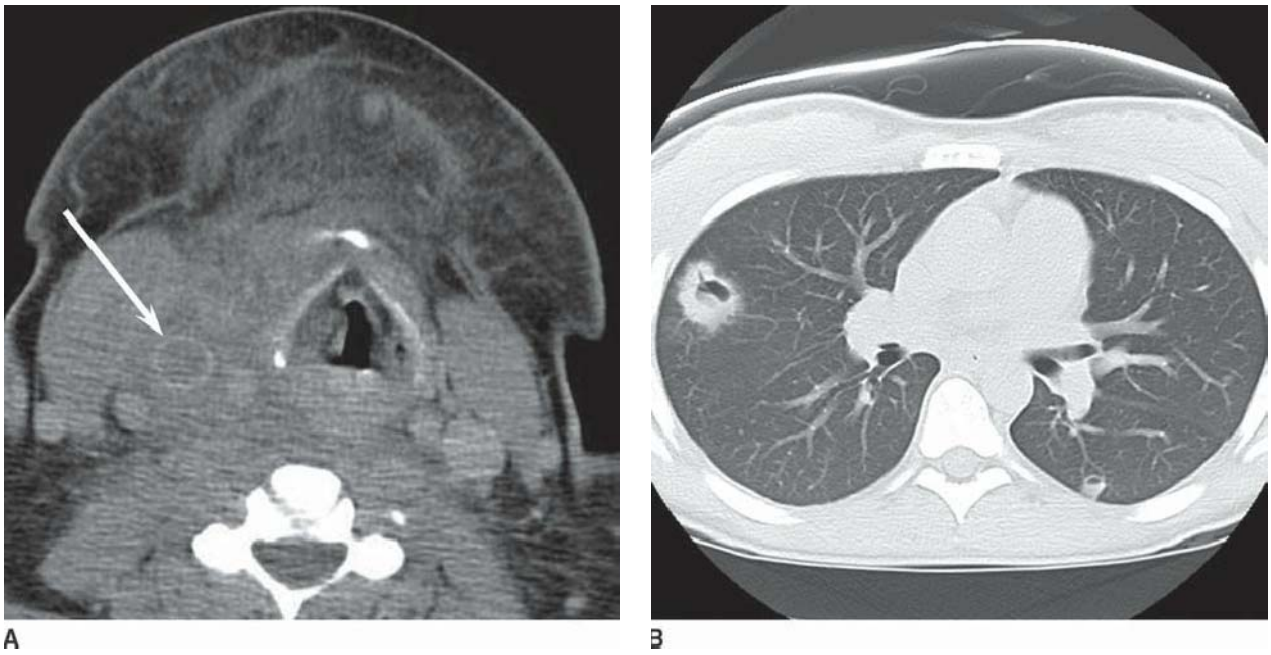


Figure 55.8 Internal jugular thrombophlebitis with Lemierre syndrome. **A:** Axial unenhanced CT shows hypodensity of the right IJV (*arrow*) with extensive surrounding fat infiltration. On contrast-enhanced CT, the vein would fail to enhance like the other vessels. Ultrasound may also be used to document disruption of venous flow. **B:** Axial CT on lung windows shows multiple cavitary lung masses with ill-defined borders, representing lung abscesses from infected emboli (Lemierre syndrome).

emboli, and tender swelling along the SCM and angle of the jaw (62). Diagnosis is confirmed with the finding of ring enhancement and a filling defect of the IJV due to a clot or purulence on CECT. Treatment involves beta-lactamase–resistant antibiotics with the addition of heparin anticoagulation in the presence of thrombus progression or septic emboli. Worsening symptoms or abscess formation in the setting of appropriate medical therapy is an indication for surgical ligation of the IJV (63). Retrograde spread of the thrombophlebitis may also result in a potentially fatal cavernous sinus thrombosis (64), which is managed with critical care support and intravenous antibiotics.

In addition to Lemierre syndrome, spread of infection to the upper carotid space and poststyloid parapharyngeal space may also lead to deficiencies in cranial nerves IX, X, XI, and XII (11). The classic triad of ptosis, anhydrosis, and miosis (Horner's syndrome) will be observed with involvement of the postganglionic sympathetic nerves. Central nervous system complications of DNSI spread include meningitis and intracranial abscess.

Additional Complications

Rupture of an abscess into the airway can result in serious outcomes including aspiration pneumonia, lung abscess, empyema, and even asphyxiation. Deeper spread of infection may cause osteomyelitis of the cervical vertebrae and mandible, which are generally addressed with long-term intravenous antibiotics (65). Systemic consequences of DNSIs include disseminated intravascular coagulation and sepsis, both of which carry high mortality rates despite intensive care management and resuscitative efforts (26,66).

SPECIAL CONSIDERATIONS

Mediastinitis

Extension of DNSIs from the head and neck into the mediastinum is a relatively rare but dreaded complication, carrying a mortality rate of approximately 40% (67,68). Infectious spread generally traverses the retropharyngeal, danger, prevertebral, or anterior visceral spaces with a mix of aerobic and anaerobic offending agents (69,70). Characteristic findings on physical examination include progressive chest pain and dyspnea, along with neck swelling. The classic finding on plain film or CECT scan of the chest is a widened mediastinum. Fluid collections, pneumomediastinum, and even pneumothorax may be present as well (71). Medical therapy requires broad spectrum antibiotics and ICU support. Superior mediastinal collections can generally be treated through a deep transcervical approach. Involvement of more inferior structures, however, necessitates thoracotomy with chest tube insertion (72).

Necrotizing Cervical Fasciitis

Necrotizing cervical fasciitis (NCF) is a rapid and diffuse spread of infection throughout multiple fascial planes associated with significant morbidity, and a mortality

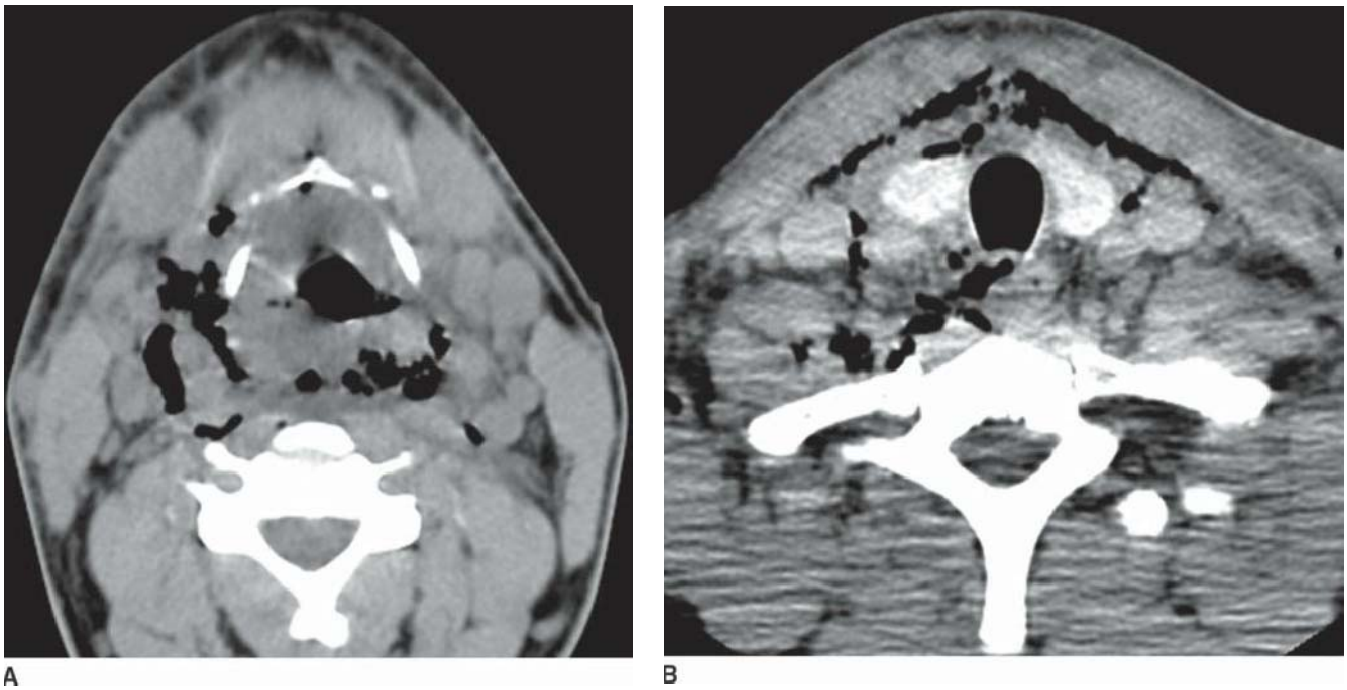


Figure 55.9 Necrotizing fasciitis. Axial unenhanced CT images at the level of the hyoid bone **(A)** and thyroid gland **(B)** show extensive gas formation throughout the deep fascial compartments of the neck. There is also extensive infiltration of the fat planes, which distinguishes this case of necrotizing fasciitis from perforation of the upper aerodigestive tract.

rate of approximately 30% (Fig. 55.9). Local extension with mediastinitis or systemic spread with sepsis is associated with an even poorer prognosis (73,74). As with most DNSIs, the predominant source is a polymicrobial odontogenic infection with a mixture of aerobes, anaerobes, *Clostridium*, and MRSA (74–76). Patients will have an extremely toxic appearance with spiking fevers. Striking ischemic discoloration of the skin, with erythema, crepitus, edema, and tenderness are observed on physical examination. Progression of the disease process may evolve into anesthetic and pale skin with blistering and sloughing (11). In addition to tissue gas, notable findings on CECT that distinguish this liquefaction necrosis from conventional cellulitis, abscess, or phlegmon include hypodense regions lacking loculations or peripheral enhancement (77). NCF is a potentially lethal entity that mandates intravenous broad-spectrum antibiotics within an ICU setting along with multiple trips to the OR for surgical debridement of nonviable tissue. Any correctible causes of immunocompromise leading to susceptibility of NCF must be addressed as well. Many patients with comorbidities including diabetes mellitus and cirrhosis succumbed to NCF, while those without these conditions usually recover (78). Adjuvant hyperbaric oxygen may be considered as an adjunctive treatment (79). Reconstruction with skin grafts or local and free tissue flaps can take place once the infectious process has resolved.

SPECIFIC DEEP NECK SPACE INFECTIONS

Retropharyngeal, Danger, and Prevertebral Spaces

The retropharyngeal space houses the nodes of Rouviere that lie just off the midline and receive drainage from the posterior two-thirds of the nose, paranasal sinuses, adenoids, pharynx, and eustachian tube. These lymphatics are rarely the cause of retropharyngeal space infections (RPSI) in children older than 5 years due to their involution by this age. Other causes, generally found in the older population, include penetrating or blunt trauma; instrumentation; intubation; placement of feeding tubes; and infection from neighboring spaces, most notably the parapharyngeal and prevertebral spaces (80).

Diagnosis of this entity may be challenging in its early stages, particularly in children. Sore throat may not be a typical complaint, but the child may refuse to eat due to discomfort. Trismus is not expected to be associated with RPSI, and its presence should raise the suspicion of parapharyngeal space extension. Swelling in the posterior nasopharynx may be confused with inflammation of the adenoids. Swelling below the nasopharynx will present along the posterior pharyngeal wall, usually seen off the midline. Additional findings include cervical adenopathy, slight elevation of temperature, and a muffled voice secondary to supraglottic swelling. Children may also feature irritability and nuchal



Figure 55.10 Retropharyngeal abscess. Axial contrast-enhanced CT shows a round abscess (*asterisk*) with an enhancing rim in the lateral retropharyngeal space. There is substantial surrounding edema. A lateral abscess such as this is likely the result of a suppurated node, whereas medial collections arise from direct inoculation.

rigidity. Mediastinal extension must be considered in the setting of respiratory distress. Lateral neck radiographs help confirm the diagnosis, with the classic measurement of the retropharyngeal space at level C-2 in adults or children of greater than 7 mm denoting an abnormality. At level C-6, retropharyngeal thickness greater than 22 mm in adults or 14 mm in children also denotes an abnormality. However, due to difficulty in positioning, interpretation of this area in infants is less reliable. CECT (Fig. 55.10), when possible, will help delineate the extent of the infection and possible spread to neighboring spaces (80,81). The workup will be augmented by aspiration of possible purulent fluid and culture specimens from the mass with an 18-gauge spinal needle.

Control of the airway prior to drainage of an RPSI can be accomplished with endotracheal intubation in uncomplicated cases. However, tracheostomy is recommended in the presence of an urgent need for airway control and large abscess due to the risk of rupture and subsequent purulent aspiration during intubation. With collections that are limited to the retropharyngeal space, above the hyoid bone, and easily visualized; a transoral approach to drainage can be undertaken (82,83). This procedure is performed with the patient in the Rose position in order to keep any drainage within the nasopharynx. RPSI that involve multiple spaces are located below the hyoid bone, and/or are difficult to visualize, are to be drained externally. A vertical incision can be made along the anterior border of the SCM muscle, or a horizontal curvilinear incision can be utilized. Dissection is carried down through the platysma muscle and superficial layer of the deep cervical fascia. The abscess cavity is then exposed following medialization of the trachea, and esophagus, and lateral retraction of the carotid sheath and SCM (83). Based on CECT findings, spread of infection below the clavicle into the mediastinum to the level of the fourth thoracic vertebra is an indication for a thoracic surgery consultation. Thoracic surgical intervention can range from superior mediastinotomy for upper mediastinal infections, to external lateral thoracotomy in the presence of significant extension into the chest cavity.

Prevertebral space infections may have a clinical course that differs from RPSI. Possible causes of prevertebral space and danger space infections include tuberculous Pott's abscesses, posterior extension of RPSI, trauma, previous spinal surgery, and extension of osteomyelitis. If located within the high-cervical area, an intraoral midline bulge may be seen. In contrast to RPSI, these infections usually demonstrate a more indolent course, with patients consequently having less striking complaints. Vague neck or shoulder pain, dysphagia, or respiratory distress is inconsistently reported. Typical CECT features of a danger space abscess are demonstrated in Figure 55.11. Management of these entities is generally similar to the approach to RPSI. In addition to the typical organisms previously described, infections caused by *Mycobacterium tuberculosis* or atypical mycobacterium should be considered in patients who fail to respond to the usual antimicrobial agents. While transoral drainage of high-cervical (C1–C3) collections is possible, it may be limited by the inability to adequately remove infected bone. Access to the prevertebral and danger spaces can be achieved through incisions made anterior or posterior to the SCM. Adequate tissue and fluid sampling from these collections is of particular importance given the relative frequency of atypical organisms (81,84).

Submandibular Space and Ludwig Angina

As elaborated on earlier in this chapter, the submandibular and sublingual spaces communicate freely behind the posterior edge of the mylohyoid muscle and are generally described together as the submandibular space. Infectious processes, however, can involve each subcompartment individually or together. Radiographically, spaces within the submandibular region can also be distinguished by their relationship to the anterior belly of the digastric muscle (Figs. 55.12 and 55.13). Although a number of infections are caused by sialadenitis or lymphadenitis (85), 70% of cases originate from dental or periodontal disease (67). As outlined earlier, and based on the mylohyoid line orientation, infections involving the incisors to first molars will present initially in the sublingual space, while the second and third molars will drain primarily to the submandibular space. The latter process is not common in children owing to delayed eruption of the third molar. The most severe manifestation of this entity, Ludwig's angina (Fig. 55.14), is defined as having: (a) all the tissues and

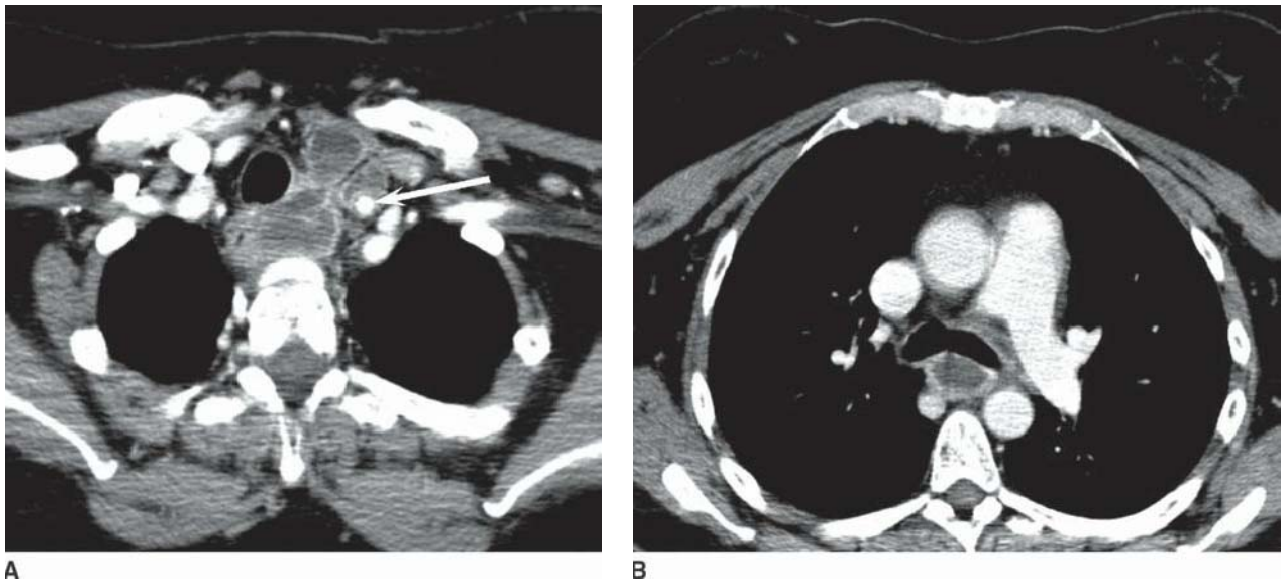


Figure 55.11 Danger space abscess. **A:** Axial contrast-enhanced CT shows a multilocular abscess of the lower neck involving the central compartment, the retropharyngeal space, and carotid sheath, with abscess surrounding the common carotid artery (*arrow*). **B:** More inferior image shows the retropharyngeal component of the abscess extending deep into the mediastinum, below the level of the T4 vertebra. Because the retropharyngeal space extends only to T2–T4, this infection must be located in the danger space, which extends to the diaphragm.

compartments of the floor of the mouth swollen and inflamed, (b) displacement of the tongue superoposteriorly toward the soft palate, (c) firm induration of the submandibular area and anterior neck, (d) trismus, and (e) voice changes and dyspnea (81).

Given that asphyxia is the most common cause of death in Ludwig's angina, airway protection is of paramount concern. Furthermore, with displacement of intraoral structures and rapid disease progression, tracheostomy is utilized much more frequently relative to other DNSIs (6,14).



Figure 55.12 Submandibular abscess. Axial contrast-enhanced CT shows an abscess within the submandibular triangle, displacing the submandibular gland (*asterisk*) posteriorly. The abscess wraps around the inferior mandible, so it likely arose from infection in a posterior molar tooth.



Figure 55.13 Submental abscess. Axial contrast-enhanced CT shows an ovoid abscess (*arrow*) medial to the anterior belly of the digastric muscle (*arrowheads*), with copious surrounding edema. Extensive fat infiltration and submandibular gland inflammation are restricted to the right side of the face and neck. Reactive edema is seen even into the right side of the larynx.

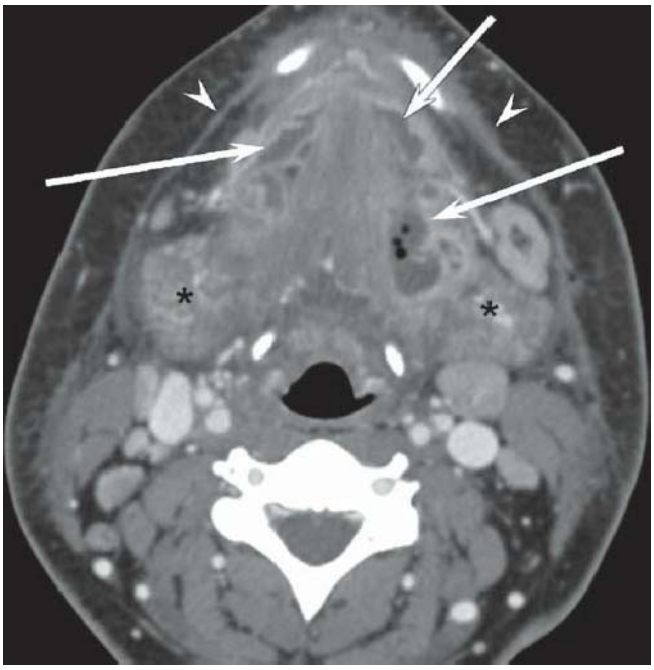


Figure 55.14 Ludwig angina. Axial contrast-enhanced CT shows diffuse infiltration of the fat planes in the submandibular, submental, and subcutaneous spaces. The platysma muscles (*arrowheads*) are thickened. The submandibular glands (*asterisks*) are inflamed. There is an extensive abscess (*arrows*) throughout the submandibular and submental spaces, with air locules indicating anaerobic infection.



Figure 55.15 Parapharyngeal abscess. Axial contrast-enhanced CT shows a large abscess involving both the peritonsillar space and the parapharyngeal space, with replacement of the parapharyngeal fat. The abscess extends laterally to the styloid process. The normal contralateral parapharyngeal fat is still visible (*arrows*).

A number of patients with confirmed Ludwig's abscess undergoing attempted fiberoptic intubation may require unplanned "slash" tracheostomies. Following control of the airway, surgical incision and drainage is indicated in the face of worsening symptoms despite the administration of appropriate antibiotics (86,87). Uncomplicated collections limited to the sublingual space can be approached intraorally. The surgical approach for Ludwig's angina, however, is accomplished with a horizontal submental incision 1 cm superior to the hyoid bone extending laterally in each direction to 3 cm below the angle of the mandible. Dissection is carried out from the hyoid bone to the mandibular symphysis through the platysma muscle and into the sublingual tissues. The cavity will generally contain a malodorous liquid material and/or frank pus. Since a true purulent collection is not always present, it is important to note that the need for surgical drainage and decompression should be dictated by physical examination findings rather than CECT scan (81).

Parapharyngeal Space

The relatively central location of the parapharyngeal space allows for the direct spread of infection from multiple neighboring deep neck spaces (Figs. 55.5 and 55.15). Common routes of extension include laterally from the peritonsillar space, posteriorly from the submandibular space, anteriorly from the retropharyngeal space, and medially from the parotid or masticator space. Consequently, a comprehensive evaluation must be carried out in order to exclude the involvement of any other spaces. The predominant organisms will also vary based on the portal of entry as discussed earlier in this chapter.

Infections of the prestyloid and poststyloid compartments will differ in presentation. The prestyloid compartment normally contains fat, connective tissue, lymph nodes, and muscle, while the poststyloid compartment houses the carotid sheath and cranial nerves IX to XII (11). Prestyloid infections typically present 7 to 10 days after an episode of tonsillitis or pharyngitis with the classic signs of trismus, swelling at the angle of the mandible, medial bulging of the pharyngeal wall, and systemic toxicity. Without involvement of the pterygoid musculature, trismus is generally absent in poststyloid infections. The medial bulge of the pharyngeal wall is not always seen in poststyloid infections, sometimes leading to a misdiagnosis such as fever of unknown origin. Potentially catastrophic neurovascular complications may be associated with poststyloid infections. Involvement of the carotid sheath can lead to IJV thrombosis, and carotid artery erosion or pseudoaneurysm. Ipsilateral Horner's syndrome or other cranial neuropathies are also possible (88).

Indications for incision and drainage of a parapharyngeal space infection include disease progression despite medical care, a demonstrable collection on imaging, or evidence of a neurologic and/or vascular complication (28,51,89). Despite the prominence of the lateral pharyngeal wall, a transoral incision is not advised due to the

risk of uncontrollable hemorrhage from the carotid sheath vessels. The functional status of all cranial nerves prior to surgical exploration should be documented to avoid attributing any preexisting deficits to the operation. The external approach is initiated with a horizontal incision two fingerbreadths inferior to the lower border of the mandible going from the lateral aspect of the hyoid tip to the anterior border of the SCM. The superficial layer of the deep cervical fascia is entered as the SCM is retracted posteriorly. The parapharyngeal space is then entered using blunt finger dissection up to the styloid process. Two additional landmarks must be noted. The tip of the greater cornu of the hyoid bone defines the inferior border of this space. Additionally, all the important neurovascular structures housed within the parapharyngeal space lie deep to the posterior belly of the digastric muscle (88).

Parotid Space

As described earlier, the parotid space is formed as the superficial layer of the deep cervical fascia envelopes the parotid gland. Diagnosis of an abscess may be difficult on physical examination alone due to the firm, adherent capsule lateral to the gland. However, medial extension of infection to the neighboring prestyloid parapharyngeal space can be observed intraorally. The infection is generally secondary to salivary stasis leading to parotitis in patients who are debilitated, postoperative, dehydrated, or have poor oral hygiene. The typical presentation is facial swelling overlying the parotid region without fluctuance or trismus. Purulent fluid may or may not be expressed from Stensen's duct (81). Parotitis is managed with rehydration and antimicrobials targeted against *S. aureus*. When a collection is evident on imaging, the abscess can be accessed through two different routes. An incision can be made through the skin over the prominence of the swelling parallel to the branches of the facial nerve. If the swelling is extensive, a Furstenberg incision can be made. This consists of a vertical preauricular incision extending from the zygoma and curving around the lobule onto the mastoid. The fascia overlying the gland is then widely exposed. Small stab incisions are then made through the fascia followed by bluntly spreading parallel to the facial nerve branches. Penrose drains can be placed for several days allowing the incision to close by secondary intention. Delayed scar revision can be done if desired (90,91).

Masticator Space

Masticator space infections generally involve the fascial sling containing the muscles of mastication: the temporalis, masseter, and pterygoids. Delay in diagnosis and treatment can lead to mandibular osteomyelitis. The most frequent infectious source is odontogenic, usually from the third molar teeth. Patients usually present with trismus and painful swelling over the angle and posterior mandible. Posterolateral swelling within the mouth may mimic a prestyloid parapharyngeal space infection (81). When imaging masticator space infections, MRI can be advantageous over CECT scan due to the lack of dental amalgam artifact (92). Management of the airway in these patients is a priority given the potential for obstruction. Severe trismus and swelling mandate awake fiberoptic intubation or tracheostomy prior to further management. Four approaches may be taken in draining masticator space collections: (a) Drainage can be performed externally. (b) An intraoral route through an incision into the alveolar–buccal groove below the third molar followed by subperiosteal dissection posteriorly deep to the masseter muscle. (c) Collections may also be drained through the offending dental socket following tooth extraction. (d) Select cases can be managed with needle aspiration and antibiotic coverage (90).

HIGHLIGHTS

- The majority of DNSIs in adults are of odontogenic origin, whereas acute pharyngitis and rhinosinusitis leading to retropharyngeal and parapharyngeal lymphadenitis is a common infectious source in children.
- Intravenous drug abuse, particularly in an inner-city environment, is a relatively common cause of DNSIs. However, it has been shown that abscesses caused by direct intravenous drug use seem to have a more favorable clinical course compared to those spreading from inflamed tissue.
- The majority of abscesses are polymicrobial. Due to differences in the portal of entry, offending microorganisms in adults and children will vary. Additionally, MRSA has been increasingly associated with intravenous drug abusers, infants, and immunocompromised patients.
- Inflammation of surrounding deep neck structures will manifest with associated signs and symptoms including pain, fever, swelling, dysphagia, odynophagia, trismus, respiratory difficulty, and toothache. The presence or absence of certain complaints will aid in identifying the specific site of infection.
- Ultrasonography is gaining popularity in the United States as an adjunct to CECT, especially in children undergoing serial image-guided therapeutic aspirations of infectious neck collections.
- Hypoxia and asphyxia remain the most common causes of mortality in DNSIs. When presented with signs of airway compromise, early intubation or tracheostomy circumvent the performance of these procedures under more dire circumstances. In situations where extubation within 48 to 72 hours is questionable or not expected, tracheotomy should be performed in favor of shorter hospital and ICU stays.
- Immunologically sound individuals should be

empirically administered a beta-lactamase–resistant penicillin combined with an agent effective against anaerobes. Antibiotics targeting specific organisms can be given once cultures and sensitivities are available.

- In most cases, immediate need for surgical drainage is obvious. In questionable cases, progression of symptoms such as fever, tenderness, swelling, and elevated leukocyte count despite 48 hours of medical management is an indication for surgical drainage or exploration. Additional indications include potential airway compromise, impending complications or septicemia, evidence of collections larger than 3 cm, or the involvement of multiple spaces.
- Complications are more common in immunocompromised hosts and in cases of a delayed presentation or diagnosis. Infections of certain spaces can lead to multiple neurovascular complications including carotid artery pseudoaneurysm or rupture, Lemierre's syndrome, or Horner's syndrome. Mediastinitis and NCF are potentially lethal entities that must be considered when managing any DNSI.
- Tracheostomy is the preferred approach to controlling the airway in Ludwig's angina and extensive masticator space infections due to the presence of obstructive tongue elevation and trismus, respectively. A surgical airway is also recommended in an urgent setting for patients with retropharyngeal collections due to the risk of abscess rupture and aspiration during intubation.

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IV

Laryngology

Milan R. Amin *Michael M. Johns III*

Upper Digestive Tract Anatomy and Physiology

56

Libby J. Smith *Roxann Diez Gross*

The upper aerodigestive tract is a single conduit that must integrate and separate two very different vital functional systems: breathing and swallowing. In the healthy state, the anatomic structures and their neural substrates exquisitely coordinate each function through sensory–motor integration. The ability to swallow safely is critical for nutrition, hydration, and quality of life; however, its significance is often taken for granted when the physiology and pathophysiology are not fully appreciated. Understanding the anatomy and physiology of deglutition is not only required to properly evaluate and treat patients with dysphagia but also necessary to maximize functional outcomes after surgical interventions for head and neck cancer.

Dysphagia is not a disease, but rather a symptom or a collection of symptoms that broadly describe difficulty swallowing. Under the umbrella term dysphagia, finer distinctions are made that refer to the phase of swallowing where impairments exist. For example, patients may have oral, pharyngeal, oropharyngeal, pharyngoesophageal, or esophageal dysphagia. Dysphagia can also vary in terms of severity from mild to severe. However, it is unknown how much aspiration in a particular patient will result in pneumonia. Some patients can only tolerate a minimal amount of aspiration, while others tolerate larger amounts. The end point of dysphagia is pneumonia or airway obstruction. Unfortunately, to date, there is no universally accepted, standardized system that can be used to objectively define severity levels. In addition, the evaluation and treatment of dysphagia are often complicated by the fact that some patients are acutely aware of difficulty swallowing, while others may not perceive its presence or recognize the symptoms.

The swallowing difficulty can develop gradually from neurologic or respiratory disease, or be acquired suddenly as a result of injury or surgery. The multitude of different etiologies for dysphagia can often be delineated with a thorough history and physical examination. Instrumental assessments of swallowing function provide additional information that will further characterize swallowing function so that treatment can be planned. Effective therapeutic interventions are based upon each patient's specific physiology. Swallowing exercises can increase muscle strength and range of motion of swallowing structures. Skill training can instruct patients to use swallowing maneuvers such as breath-holding before drinking. Compensatory strategies such as changing head position can also be used to alter swallowing biomechanics. Diet alterations can be instituted so that unsafe food consistencies are eliminated. Surgical interventions, such as vocal fold augmentation or esophageal dilatation, may be required as the primary treatment, or in addition to swallowing therapy.

The ability to eat and drink safely and efficiently is fundamental to our quality of life. The wide variety of food and liquid that we enjoy throughout each day requires precise management because of the shared function of the upper aerodigestive tract. Indeed, modern research has shown that the pharyngeal swallow is not a stereotypic reflex as it was first described; rather, it is a patterned motor response to sensory input. As such, pharyngeal muscle force and contraction duration must rapidly and consistently adjust depending upon what is to be swallowed (1,2). To accomplish this feat, separate and overlapping phases of swallowing use sensory–motor integration. Swallowing dysfunction can occur in each phase individually or collectively across them.

ANTICIPATORY PHASE

The anticipatory phase is often considered the first true step in swallowing because visual information, olfactory stimulation, and experience interact to form the initial motor plan (3). A common statement in the culinary profession is, "we eat with our eyes first." The adult has

a well-developed motor plan for swallowing different types of food and drink that is based upon appearance (visual processing), consistency (tactile processing), taste (chemical processing), and bolus size (proprioceptive processing). Most have experienced a sudden awareness that an item placed in the mouth did not match what was expected. This observation can be viewed as practical evidence that a *plan* had been violated. Another example that illustrates this concept can be seen when we perceive a liquid to be very hot or a food is suspected of being very spicy. When experience indicates these possibilities, a slower presentation to the mouth will follow and care will be taken to ensure a smaller bolus size because of the anticipated negative effects.

It is also at the anticipatory level where distinctions between food and nonfood items are made and where palatability is determined. Oral intake may be avoided as a result of the information perceived and processed during this phase. If an individual is forced to eat or drink an item that he or she has predetermined (anticipated) is unsafe or undesirable, then gagging, coughing, and dysphagic symptoms may be observed. It is important to note that these are not behaviors that can be controlled; rather, they are in response to sensory stimulation. The anticipatory phase provides the initial sensory input to cortical swallowing structures. In patients with dementia or other cognitive impairments, the sensory processing of visual, olfactory, and experiential information can be altered. As such, the motor plan implemented to swallow may not match that of the bolus itself, putting the patient at risk for dysphagia.

ORAL PREPARATORY PHASE

Once solid and semisolid food is placed in the mouth, it must first be prepared for the pharyngeal phase. The combination of mastication and saliva production is considered to be the first step in digestion. Saliva from the submental, sublingual, and parotid glands flows into the oral cavity to mix with the bolus and begin the chemical process of food breakdown. The mandible closes to crush solid food and the rotatory motion of mastication enables the molars to shear and shred the food. The muscles of mastication are the masseter, temporalis, medial pterygoid, and lateral pterygoid muscles (Table 56.1). The masseter, temporalis, and medial pterygoid muscles elevate the mandible,

TABLE 56.1 SUMMARY CHART OF PERIPHERAL SENSORY AND MOTOR COMPONENTS OF DEGLUTITION

Swallowing Phase	Action	Muscle	Nerve
Oral preparatory	Labial closure	Orbicularis oris	Facial nerve (CN VII)
	Mastication	Masseter	Mandibular nerve (CN V3)
		Temporalis	Mandibular nerve (CN V3)
		Medial pterygoid	Mandibular nerve (CN V3)
		Lateral pterygoid	Mandibular nerve (CN V3)
		Buccinator	Facial nerve (CN VII)
	Bolus formation	Genioglossus	Hypoglossal nerve (CN XII)
		Hypoglossus	Hypoglossal nerve (CN XII)
		Styloglossus	Hypoglossal nerve (CN XII)
		Palatoglossus	Pharyngeal branch (CN X)
	Tongue sensation	Anterior two-third	Lingual nerve (CN V3)
		Posterior one-third	Glossopharyngeal nerve (CN IX)
	Tongue taste	Anterior two-third	Chorda tympani nerve (CN VII)
		Posterior one-third	Glossopharyngeal nerve (CN IX)
Pharyngeal	Soft palate depression	Palatoglossus	Pharyngeal branch (CN X)
	Velopharyngeal closure	Levator veli palatini	Pharyngeal plexus (CN X)
		Tensor veli palatini	Trigeminal nerve (CN V3)
		Palatoglossus	Pharyngeal branch (CN X)
		Superior constrictors	Pharyngeal plexus (CN X)
	Vocal fold closure	Lateral cricoarytenoid	Recurrent laryngeal nerve (CN X)
		Interarytenoid	Recurrent laryngeal nerve (CN X)
		Thyroarytenoid	Recurrent laryngeal nerve (CN X)
	Laryngeal elevation	Mylohyoid	Trigeminal nerve (CN V3)
		Anterior belly, digastric	Trigeminal nerve (CN V3)
		Stylohyoid	Facial nerve (CN VII)
		Posterior belly, digastric	Facial nerve (CN VII)
		Geniohyoid	Cervical 1 (C1)
		Thyrohyoid	Cervical 1 (C1) via hypoglossal nerve (CNXII)
Esophageal	Upper esophageal segment *relaxation*	Cricopharyngeus	Pharyngeal plexus, recurrent laryngeal nerve (CN X)

while the lateral pterygoid depresses the mandible, thereby opening the mouth. Contraction of the masseter and medial pterygoid muscles also results in lateral mandible movements required for the rotary motions. Sensory and motor innervation to the muscles of mastication and salivary glands is provided by several branches of the trigeminal nerve. The cyclic motion of the mandible and motions of the tongue are mediated, in part, by a cortical central pattern generator (CPG). A CPG is essentially neural circuitry that generates rhythmic movement. It is important to remember that during this phase, the airway is open and active breathing continues. During mastication, respiratory rate becomes more rapid and irregular when compared to tidal breathing (4). If the bolus is not well controlled, solid food may fall into the open airway resulting in aspiration or asphyxiation. Also during mastication, the circular fibers of the orbicularis oris muscle work to actively close the lips and maintain the food or liquid within the oral cavity. An incompetent oral sphincter will result in drooling of saliva or loss of food and liquid out of the mouth. This circumstance is very embarrassing for patients and severely impacts the social aspects of meals. Neurologic diseases and surgical resections that prevent labial closure or impair sensation can cause anterior oral loss of food or liquid.

During mastication, the complex motions of the tongue move and guide prandial material by placing it between the molars, shifting food from side to side, and ultimately collecting it to form a single, cohesive, prepared bolus. Tongue motion is highly complex because it is composed of several intrinsic and extrinsic muscles that are oriented in multiple directions. The intrinsic lingual muscles are the superior and inferior longitudinal muscles, the transverse muscle (transverse lingualis), and the vertical muscle (vertical lingualis). Extrinsic lingual muscles are the genioglossus muscle that protrudes the tongue, the hypoglossus muscle to depress the tongue, and the styloglossus muscle that elevates and retracts the tongue. All of these muscles are innervated by the hypoglossal nerve (cranial nerve [CN] XII). The palatoglossus muscle is innervated by the pharyngeal branch of the vagus nerve (CN X) and elevates the back of the tongue to prevent premature spillage into the pharynx. In addition to muscle strength and coordination, adequate sensory input is necessary for safe swallowing.

Sensory processing by the tongue and oral cavity is required to adequately prepare the bolus and maintain its cohesion. Tactile sensation to the anterior two-thirds tongue is mediated by the lingual nerve (CN V3) and taste sensation is provided to this region by the chorda tympani nerve (CN VII). The glossopharyngeal nerve (CN IX) provides both sensory and taste to the posterior one-third of the tongue. Oral sensation is also basic to proprioception because the oral structures and changing bolus characteristics must continually interact until the bolus is perceived to be fully prepared to swallow.

Oral preparation through mastication essentially places everyone on a "pureed" diet, since humans do not swallow solid food whole. Difficulty swallowing pills can be attributed to both the anticipatory phase where fear and anxiety affect swallowing function in addition to volitional inhibition of mastication. Maintaining bolus cohesion and control is also needed for liquids and puree consistencies so that the next phase of swallowing can be accomplished.

ORAL TRANSFER PHASE

Once the bolus is prepared, it must be collected into a cohesive unit and moved to the posterior oral cavity. Oral transfer is accomplished by containing the bolus within the center of the tongue while the tongue tip contacts the alveolar ridge and pushes the bolus back across the hard palate using a wave-like propulsive force. During both the preparatory and transfer phases, sensory information is gathered in relation to bolus size and texture. Although it is not understood how humans have an intrinsic knowledge in relation to swallowing safety, the bolus will be subdivided if it is determined to be too large. Once the bolus reaches the posterior oral cavity, the lateral portions of the tongue press on the anterior facial pillars (innervated by CN IX) to terminate the oral phase and subsequently trigger the pharyngeal phase. Throughout the oral preparatory and transfer phases, the soft palate is pulled down and forward by the palatoglossus muscle (innervated by the pharyngeal branch, CN X) to maintain contact with the posterior tongue, thus sealing the oral cavity from the nasopharyngeal airway (Table 56.1). This mechanism allows maintenance of the bolus within the oral cavity while continuing to breathe through the nose (Fig. 56.1).

Oral dysphagia is present when the bolus is inadequately prepared or controlled. Poor dentition can lead to an inadequately prepared solid bolus that may have the potential to block the airway if aspirated. Failure to clear the oral cavity after a primary or secondary swallow can also result in aspiration after or between swallows. Reduced posterior oral control and/or weak velar depression may produce premature loss or "premature spillage" of a bolus into the pharynx or larynx before the pharyngeal phase of swallowing is "triggered." If the bolus cannot be controlled or transferred, gavage feedings may be necessary in order to bypass the oral cavity. A significant delay or failure to elicit the pharyngeal phase is classified as oral dysphagia, regardless of bolus location, since it is the oral tongue that must trigger the pharyngeal response. Impaired cognitive function or poor sensation can cause patients to "forget" to elicit the pharyngeal swallow. Significantly reduced lingual range of motion, as a result of surgery or neurologic disease, can impair tongue strength or prevent the posterior tongue from reaching the facial arches to trigger the swallow. Oral dysphagia can occur in isolation or concomitant with pharyngeal dysphagia. It is important to always keep in mind that the airway remains open during the oral preparatory and transfer phases because the patient is breathing; therefore, prandial aspiration can occur both before and after the swallow.

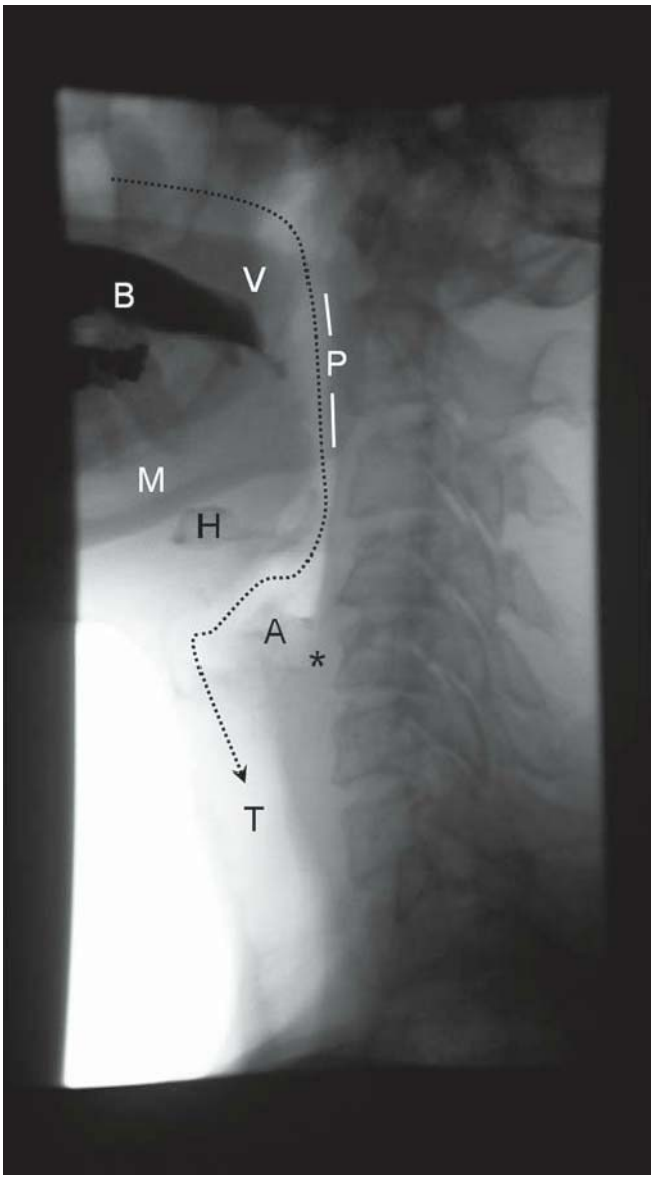


Figure 56.1 Posterior oral containment of the bolus. Note velar depression and airway continuity from the nasal passages to the trachea (*dotted line*). B, bolus; V, velum; M, mandible; H, hyoid; A, arytenoid; P, posterior pharyngeal wall, *, UES; T, trachea.

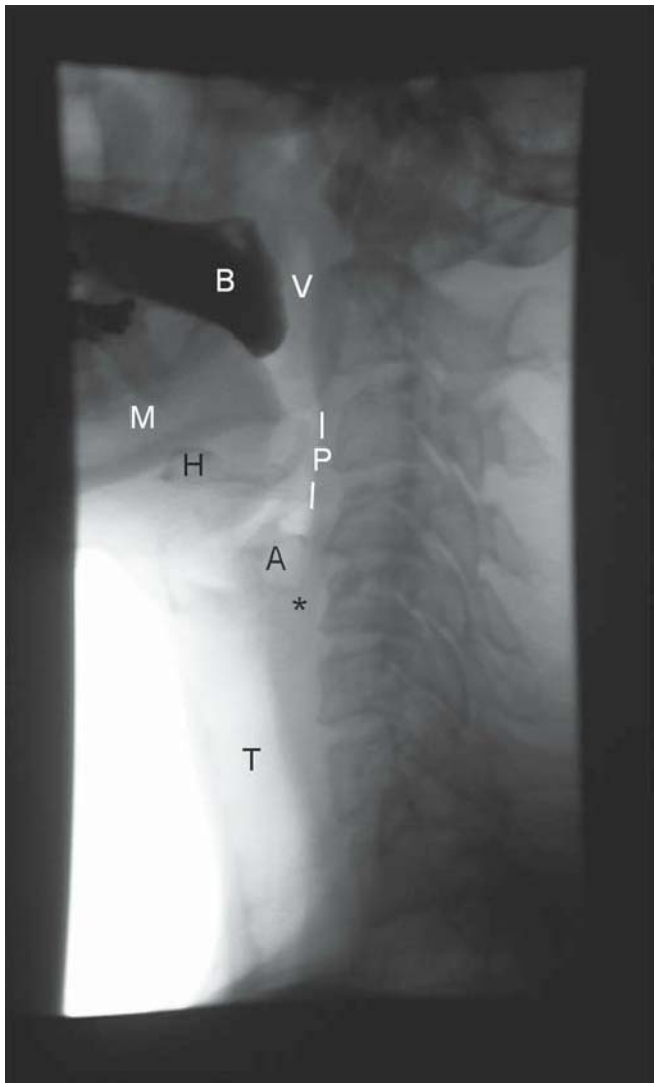


Figure 56.2 Elevation of the velum with subsequent closure of the nasopharynx. The hyoid and larynx are elevating. The arytenoids are about to approximate the petiole of the epiglottis to close the laryngeal aditus. B, bolus; V, velum; M, mandible; H, hyoid; A, arytenoid; P, posterior pharyngeal wall; *, UES; T, trachea.

PHARYNGEAL PHASE

The pharyngeal phase begins with elevation of the soft palate to seal the nasopharynx from the oropharynx (Table 56.1). Mediated by the sensory and motor fibers that are primarily contained in the pharyngeal plexus, velopharyngeal closure is the result of elevation and tensing of soft palate and contraction of the palatopharyngeal muscles, combined with anterior motion of the posterior pharyngeal wall (Passavant ridge, superior pharyngeal constrictor muscle). The adenoid pad and uvula may also aid in velopharyngeal closure. If the patient has velopharyngeal incompetence, they can experience nasal regurgitation during the swallow. Within milliseconds of velar elevation, the posterior tongue lowers to enable the bolus to enter the oropharynx (Fig. 56.2). The base of tongue retracts and exerts the primary propulsive force on the bolus. The upright epiglottis protects the airway by dividing the bolus and directing it into the lateral channels of the pharynx toward the hypopharynx. The larynx begins to elevate, moving in a superior and anterior trajectory. Activation of the thyrohyoid muscle (innervated by the first cervical nerve via the hypoglossus nerve) and the suprahyoid musculature (mylohyoid, anterior and posterior digastrics, stylohyoid, and geniohyoid muscles) results in the superior and anterior thrust of the hyoid bone to the mandible. During laryngeal elevation, the true and false vocal folds adduct (lateral cricoarytenoid, interarytenoid, and thyroarytenoid muscles, all innervated by the recurrent laryngeal nerve, CN X) as the arytenoid cartilages are drawn forward (5). Vocal

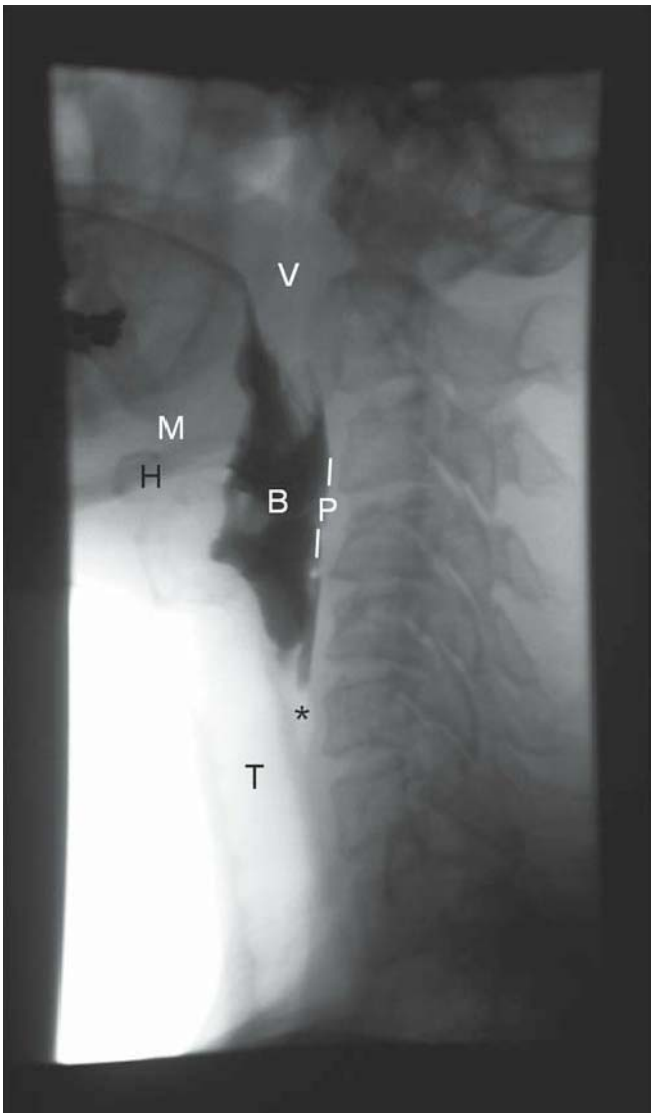


Figure 56.3 The hyolaryngeal complex elevated, with complete closure of the airway. The bolus is about to enter the UES. B, bolus; V, velum; M, mandible; H, hyoid; P, posterior pharyngeal wall; *, UES; T, trachea.

fold paralysis or severe vocal fold atrophy often results in glottic incompetence, which can result in aspiration during the swallow. The complex combination of base of tongue retraction, laryngeal elevation, and contraction of the ary-epiglottic muscles creates contact between the arytenoids and the epiglottic petiole (Fig. 56.3). This mechanism closes the laryngeal vestibule during pharyngeal bolus transit. Strong closure of the laryngeal entrance (aditus) can prevent aspiration and compensate for reduced glottal closure.

A common misconception is that the epiglottis inverts to protect the airway (6,7). In fact, the epiglottis has no motor innervation and cannot actively move. An upright epiglottis protects the airway by capturing and containing material within the valleculae. Epiglottic inversion is then biomechanically created by the combination of the tongue

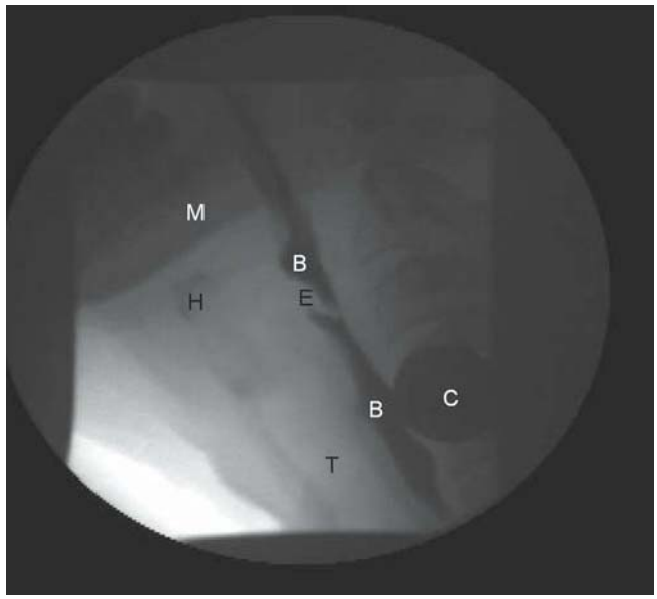


Figure 56.4 The inverted epiglottis within the bolus stream. The opaque circle is a coin, which is used to correct for magnification. B, bolus; M, mandible; H, hyoid; E, epiglottis; T, trachea; C, coin.

base retraction, hyolaryngeal elevation, and the weight of the bolus (Fig. 56.4). The inverted epiglottis can enter the upper esophageal sphincter (UES) and may help to direct the bolus into the esophagus. When epiglottic inversion does not occur, it suggests the presence of base of tongue weakness and/or is often associated with reduced hyolaryngeal elevation. Sometimes, all that is needed to promote epiglottic inversion is to increase bolus size or to alter the biomechanics by having the patient tuck the chin toward their chest during the swallow.

For the bolus to enter the esophagus, the tonic muscle fibers of the UES must relax to allow the bolus to enter the esophagus. The superior and anterior motion of the hyoid and larynx during the pharyngeal phase creates a traction force that opens the lumen. Hyolaryngeal elevation must be of sufficient height and duration to allow the entire bolus to pass through to the upper esophagus (Fig. 56.5). If the UES opening is limited in width and/or duration, truncation of the bolus and resultant residue in the post-cricoid region and/or pyriform sinuses (hypopharynx) can result. Aspiration of this residue can then occur after the swallow when the airway reopens for breathing.

Following the tail of the bolus by several milliseconds is a sequential contraction of the pharyngeal muscles starting with the superior constrictor, followed by the middle constrictor and then the inferior constrictor. The wavelike motion of the pharyngeal constrictors is often mistaken for peristalsis; however, peristalsis can only be present in a circumferential "tube." The function of the sequential motion of the pharyngeal constrictors is to maintain a closed system within the pharynx during bolus transit (by contacting the tongue base) and to provide a "clearing wave" to assure that the entire bolus leaves the pharynx in anticipation of

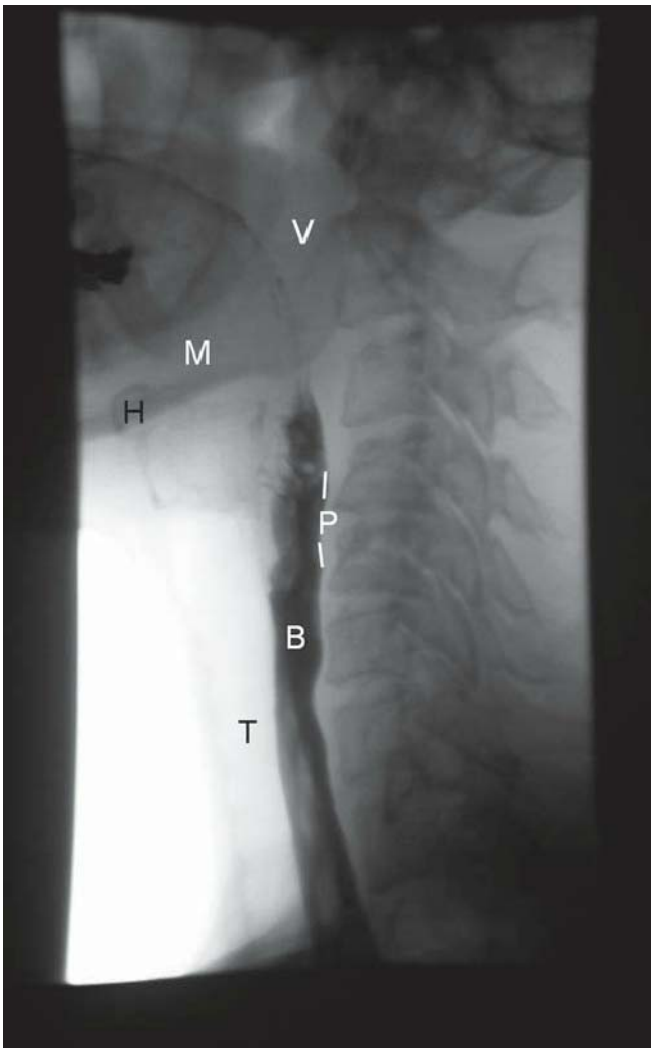


Figure 56.5 A relaxed UES, with the opening into the esophagus maintained by hyolaryngeal elevation. B, bolus; V, velum; M, mandible; H, hyoid; P, posterior pharyngeal wall; T, trachea.

airway opening. Patients who have had chemoradiation for the treatment of cancer in this region often have inadequate clearing of material due to weakness and reduced range of motion of these muscles, putting them at risk for dysphagia. The pharyngeal phase of swallowing transpires in approximately 1 second or less. This rapid sequence of events is controlled by bilateral CPGs located within the brainstem.

ESOPHAGEAL PHASE

Active closure of the UES prevents air from entering the esophagus during breathing and also protects the airway from invasion by refluxate from the esophagus and/or stomach. The primary muscle of the UES is the cricopharyngeal (CP) muscle within the inferior constrictor muscles, with dual innervations from the glossopharyngeal nerve (CN IX) via the pharyngeal plexus and the recurrent laryngeal nerve (CN X) (Table 56.1). Once the bolus enters the esophagus, the circular and longitudinal muscles enable peristalsis to transport the bolus until it reaches the lower esophageal sphincter (LES) at the distal esophagus. The LES is a single muscle that, like the UES, is tonic at rest. The LES relaxes with swallowing, enabling prandial material to enter the stomach. Esophageal dysphagia is present when either of the sphincter muscles (UES or LES) fails to open during deglutition (achalasia). Achalasia can be caused by a neurologic failure within the enteric nervous system scarring from radiation, or possibly repeated acid reflux.

A CP "bar" is a common finding on fluoroscopic swallowing studies but is not always a source of dysphagia unless it *impedes* bolus flow (Fig. 56.6). This finding can be due to hypertonicity and/or fibrosis of the muscle. This finding can also be the result of compensation to provide laryngeal protection in the face of esophageal dysmotility (esophageal–pharyngeal reflux). High-resolution esophageal manometry may be helpful in characterizing different types of esophageal dysphagia.

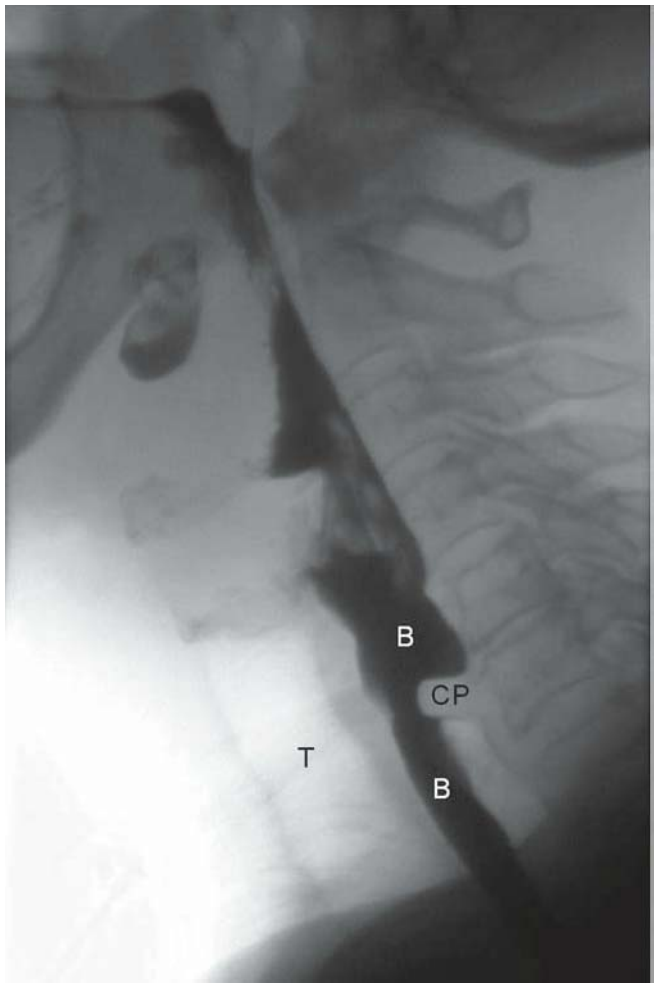


Figure 56.6 A CP bar. Although the fibers have not relaxed fully, the bar diverts but does not obstruct bolus flow. B, bolus; T, trachea; CP, cricopharyngeal muscle.

BREATHING AND SWALLOWING COORDINATION

The dual nature of the upper aerodigestive tract necessitates central inhibition of respiratory muscles during each swallow. Cessation of breathing, combined with airway closure is called deglutitive apnea. Another common misconception is that babies can simultaneously breathe and swallow; nonetheless, vocal fold adduction and deglutitive apnea are also present in infants (8,9).

Several investigators have identified a preferred coordination between breathing and swallowing, finding that most swallows are timed to occur during mid to early exhalation (10,11). Exhalation has been reported to occur almost exclusively following every swallow, even those that occur during the inhalation phase. A target lung volume was recorded in healthy subjects who were found to consistently swallow between 51% and 56% of their vital capacity, irrespective of respiratory pattern (12). Lung volumes above functional residual capacity are associated with positive subglottic air pressures that are generated during each swallow (13,14). Lung-thoracic unit recoil creates the positive pressure by compressing the closed respiratory system during deglutitive apnea. Spontaneous changes in pharyngeal swallowing function have been measured in healthy adults when swallows are timed to occur at extremes in lung volume. Changes in lung volume are associated with changes in the amount of subglottic pressure that is generated, indicating that respiratory signaling is also integrated into the sensory portion of each swallow. Emerging research points to the sensory receptors in the subglottis as the most likely structure that communicates the status of the respiratory system to the swallowing CPG (15–18). Due to the link between the respiratory system and swallowing, pulmonary disease such as chronic obstructive pulmonary disease is considered to be a primary risk factor for dysphagia because of the additional demands that deglutition places on the respiratory system (16,17)

HIGHLIGHTS

- Swallowing is not a stereotypic reflex, but rather a patterned motor response based upon the type of liquid or food to be swallowed.
- Diseases and treatments of the head and neck, such as cancer, can alter the ability to swallow, and therefore a high index of suspicion is necessary for these patients.
- Termination of the oral phase and triggering of the pharyngeal phase is created by the tongue contacting the facial pillars. Therefore, reduced tongue motion/strength could impair this transition to the next swallowing phase.
- The epiglottis does not move independently but rather is moved by other structures. An upright epiglottis splits the bolus around the larynx into the pyriform sinuses. With base of tongue motion, hyolaryngeal elevation, and the weight of the bolus, the epiglottis inverts. The lack of epiglottic inversion points to a deficiency in one or more of the factors that lead to its movement.
- Glottal incompetence can result in aspiration during the swallow. Strong closure of the laryngeal aditus superior to the level of the true vocal folds provides a layer of airway protection in this case.
- The superior-anterior motion of the larynx creates opening of the UES. Deficiencies in this movement due to surgery (such as suprahyoid release), scarring (such as chemoradiation), or neurologic deficiencies, will result in a shorting opening phase of the UES, despite normal relaxation of the cricopharyngeus muscle itself. This increases the possibility of postcricoid residue, which may be at risk of aspiration after the swallow is completed.
- Proper coordination of breathing and swallowing can improve the strength, and therefore efficiency, of the swallow.

SUMMARY

Oropharyngeal swallowing is a multifactorial process that requires precise coordination of multiple muscles and nerves. The wide variety of consistencies that are consumed necessitates a high degree of sensory input to assure that the motor output will provide the safest and most efficient swallow. Sensory processing begins before food is placed in the mouth and continues in the oral and pharyngeal cavity. A portion of sensory input is also received from the respiratory system. Dysphagia can develop when there is a disruption at any level of sensory-motor integration. Therefore, knowledge of the anatomy and physiology of the upper aerodigestive tract in relation to swallowing is critical for the optimal care of patients.

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Functional Assessment of Swallowing

57

Maggie A. Kuhn *Peter C. Belafsky*

Dysphagia is common and costly. The prevalence of swallowing disorders in adults over 50 ranges from 7% to 22% (1,2), with estimations as high as 50% in high-risk individuals (3). Dysphagia affects 30% of patients in hospitals and as many as 75% of individuals in nursing homes. Risk factors for dysphagia are numerous and include advancing age, acid reflux, stroke, head and neck cancer, head injury, amyotrophic lateral sclerosis, pseudobulbar palsy, Alzheimer disease, Parkinson disease, multiple sclerosis, muscular dystrophy, and myasthenia gravis. Dysphagia is a leading cause of death in most of these disorders (4,5). The incidence of dysphagia after stroke has been reported to be as high as 81% (3,6). Concurrent chemoradiation for head and neck cancer is associated with a 45% incidence of prolonged feeding tube-dependent dysphagia and an incidence rate for aspiration of 59% (7,8). Complications of dysphagia include malnutrition, dehydration, aspiration pneumonia, pulmonary abscess, and death. In 2001, the yearly expenditure for an individual dependent on tube feeding was $30,000 and Medicare spent 6% of its annual durable medical equipment budget ($670 million) on enteral feeding supplies alone. The cost of treating community-acquired pneumonia in the United States is $4.4 billion annually. The otolaryngologist is frequently the first specialist consulted to evaluate individuals with dysphagia. The purpose of this chapter is to review the indications and techniques for the functional assessment of swallowing.

DYSPHAGIA SYMPTOM INDICES

Dysphagia is a symptom not a disease. The symptoms of dysphagia can range from the isolated sensation of a lump in the throat to profound swallowing dysfunction and complete dependence on nonoral tube feedings. A significant percentage of patients reporting dysphagia will have no objective evidence of swallowing dysfunction. In addition, some patients with profound swallowing dysfunction will report only mild symptoms. Because dysphagia is frequently a symptom-driven disease, it is important to be able to accurately quantify the severity of the patient's complaints. The 10-item Eating Assessment Tool (EAT-10) is a validated self-administered disease-specific symptom inventory for dysphagia (Table 57.1) (9). It has proven useful in assessing initial symptom severity and in monitoring treatment efficacy. It has recently been translated into Spanish, Chinese, Japanese, and Portuguese. Dysphonia and reflux often accompany the symptom of dysphagia, and all patients presenting to our center also receive the 10-item Voice Handicap Index and the 9-item Reflux Symptom Index (Tables 57.2 and 57.3) (10,11).

CLINICAL SWALLOW EVALUATION

The clinical swallow evaluation (CSE) is used for the initial assessment of patients with dysphagia. Simply stated, the CSE consists of a comprehensive deglutition-focused history and physical as well as observing patients as they consume food or liquid. The study is usually performed before proceeding with a diagnostic instrumental swallowing examination as it helps assess and direct the need for further instrumental assessment. The CSE is indicated in patients reporting dysphagia or in individuals with suspected swallowing dysfunction suggested by weight loss, vocal fold immobility, malnutrition, history of prolonged intubation, dementia, head injury, head and neck cancer, recent cardiothoracic or head and neck surgery, stroke, or progressive neurologic disease.

The CSE begins with a comprehensive medical and feeding history from the patient, family member, or collateral source if the patient is incapable of communicating. The history begins with details of the patient's complaint or indication for the referral. It is important to review the

TABLE 57.1 THE EATING ASSESSMENT TOOL-10

To What Extent are the Following Scenarios Problematic for you?	0 = No Problem, 4 = Severe Problem				
1. My swallowing problem has caused me to lose weight.	0	1	2	3	4
2. My swallowing problem interferes with my ability to go out for meals.	0	1	2	3	4
3. Swallowing liquids takes extra effort.	0	1	2	3	4
4. Swallowing solids takes extra effort.	0	1	2	3	4
5. Swallowing pills takes extra effort.	0	1	2	3	4
6. Swallowing is painful.	0	1	2	3	4
7. The pleasure of eating is affected by my swallowing.	0	1	2	3	4
8. When I swallow food sticks in my throat.	0	1	2	3	4
9. I cough when I eat.	0	1	2	3	4
10. Swallowing is stressful.	0	1	2	3	4
Total EAT-10					

primary medical diagnosis, past medical and surgical history, comorbid conditions, and medications. A directed review of systems should focus on the presence of any tubes as well as the patient's airway, pulmonary, gastrointestinal, and neurologic status. History of prior speech or swallow dysfunction and any therapy or medical treatment received is elicited. Attention should also be paid to the individual's psychiatric and cognitive status, memory, and social history.

The feeding history helps the clinician establish a differential diagnosis and identify the site of suspected swallowing dysfunction. It begins with a thorough description of the patient's current feeding practices, specifically the type and amount of substances consumed, methods of feeding (straw, cup, utensils) and timing (duration and frequency) of feeding. Details regarding the onset and severity of the swallowing problem are elicited. When and where the problem occurs, localization of the problem, presence of coughing, choking, pain (odynophagia) or sticking, associated weight loss as well as the impact on the individual's quality of life are assessed. A patient's report of "cervical" dysphagia is unreliable, however, as 30% of individuals localizing the swallowing dysfunction to the neck will have a primary esophageal etiology

TABLE 57.2 THE VOICE HANDICAP INDEX (VHI-10)

Check the appropriate response. *Date:*

1. My voice makes it difficult for people to hear me.				
☐ *Never*	☐ *Almost never*	☐ *Sometimes*	☐ *Almost always*	☐ *Always*
2. People have difficulty understanding me in a noisy room.				
☐ *Never*	☐ *Almost never*	☐ *Sometimes*	☐ *Almost always*	☐ *Always*
3. My voice difficulties restrict personal and social life.				
☐ *Never*	☐ *Almost never*	☐ *Sometimes*	☐ *Almost always*	☐ *Always*
4. I feel left out of conversations because of my voice.				
☐ *Never*	☐ *Almost never*	☐ *Sometimes*	☐ *Almost always*	☐ *Always*
5. My voice problem causes me to lose income.				
☐ *Never*	☐ *Almost never*	☐ *Sometimes*	☐ *Almost always*	☐ *Always*
6. I feel as though I have to strain to produce voice.				
☐ *Never*	☐ *Almost never*	☐ *Sometimes*	☐ *Almost always*	☐ *Always*
7. The clarity of my voice is unpredictable.				
☐ *Never*	☐ *Almost never*	☐ *Sometimes*	☐ *Almost always*	☐ *Always*
8. My voice problem upsets me.				
☐ *Never*	☐ *Almost never*	☐ *Sometimes*	☐ *Almost always*	☐ *Always*
9. My voice makes me feel handicapped.				
☐ *Never*	☐ *Almost never*	☐ *Sometimes*	☐ *Almost always*	☐ *Always*
10. People ask, "What's wrong with your voice?"				
☐ *Never*	☐ *Almost never*	☐ *Sometimes*	☐ *Almost always*	☐ *Always*

TABLE 57.3 THE REFLUX SYMPTOM INDEX

Within the Last Month, how did the Following Problems Affect you?	0 = No Problem, 5 = Severe Problem					
1. Hoarseness or a problem with your voice	0	1	2	3	4	5
2. Cleaning your throat	0	1	2	3	4	5
3. Excess throat mucous or postnasal drip	0	1	2	3	4	5
4. Difficulty swallowing food, liquids, or pills	0	1	2	3	4	5
5. Breathing difficulties or choking episodes	0	1	2	3	4	5
7. Troublesome or annoying cough	0	1	2	3	4	5
8. Sensations of something sticking in your throat or a lump in your throat	0	1	2	3	4	5
9. Heartburn, chest pain, indigestion, or stomach acid coming up	0	1	2	3	4	5
Total						

for their symptom. Alternatively, an individual localizing the dysphagia to the chest will almost always have an esophageal phase swallowing disorder. The effect of diet modification such as food consistency, lubrication, temperature, timing, and postures should also be noted. In general, solid food dysphagia suggests an obstructive problem whereas liquid dysphagia suggests a neurologic disorder.

The clinician then performs the examination and observation portion of the CSE. Minimal equipment is required and includes a tongue blade, light source, food, and liquid as well as feeding devices such as a spoon, syringe, or straw. It is useful to have suction available during the observed swallow.

General characteristics of the patient are assessed including level of alertness, ability to participate in the examination as well as overall posture and tone. Careful attention should be paid to the patent's articulation, resonance, voice quality, and pitch. A wet vocal quality suggests laryngeal penetration and difficulty managing saliva. The presence of dysarthria or hypernasality is an ominous sign and frequently indicates a progressive neurologic disorder. The rate and quality of breathing as well as the presence of a tracheotomy are noted.

Evaluation of the oral cavity and oropharynx includes inspection of the lips, tongue, jaw, teeth, and palate for general structure, quality, symmetry, and sensation. Voluntary movement of the jaw, tongue, lips, and velum is assessed with particular attention to strength, symmetry, accuracy, and range of motion. A tongue blade is used to elicit a gag reflex by touching the tonsillar pillar or tongue base. A normal response involves tongue protrusion, pharyngeal contraction, and jaw extension. The relationship between an intact gag reflex and safe swallowing function, however, has been brought into question (12). Other involuntary movements such as the transverse tongue reflex (lateral tongue motion in response to tactile stimulus on the lateral tongue border) may be assessed. The abnormal presence of primitive reflexes (biting, routing) should be noted. The oral cavity is inspected for the presence, quality, and quantity of secretions.

The remaining structures of the pharynx and larynx are hidden from direct examination during the CSE. The clinician may assess the suppleness of the neck musculature and the movement of the larynx during a dry swallow. If the larynx does not palpably elevate with swallowing, the patient will have a diminished ability to open the upper esophageal sphincter (UES) and deglutition may be affected. The patient is asked to cough and throat clear to confirm the presence of these protective mechanisms. Though the subjective evaluation of cough strength and quality have not been shown to accurately predict swallowing dysfunction (13), objective aerodynamic measures, particularly expiratory phase peak flow during voluntary cough, are associated with penetration and aspiration among those with neurologic disorders (14,15).

For observed swallowing trials, ice chips, water, or food is selected by the clinician based on the suspicion for aspiration given the patient's history and physical examination. Use of straws, utensils, and syringes may be used by the patient or examiner to facilitate entry into the mouth. The patient's ability to hold the bolus in the oral cavity is assessed and is best accomplished with pureed and solid foods. During and immediately following the swallow, the examiner monitors for cough, repeated swallows, wet vocal quality, and voice changes. The effort required for swallow as well as a rough timing of the swallow can be assessed. Only one swallow should be required to pass an administered bolus. The presence of a second or third swallow for a single bolus suggests disordered swallowing.

The clinical swallow evaluation serves a variety of purposes. Most critically, it attempts to identify those at risk for aspirating oral intake. Its accuracy for this task is disputed and continues to be studied. The CSE has been criticized for its inability to detect pharyngeal phase swallowing dysfunction and for its poor sensitivity in predicting aspiration (16). Silent aspiration, by definition, is identified only by direct observation of the pharyngeal

phase of swallowing and is reported in up to 59% of dysphagic patients (17). The consequences of missed aspiration on CSE may be significant (18). Videofluoroscopic swallow studies (VFSS) and flexible endoscopic evaluation of swallowing (FEES) may detect silent aspiration in one-quarter to one-third of individuals missed by CSE (19–21). When compared with FEES to evaluate dysphagic patients following acute stroke, the presence of two or more positive findings on CSE has revealed a sensitivity for aspiration of 86% and a specificity of only 30% (22). Adding pulse oximetry to a water swallow may improve the sensitivity for aspiration in acute stroke patients (23). Daniels et al. (24) retrospectively reviewed acute stroke patients with fewer than two positive findings on CSE and found that they had no increased risk of poor outcome, namely aspiration pneumonia, than their counterparts who underwent VFSS. However, given the morbidity associated with aspiration, the CSE yields unacceptably high false negative and positive rates to be an effective unimodality screening exam or reliable diagnostic tool for swallowing dysfunction. Dysphagic patients with an abnormal CSE or those with a normal CSE who are at a high risk of aspiration will require further evaluation with an instrumental assessment of swallowing function.

FLEXIBLE ENDOSCOPIC EXAMINATION OF SWALLOWING/FLEXIBLE ENDOSCOPIC EVALUATION OF SWALLOWING WITH SENSORY TESTING

FEES was first described by Susan Langmore et al. (25) in 1988. The study provides direct visualization of the pharynx and larynx immediately before and after a swallow. The equipment required to perform FEES includes a flexible endoscope, viewing monitor, recording equipment, and commercially available food testing materials. Although the examination requires an endoscope and recorder, technologic advances and equipment miniaturization allow the study to be performed in the clinic or at the bedside in a hospital or nursing home setting. The examination can be performed by a solo practitioner but it is easier to have an assistant available to help feed the patient.

The patient is seated upright in a position appropriate for eating. Topical nasal anesthesia is commonly avoided although standardized doses of atomized saline, oxymetazoline, and cocaine have not been shown to have an effect on laryngopharyngeal (LP) sensory thresholds (26). The endoscope is passed through the more patent nasal cavity. The velum and ability of the palate to close against the posterior nasopharyngeal wall is evaluated. The velopalatal port should close completely and can be assessed with a swallow, hum, or nasal phoneme. After assessing the palate, the symmetry of the pharynx at rest and the quantity of pooled secretions in the pyriform sinuses and endolarynx is assessed. Pooled saliva in the pyriforms suggests profound swallowing dysfunction and is predictive of the presence of aspiration (27). The larynx is inspected for lesions, inflammation, and vocal fold mobility. Vocal fold movement is assessed with the patient performing the "/eee/-sniff" maneuver. Vocal fold immobility is highly predictive of aspiration and nearly 25% of individuals with unilateral immobility will aspirate thin liquids (28). The endoscope is positioned in the "home" position in the pharynx just above the tip of the epiglottis (Fig. 57.1). The patient's ability to close the supraglottis and protect the airway is assessed with the breath hold maneuver. The degree of pharyngeal muscular contraction is evaluated by having the patient perform the pharyngeal squeeze maneuver (PSM) (29). The patient is instructed to deliver a voluntary, forceful, high-pitched "/eee/," and pharyngeal muscular contraction is evaluated by assessing the motion of the lateral hypopharyngeal walls and corresponding narrowing of the pyriform sinuses (Fig. 57.2). The PSM is classified as normal or abnormal only. Attempts at quantifying the degree or laterality of pharyngeal weakness with the PSM have lacked reproducibility (30). The PSM has been validated with objective assessments of pharyngeal strength on fluoroscopy (31). Patients with an absent PSM are significantly more likely to aspirate. After the assessment of pharyngeal strength, LP sensory testing is performed.

The addition of sensory testing to the FEES procedure is termed flexible endoscopic evaluation of swallowing with sensory testing (FEESST). FEESST directly evaluates LP sensation by assessing the ability of a tactile stimulus to elicit the laryngeal adductor reflex (LAR) (32–34). Sensory

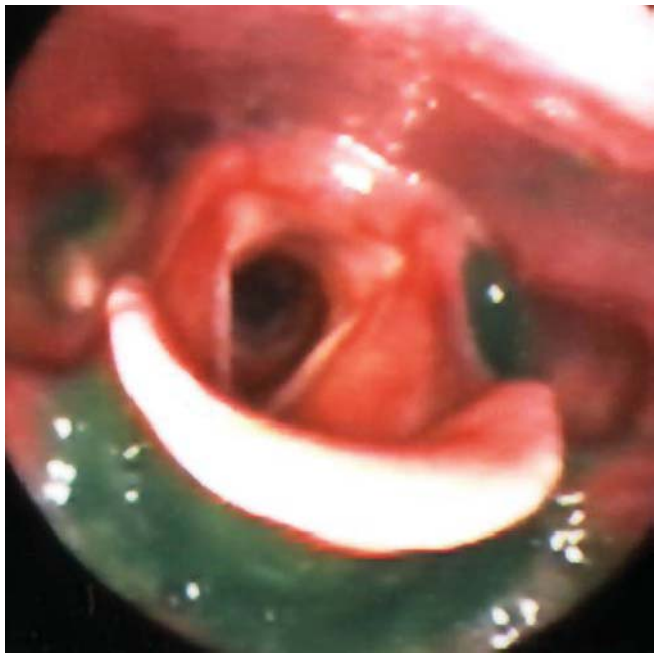


Figure 57.1 FEES with the tip of the endoscope in the home position just above the tip of the epiglottis. Note the premature spillage of green liquid into the vallecula and down the hypopharyngeal gutters into the pyriform sinuses.

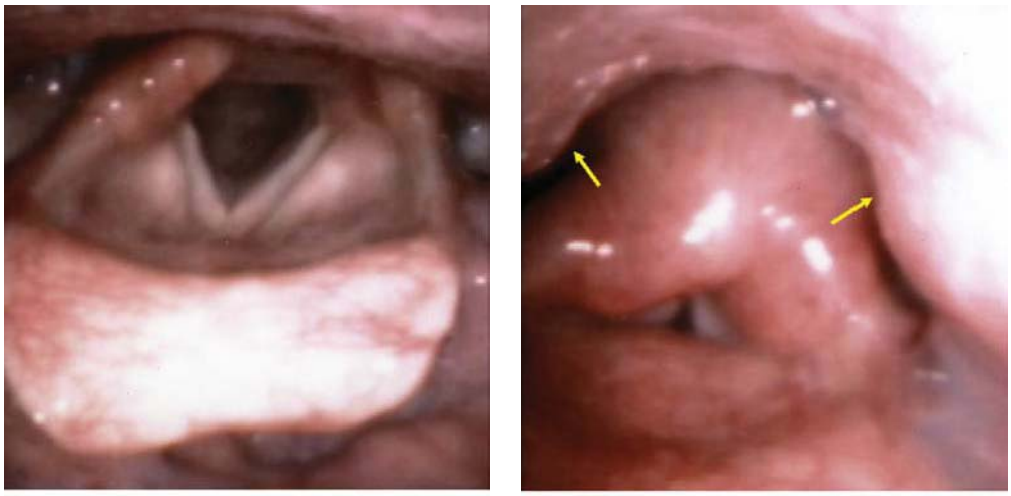


Figure 57.2 PSM. **A:** The pharynx is relaxed at rest. **B:** An intact PSM. The patient says a forceful /eee/ and the lateral hypopharyngeal walls contract and obliterate the pyriform sinuses (*arrows*).

testing may be grossly performed with the tip of the flexible endoscope or formally quantified with a LP air-pulse stimulator. A pulse of air is delivered to the mucosa over the aryepiglottic fold through a side-channel on the flexible endoscope. The pressure of the air-pulse delivered through the endoscope (mm Hg) may be varied to quantify the amount of stimulus required to elicit the LAR.

The LAR is a brainstem-mediated, involuntary reflex arc providing airway protection from ingested material (35). The LP mucosa receives innervation from the internal branch of the superior laryngeal nerve and is the afferent component of the LAR. The recurrent laryngeal nerve is the efferent component, and in response to a unilateral stimulus, produces brief and rapid bilateral contraction of the thyroarytenoid muscles. Aviv et al. (36) described normative sensory thresholds to calibrated pulses of air. An individual with normal LP sensation demonstrates LAR at a pulse pressure of less than 4 mm Hg. Those requiring greater pressure are identified as having moderate (4 to 6 mm Hg) or severe sensory impairment (greater than 6 mm Hg). These thresholds correlate with psychophysical testing, or patient-reported sensation of delivered air pulses (33). Aviv et al. (37) reported a strong association between pharyngeal motor dysfunction on the PSM and decreased LP sensation. They demonstrated that isolated pharyngeal motor dysfunction with intact LP sensation is predictive of penetration and aspiration with pureed consistencies, and an isolated LP sensory deficit with an intact PSM is predictive of penetration and aspiration with thin liquids. Nearly all patients with an absent LAR and absent PSM aspirate both thin liquids and puree (38,39). After the assessment of LP sensation, the patient is administered food and beverage.

Before the patient is fed, s/he is asked to take a "dry" swallow. During the swallow, eversion of the epiglottis that occurs as a consequence of laryngeal elevation and lingual retraction causes a *whiteout* on the video monitor. Assessments of swallowing function must be made before and after the whiteout occurs. The inability to achieve whiteout on a dry swallow suggests profound swallowing dysfunction. All food and beverage is impregnated with green food coloring (McCormick & Co, Inc., Sparks, MD). The decision to begin the examination with food, liquid, or ice chips is determined by the information garnered from the initial examination. If the patient has an intact LAR but absent PSM, the patient is first administered water. The water is fed by teaspoon if limited bolus sizes are desired. If larger bolus sizes are administered, the patient is asked to sip from a straw. A cup sip is difficult to perform with a flexible endoscope in the nose, and a flexible straw that articulates to 90 degrees is an important piece of equipment to have available during the examination. If the patient has an absent LAR but an intact PSM, the patient is first administered puree. We utilize applesauce as our standard puree substance (Mott's Inc., Rye Brook, NY). The applesauce has a long shelf life, does not require refrigeration, and can be kept in the examination room. If the patient has an absent LAR and absent PSM, the patient is first administered a small ice chip. Ice chips are preferred in this situation for several reasons. The cold from the ice provides additional sensory information to the patient that may assist with deglutition. Furthermore, ice is easier to control in the oral cavity than thin liquid and, if aspirated, will readily melt and poses little harm to the patient. Suspected aspiration of a given bolus requires repetition of the same volume and viscosity to confirm aspiration. Determining that a particular consistency is safe occurs only after repeated successful trial as dysfunction is often uncovered after fatiguing the swallowing apparatus or triggering an irregular breathing pattern. If the patient passes the water and puree consistencies, more challenging solids or pills may be administered.

The food is placed in the oral cavity and the patient is instructed not to swallow until instructed. Loss of the bolus into the pharynx before the initiation of swallow is called premature spillage. Following the swallow, the endoscope is advanced from the home position into the laryngeal vestibule and the passage of material into the laryngeal inlet (penetration) or passage of material below the vocal folds (aspiration) is evaluated. The ability for slow motion video playback is essential to evaluate the presence of aspiration during the swallow. Penetration and aspiration may occur before, during, or after the swallow. In general, aspiration before the swallow occurs in 25% of cases of aspiration and indicates oral and pharyngeal dysfunction, aspiration during the swallow occurs in 10% of cases of aspiration and indicates a neurologic disorder with a sensory deficit, and aspiration after the swallow occurs in 65% of cases of aspiration and indicates lingual or pharyngeal weakness or outlet obstruction through the UES. The presence of penetration and aspiration can be quantified with the penetration aspiration scale (PAS) (40) (Table 57.4). Also noted are pharyngeal residue, coughing, throat clearing, or a secondary reswallow. Postswallow regurgitation out of the esophagus into the pharynx (esophagopharyngeal reflux) is called "the rising tide sign" and may indicate the presence of a Zenker diverticulum or profound esophageal dysmotility. In the presence of intact pharyngeal strength and diminished or absent LP sensation, it may be difficult to determine if aspiration occurred during the whiteout phase of the examination. In this case, a brief tracheoscopy may be performed at the end of the FEES to identify silent aspiration.

TABLE 57.4 PENETRATION ASPIRATION SCALE

Score	Description
1	Food/beverage does not enter the airway
2	Food/beverage enters the airway, remains above the vocal folds with no visible residue present after the swallow
3	Food/beverage enters the airway, remains above the vocal folds with visible residue present after the swallow
4	Food/beverage penetrates to the level of vocal folds with no visible residue present after the swallow
5	Food/beverage penetrates to the level of vocal folds with visible residue present after the swallow
6	Food/beverage penetrates below the level of vocal folds with no visible residue present in the subglottis after the swallow
7	Food/beverage penetrates below the level of vocal folds with visible residue present in the subglottis despite a patient's response to clear
8	Food/beverage penetrates below the level of vocal folds with visible residue present in the subglottis and an absent patient response to clear

For individuals who demonstrate abnormal swallowing, modified consistencies and therapeutic maneuvers may be performed at the end of the examination. The chin tuck may help eliminate vallecular residuals. The supraglottic swallow and food thickeners may address premature spillage and aspiration occurring before and during the swallow. An ipsilateral head turn to the side of vocal fold immobility or pharyngeal weakness will divert the bolus away from the affected location and may improve swallowing safety. A monitor positioned across from the patient will allow the clinician to perform FEES biofeedback or "bioFEESback." This can assist with teaching airway protection and with communicating the effectiveness of various swallowing maneuvers.

Various clinicians have attempted to compare the utility of FEES with VFSS. A number of studies have confirmed that FEES provides information about swallow initiation, penetration, aspiration, and presence of pharyngeal residue that is at least as reliable as that obtained from VFSS (20,41–44). FEES may be a more sensitive indicator of penetration and aspiration than VFSS (45,48). Investigation suggests that both studies have good inter-rater reliability when the standardized PAS is used (42,45). Advantages of FEES include its portability, relatively low cost, lack of radiation exposure in addition to the ability to evaluate various food substances and assess for pooling of saliva, laryngeal inflammation, neoplasm, and vocal fold function. The primary benefits of VFSS include the ability to evaluate bolus movement through the pharyngoesophageal segment (PES), the ability to screen the esophagus, and the ability to precisely quantify objective swallowing parameters such as PES opening, laryngohyoid displacement, and pharyngeal timing measures. Table 57.5 compares the relative advantages of FEES and VFSS.

TABLE 57.5 FEESST VERSUS FLUOROSCOPY

Ability to Evaluate	FEESST	Fluoroscopy
Vocal fold function and anatomy	++++	++
LP sensation	++++	+
Spillage	++++	++++
Aspiration	++++	++++
Laryngeal penetration	++++	++++
Pharyngoesophageal and cricopharyngeus muscle evaluation	+	++++
Pooling of secretions	++++	+
Ability to determine objective swallowing parameters	+	++++
Oral cavity	++	++++
Laryngohyoid elevation	++	++++
Esophageal phase of deglutition	+	++++

+, poor ability to evaluate; ++, average ability to evaluate; +++, good ability to evaluate; ++++, excellent ability to evaluate.

VIDEOFLUOROSCOPIC SWALLOW STUDY

Radiographic assessment of swallowing function evaluates the laryngopharynx, esophagus, or both. The VFSS traditionally refers to the radiographic swallow evaluation of the oral cavity and pharynx and represents the gold-standard modality to evaluate the UES. Alternatively, radiographic visualization of the esophagus is termed an esophagram or barium swallow (46).

Because patients are exposed to radiation during VFSS, appropriate indications should be identified before a patient undergoes the evaluation. Indications include dysphagia, odynophagia, aspiration, chronic cough, and postoperative evaluation. The purpose of VFSS is to identify behaviors and abnormalities that result in risks to a patient's nutritional status or the respiratory system during feeding. Given that the evaluation itself may expose the dysphagic examinee to risk of aspiration, the examiner must choose following each swallow exercise whether or not to continue. As such, the evaluation may be truncated for safety at the expense of gathering information.

Unlike FEES and CSE, VFSS allows for thorough evaluation of the oral phase of swallowing. Bolus formation, effective tongue motion, and swallow initiation are uniquely and readily characterized during VFSS (47). Additionally, the function of the linguapalatal valve, which alternately contains the bolus within the oral cavity and releases it into the pharynx, is only adequately assessed on lateral projections during VFSS. When compared to FEES, VFSS offers the additional advantages of velopharyngeal valve assessment, evaluation of UES opening, real-time recording of transitions between phases of swallowing and esophageal screening, which can be readily performed as an adjunctive evaluation in the same setting as VFSS.

VFSS is performed with a patient seated in a fluoroscopic radiography suite with equipment capable of rapid sequence image capture. During the examination, swallows of different quantities and consistencies of barium are captured in both lateral and frontal projections. The frontal view allows for superior visualization of the vallecula and piriform sinuses as well as certain abnormalities such as Zenker diverticulum. Owing to the propensity of esophageal abnormalities to result in dysphagia, a screen of the esophagus is also performed.

A standardized protocol of bolus consistencies and volumes should be followed for all examinations to allow for comparisons between sequential exams, different patients, and normative data. Complaint-specific tasks, such as pill swallows, should also be included if possible and safe. Following the standardized protocol, abnormalities may be targeted by specific compensatory maneuvers. The efficacy of compensatory strategies can be evaluated fluoroscopically.

Reporting objective measures when evaluating VFSS has been advocated to aid in standardizing the description of swallowing dysfunction and predicting success of intervention (48). Objective data gathered from fluoroscopic exams allow for comparisons to normative values, serial examinations, and other individuals. Included in these objective data are measures of timing and displacement. Timing measures reflect both bolus transit and timing of swallowing gestures, including hyoid displacement and PES opening. Calculation of bolus transit and gesture timing as well as their resultant coordination allows for characterization of "delayed" and "prolonged" swallowing abnormalities. Both result in increased risk of aspiration to the examinee.

With proper patient positioning and calibration, spatial measurements can be made on digitized images collected during VFSS. Commonly measured are maximum hyoid displacement, pharyngeal constriction ratio (PCR), maximum PES opening, and maximum approximation of the larynx and hyoid. The PCR is a surrogate measure of pharyngeal clearance pressure (49), traditionally measured by pharyngeal manometry. It is calculated by dividing the lateral pharyngeal area during maximal contraction by the area while a 1cc bolus is held in the oral cavity. Normative data for the PCR have been described (50). A normal PCR (within two standard deviations for an age-matched control) predicts a satisfactory result following an intervention to increase UES size, such as cricopharyngeal myotomy. The increased availability of VFSS compared to pharyngeal manometry yields this measurement especially valuable.

TRANSNASAL ESOPHAGOSCOPY

Advances in flexible endoscopic technology have led to the evolution of ultrathin endoscopes that are easily and safely passed transnasally for evaluation of the upper aerodigestive tract in the unsedated patient (51). Since 2000, transnasal esophagoscopy (TNE) has been popularized by otolaryngologists, and its applications continue to expand (52–54). Though initially thought to be inferior to conventional peroral esophagoscopy in image quality and diagnostic ability (55,56), TNE using the ultrathin distal chip videoendoscope has been shown to offer equivalent image quality and diagnostic accuracy as standard methods of sedated, peroral esophagoscopy (57–59). Furthermore, TNE affords both direct and indirect cost savings, improved safety profile, and better patient tolerance when compared to conventional esophagogastroduodenoscopy (EGD) (60,61). Comparison studies have found patient tolerance of unsedated TNE to be equivalent or superior to sedated EGD (62,63). Over 70% of patients prefer to have unsedated TNE (64).

Indications for TNE may be esophageal, extraesophageal, and interventional (65). The most common indication for TNE is a screening evaluation for patients with reflux, dysphagia, and globus, accounting for 80% of examinations (66). Although the need to screen the esophagus in patients with symptoms of LP reflux is uncertain, there is evidence that extraesophageal reflux symptoms,

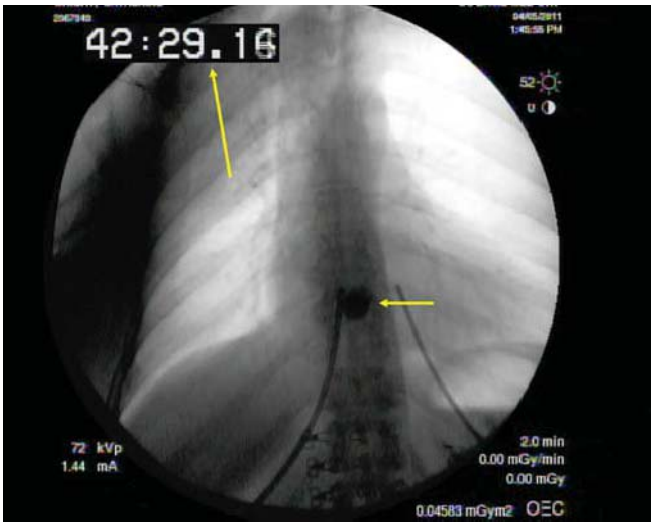


Figure 57.3 Fluoroscopic video-esophagram displaying a 13 mm barium tablet stuck in the midportion of the esophagus (*short arrow*). The patient is localizing the location of dysphagia to the cervical region with her right hand (*long arrow*).

especially chronic cough, better predict the presence of esophageal adenocarcinoma than the typical reflux symptoms of heartburn and regurgitation (67). Other less common indications for TNE include unexplained weight loss, hemoptysis, chest pain, odynophagia, and evaluation of suspected esophageal foreign body. Esophageal pathology is extremely common in patients after definitive treatment for head and neck cancer. Among head and neck cancer patients evaluated with TNE greater than 3 months after treatment, 63% had esophagitis, 23% had esophageal stricture, 9% had candidiasis, 8% had Barrett metaplasia, and 4% had a second primary malignancy (68). Thus, we routinely perform esophagoscopy in all individuals 3 months after definitive treatment for head and neck cancer.

Patients do not accurately identify the source of their dysphagia. Approximately one-third of patients who localize their swallowing dysfunction to the cervical region will have an esophageal etiology for their symptom (Fig. 57.3). Thus, in the absence of an identifiable oropharyngeal cause of the symptom of dysphagia, patients with solid food dysphagia should have their esophagus screened regardless of where they localize the symptom. TNE has enabled the otolaryngologist to perform a variety of office-based interventions. The expanding list of unsedated office procedures performed via TNE includes biopsy, stricture and web dilation, botulinum toxin injection, foreign body retrieval, tracheoesophageal puncture, and feeding tube insertion (69,70).

To perform TNE, an unsedated patient is seated upright in a standard ENT examination chair (Fig. 57.4). Cardiac monitoring is not necessary and ideally the patient is kept nil per OS for 3 hours prior to the procedure. Although a full stomach may enhance nausea, it is not a contraindication to the procedure. The patient's nasal cavity is sprayed with 1:1 oxymetazoline 0.05% and lidocaine 4%. If the patient has a hypersensitive gag reflex, the patient may

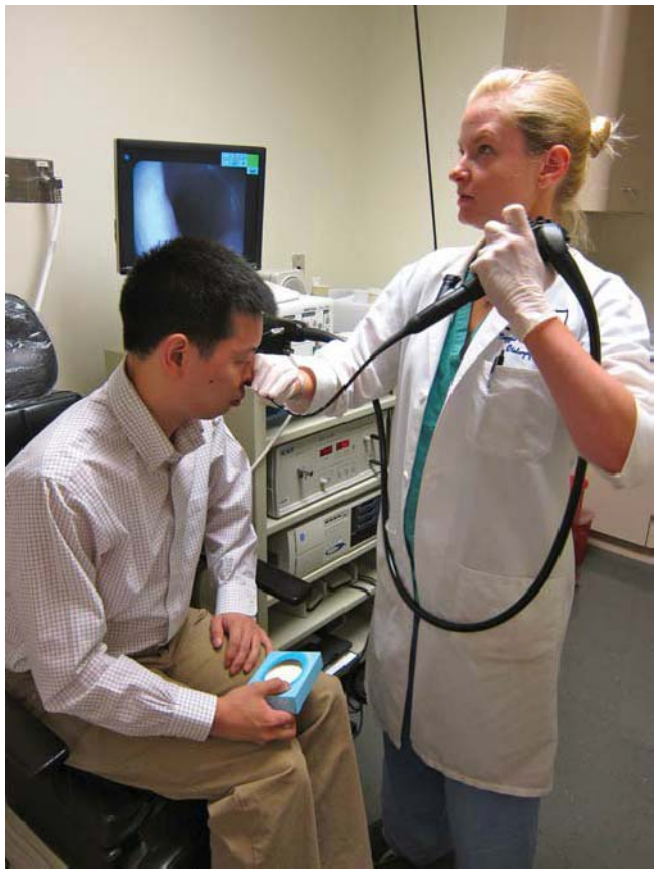


Figure 57.4 Positioning for office-based unsedated TNE.

be given two teaspoons of 2% viscous lidocaine to gargle and swallow. Distal chip esophagoscopes are capable of air insufflation, water instillation, and suction and have a working port allowing for biopsy, injection needle, laser fiber, and guide wire placement.

The endoscope is lubricated with 2% viscous lidocaine and passed through the more patent nasal cavity. Supraesophageal structures including the nasopharynx, velum, oropharynx, larynx, and hypopharynx are first examined. After the laryngeal examination, the endoscope is placed just above the tip of the epiglottis in the home position. A hand is placed on the patient's shoulder and the patient is asked if s/he is comfortable enough to continue. Eye contact is made with the patient and s/he is then instructed that s/he will be asked to swallow the endoscope. The eye contact and human touch are essential to keep the patient at ease and reduce anxiety. The esophagus is entered by placing the tip of the endoscope into the pyriform sinus and asking the patient to lean forward, flex the chin toward the neck, and swallow. Instructing the patient to "close your lips and pretend you are swallowing a big piece of spaghetti," often provides reassurance as to the benign nature of the procedure. While the patient swallows, the scope is advanced through the UES into the cervical esophagus (71). If there is difficulty passing the scope into the esophagus, a teaspoon of 2% viscous lidocaine may be placed into the

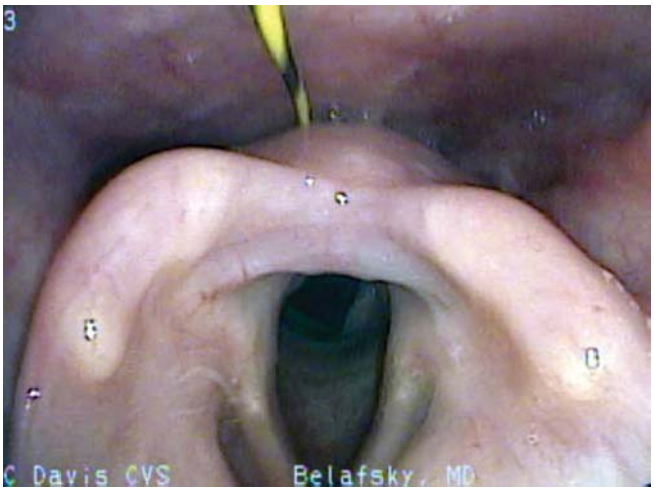


Figure 57.5 Placement of a guide wire through the transnasal endoscope and into the esophagus in a patient with a Zenker diverticulum. The endoscope can be advanced over the guide wire once it has been safely passed 30 to 40 cm into the esophagus.

patient's oral cavity. The patient is instructed to hold the lidocaine in the mouth and, as the endoscope is positioned in the pyriform sinus near the esophageal inlet, the patient is asked to flex their chin toward the chest and swallow. The lidocaine bolus will open the UES during deglutition and will lubricate the endoscope as it passes into the esophagus. If this is not successful in allowing entrance into the esophagus, the examination should be terminated and a fluoroscopic swallow study obtained to rule out the presence of cricopharyngeal dysfunction or a Zenker diverticulum. If known cricopharyngeal dysfunction or Zenker diverticulum exists, intubating the esophagus can be performed with the assistance of a guide wire (Hydra Jagwire Guidewire, Boston Scientific, Natick, MA). The guide wire is placed through the esophagoscope and advanced under direct vision into the esophagus as the patient is instructed to swallow (Fig. 57.5). If the guide wire enters a diverticulum or cannot traverse an obstructing cricopharyngeus or cervical stenosis, it will curl and be seen reentering the pharynx. If the guide wire can be passed 30 to 40 cm without curling back into the pharynx, the clinician can be assured that it has safely traversed the diverticulum and UES. The esophagoscope can then be passed safely over the guide wire into the esophagus without the risk of perforation. Once the endoscope is safely in the midesophagus, the wire can be removed.

Once the esophagus is entered, the endoscope is immediately advanced to the midportion of the esophagus. Keeping the tip of the endoscope in the region of the UES is uncomfortable and will promote gagging. This region will be thoroughly examined at the end of the procedure as the endoscope is withdrawn. The esophagus is immediately suctioned of air and fluid and the examiner's free hand is again placed on the patients shoulder and eye contact is made. The patient is reassured that "this is as bad as the procedure is going to get" and asked "are you comfortable enough to proceed with the examination?" If there is noticeable discomfort or gagging, the procedure is terminated and an examination under intravenous sedation is scheduled. The midportion of the esophagus is then insufflated with air and the esophagoscope is advanced to the gastroesophageal (GE) junction. The presence of diverticula, abnormal dilation, foreign body, motility abnormality, esophagitis, web, ring, stricture, or neoplasm is noted. Figure 57.6 displays the most common findings identified

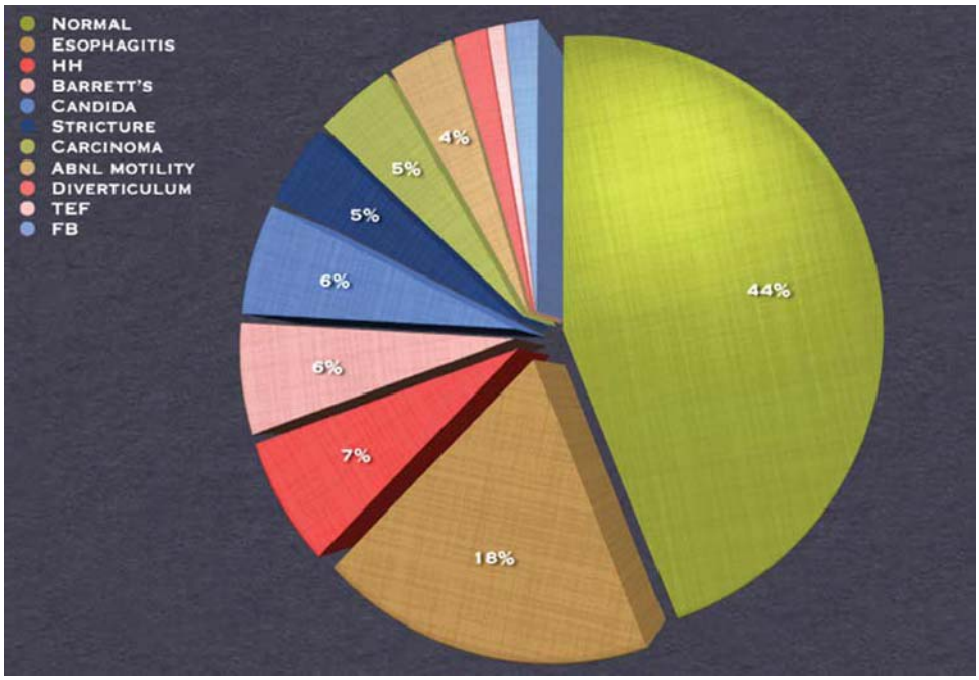


Figure 57.6 Most common findings reported on unsedated TNE. (HH, hiatal hernia; TEF, tracheoesophageal fistula; FB, foreign body).

on TNE. Lastly, the position of the squamocolumnar junction (Z-line), normally situated at the GE junction, is noted from above the lower esophageal sphincter (LES) and from below the LES during a retroflexed view from within the stomach. The stomach is suctioned free of air at the end of the procedure and the esophagoscope is carefully withdrawn. Withdrawing the endoscope will center the tip and provide an optimal view during removal.

Complications from TNE are rare. In 3% of patients, the 5.1 mm endoscope cannot be passed through a tight nasal vault (53). Epistaxis and vasovagal reaction, the most commonly reported complications, occur in fewer than 3% of patients (72). Because TNE is performed on unsedated patients, cardiopulmonary complications associated with traditional peroral esophagoscopy under sedation are reduced (73).

A functional esophagoscopy, or a *FEES of the esophagus* may be performed in patients with suspected esophageal phase dysphagia. The examination was initially described by Belafsky and Rees (74) in 2009 and is entitled **G**uided **O**bservation **O**f **S**wallowing in the **E**sophagus (GOOSE). A FEES is initially performed with the transnasal esophagoscope per the description earlier in the chapter. At the end of the FEES, the endoscope is passed through the UES into the cervical esophagus. Normal esophageal emptying time is approximately 13 seconds. Any residue present in the esophagus after this time suggests an esophageal abnormality (74). The GOOSE may be performed by offering the patient boluses of puree, liquid, cracker, and pills with the scope held in a series of three positions: above the aortic compression, above the LES, and retroflexed within the stomach (Fig. 57.7) (74). During this procedure, organic esophageal pathology, abnormal esophageal motility, and bolus transit time may be evaluated. In a study comparing the utility of GOOSE to fluoroscopy and manometry, GOOSE had a 71% concordance with fluoroscopy and an 83% concordance with manometry (74). GOOSE identified pathology not recognized on fluoroscopy and manometry in 62% of patients.

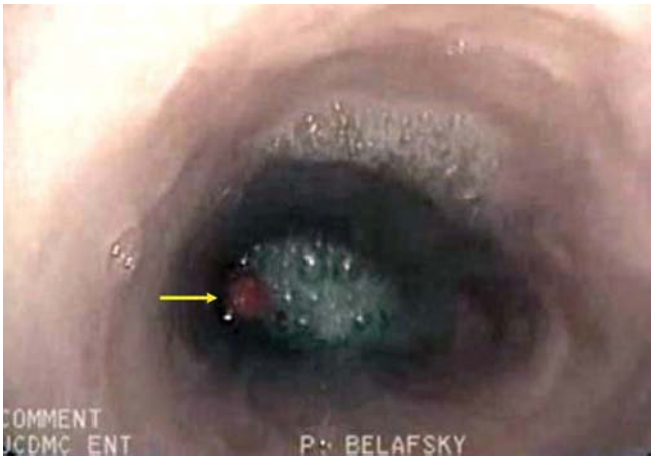


Figure 57.7 GOOSE in a patient with the complaint of pills getting stuck in the cervical region displays a pill (*arrow*) and liquid esophageal stasis above a distal esophageal peptic stricture. The stricture is not visualized on the image distal to the stasis.

HIGH-RESOLUTION MANOMETRY

Although endoscopy provides a direct view of the aerodigestive tract from the nasal vestibule to gastric body, it is limited in its ability to objectively quantify pharyngeal and esophageal motility and upper and LES function. The introduction of high-resolution manometry (HRM) into the functional assessment of swallowing significantly increases the clinician's ability to diagnose and classify disordered deglutition. Solid-state HRM typically has 36 circumferential sensors spaced 1 cm apart. Pharyngeal and esophageal motility are characterized by using pressure topography plots (Fig. 57.8). HRM has proven beneficial in distinguishing between pharyngeal weakness, poor pharyngeal and UES relaxation, incomplete upper esophageal relaxation, esophageal body motility, and LES function. Our HRM protocol involves a 5-minute assessment of UES and LES baseline function followed by the evaluation of twelve 5-mL water swallows. Pharyngeal peak pressures are evaluated from the soft palate to the UES. Then UES baseline, UES relaxation, and pharyngeal-UES coordination are evaluated. These pressure relationships are essential in evaluating a patient for surgery on the UES. The best candidates for cricopharyngeus muscle myotomy have elevated UES residual pressure, elevated hypopharyngeal intrabolus pressure, and normal pharyngeal and hypopharyngeal peak pressures. Individuals with absent hypopharyngeal pressure are unlikely to get benefit from myotomy (Fig. 57.9). A comprehensive discussion regarding the classification of esophageal motility disorders on HRM is beyond the scope of this chapter. Table 57.6, however, depicts the Chicago Classification of esophageal motility disorders on HRM (75).

TABLE 57.6 THE CHICAGO CLASSIFICATION OF ESOPHAGEAL MOTILITY DISORDERS ON HRM

Classification	Description
Esophageal aperistalsis without impaired LES relaxation	Failed peristalsis in all tests swallows with or without a hypotensive LES. If associated with a hypotensive LES is considered consistent with scleroderma
Achalasia	Esophageal aperistalsis with impaired LES relaxation
Hypertensive esophageal peristalsis	Further classified as distal esophageal spasm, compartmentalized esophageal pressurization, and nutcracker esophagus
Functional esophageal obstruction	Incomplete deglutitive LES relaxation in the setting of preserved esophageal peristalsis

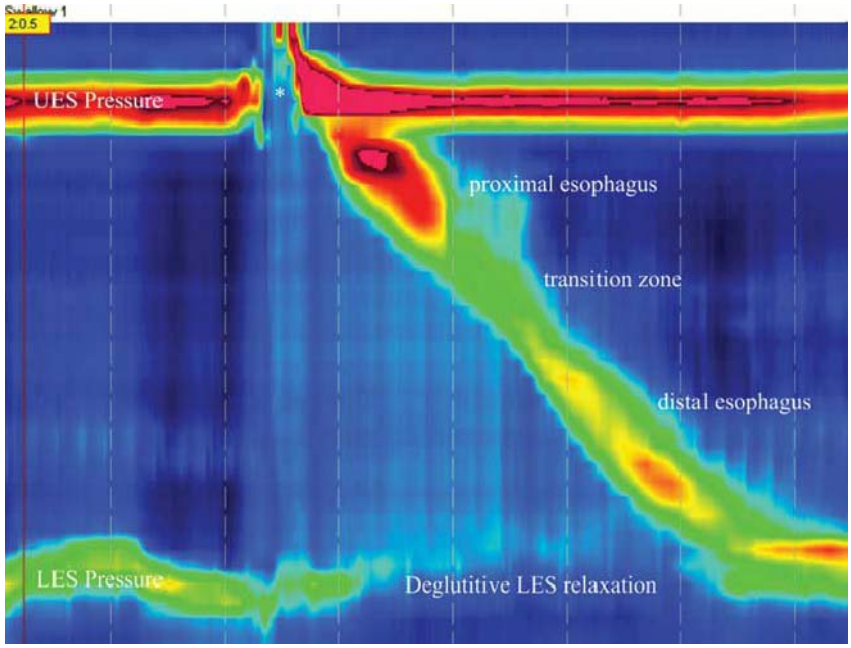


Figure 57.8 Normal high-resolution manometry pressure topography plot. UES, upper esophageal sphincter; LES, lower esophageal sphincter.

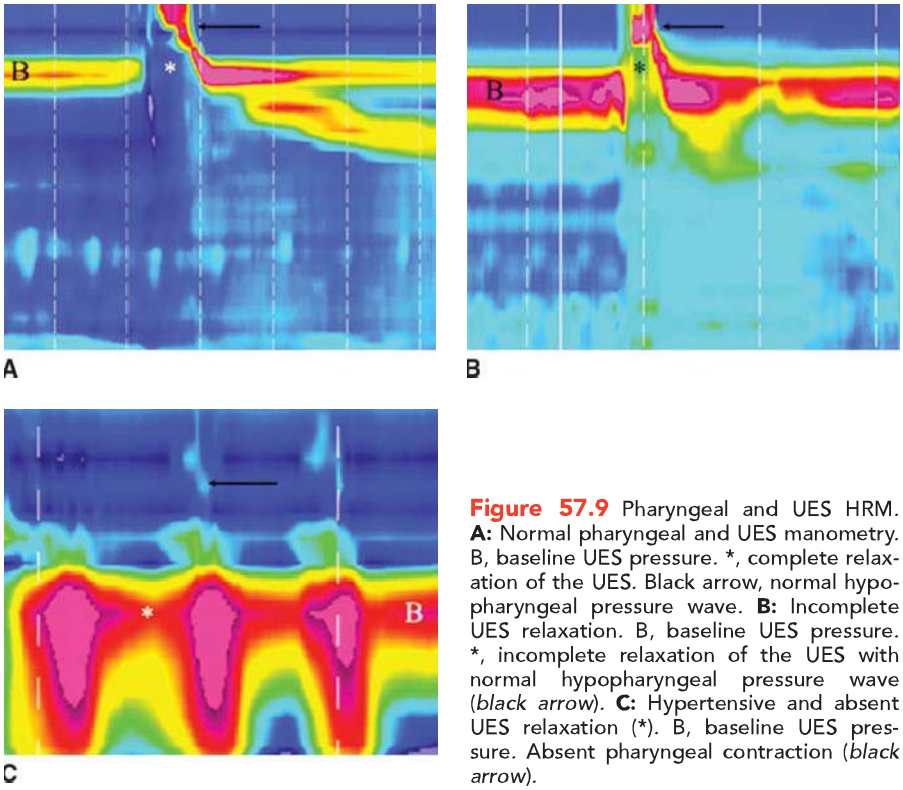


Figure 57.9 Pharyngeal and UES HRM. **A:** Normal pharyngeal and UES manometry. B, baseline UES pressure. *, complete relaxation of the UES. Black arrow, normal hypopharyngeal pressure wave. **B:** Incomplete UES relaxation. B, baseline UES pressure. *, incomplete relaxation of the UES with normal hypopharyngeal pressure wave (*black arrow*). **C:** Hypertensive and absent UES relaxation (*). B, baseline UES pressure. Absent pharyngeal contraction (*black arrow*).

HIGHLIGHTS

- The EAT-10 is useful for evaluating dysphagia symptom severity and monitoring response to therapy.
- The CSE is indicated for initial assessment of swallowing complaints. Cough, wet vocal quality, and repeat swallows are indicative of swallowing dysfunction.
- CSE fails to identify silent aspiration that would otherwise be detected by VFSS or FEES.
- VFSS affords evaluation of oral, pharyngeal, and esophageal phases of swallowing.
- Objective measures of timing and displacement obtained during VFSS allow for comparisons among serial examinations, populations of individuals, and normative data.
- During FEES, swallow trigger delay, presence of residue, vocal fold mobility, and pharyngeal strength can be assessed.
- LP sensation is evaluated by eliciting the LAR during FEESST.
- TNE can be performed safely and comfortably in the office with only topical anesthesia, obviating the need for sedation and cardiac monitoring.
- TNE detects a variety of esophageal abnormalities including motility disorder, stricture or ring, foreign body, diverticulum, Z-line irregularity, esophagitis, and hiatal hernia.
- HRM is a useful adjunctive instrument for assessing pharyngeal and esophageal motility, sphincter pressure, and coordination.

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58 Nonsurgical Management of Swallowing Disorders

Shaum S. Sridharan *Cathy L. Lazarus* *Milan R. Amin*

Swallowing disorders refer to any dysfunction in the complex cascade of normal deglutition. It is the task of the clinician to not only investigate the site of dysfunction, but also to try to help rebalance the system to prevent symptoms of dysphagia and aspiration pneumonia. This chapter provides a comprehensive overview of medical and rehabilitative modalities in the management of swallowing disorders. With the proper identification of the underlying reason(s) for dysphagia, appropriate therapy can be initiated by physicians and speech and language pathologists.

Treatment for oropharyngeal dysphagia should be based on a thorough instrumental assessment of oropharyngeal swallowing, including the modified barium swallow (MBS) procedure (1–4). This radiographic procedure, also known as a Videofluoroscopic Swallow Study (VFSS), involves giving a patient specific bolus types of various volumes and consistencies (calibrated bolus volumes of liquids, cup sips, pudding, and masticated consistencies, as appropriate) and examining their effects on the swallow. The radiographic examination provides a view of the oropharyngeal anatomy and allows the clinician to identify any abnormalities of the oropharyngeal swallow. The radiographic study should identify the patient's physiologic swallow disorders, rather than merely symptoms of the disorders, such as penetration (material in the airway entrance), aspiration (material below the vocal folds), and residue (food remaining in the oral cavity, valleculae, pharyngeal wall, pyriform sinuses). Appropriate treatment strategies cannot be determined until the physiologic swallow abnormalities (such as reduction in tongue base posterior motion, reduction in laryngeal elevation, and anterior motion) have been identified.

Once the anatomic and/or physiologic swallow disorders have been defined on fluoroscopy, the clinician determines the effects of rehabilitative strategies on the patient's swallow. The goal of the rehabilitative strategies is to improve swallow safety (i.e., elimination of aspiration) and efficiency (i.e., improving the speed of the swallow and reducing the amount of residue within the oral cavity and pharynx). These strategies can be compensatory in nature, including postures and sensory augmentation, or can be direct treatment techniques designed to alter swallow physiology, including swallow maneuvers. Some patients are able to begin or resume some type of oral diet using the postures that demonstrated success on fluoroscopy. Others may require use of swallow maneuvers during meals. Some patients, however, exhibit swallow function that is so impaired as to preclude an oral diet. The treatment strategies will be based on the patient's oropharyngeal anatomy and abnormal swallow physiology. In addition, the strategies employed will be determined by the patient's medical diagnosis, including the patient's overall medical condition, mental status, cognitive ability, motivation level, and speech/language ability. Thus, treatment planning begins at the time of the diagnostic procedure. The report of the VFSS should identify the symptoms of the swallow disorders, the physiologic swallow disorder, the rehabilitative strategies tried on fluoroscopy and their effects, and the specific treatment plan.

COMPENSATORY TREATMENT PROCEDURES

Compensatory treatment techniques are designed to redirect the bolus flow through the oral cavity and pharynx. They are techniques that are designed to eliminate aspiration, one of the symptoms of dysphagia, but are not designed to alter the swallow physiology. These techniques can be implemented by caregivers, and, therefore, are useful for patients of all ages and cognitive levels. Compensatory treatments include: (a) postures; (b) heightening sensory input; (c) modifying bolus volume and speed of feeding; (d) modifying food viscosity/texture, and (e) intraoral prosthetics.

Postures

Postures alter the flow of the bolus through the oral cavity and pharynx (Table 58.1). *Chin tuck posture* is used when the pharyngeal swallow (i.e., pharyngeal motor response) is delayed and aspiration occurs before the swallow triggers (1). This posture widens the vallecular space, creating a space for liquids and food to catch in the valleculae during the delay. Chin tuck posture also narrows the airway entrance, with closer approximation of the arytenoids to the epiglottic base and is useful for patients who demonstrate reduced airway closure (5). The tongue base is situated closer to the posterior pharyngeal wall (PPW) during chin tuck posture, providing additional airway protection by deflecting the bolus more posteriorly during the swallow (1,6,7). In addition, for those patients with reduced tongue base posterior motion, resulting in poor bolus clearance past the tongue base and residue on the tongue base, valleculae, and pharyngeal wall, chin tuck posture improves bolus clearance within this region, resulting in reduced upper pharyngeal residue (7). This technique has been found useful in eliminating aspiration in neurologically impaired and in surgically treated head and neck cancer patients (8–10).

The *head back posture* is useful for those patients who demonstrate difficulty propelling the bolus out of the oral cavity into the pharynx, as frequently observed in oral cancer patients and dysarthric patients with impaired tongue mobility (1). This posture allows gravity to propel the bolus into the pharynx. This posture, however, should be used with caution, since patients may aspirate more easily, particularly on thin liquids. Voluntary airway closure techniques, described below, are useful in protecting the airway during use of this posture. Patients with fairly severe pharyngeal phase swallow disorders should not use this posture.

The *head rotation posture* is useful for those individuals who demonstrate unilateral muscular disorders. For example, patients with unilateral pharyngeal weakness typically demonstrate residue on the weak side of the pharynx. Patients will benefit from head rotation to the weaker side, since this posture effectively closes off the weaker side and allows the bolus to clear through the pharynx and pyriform sinus region on the undamaged side (1). This posture is also useful for those patients with reduced cricopharyngeal opening, which can result in pyriform sinus residue that can enter the airway after the swallow (11,12). Head

TABLE 58.1 RATIONALE FOR USE OF COMPENSATORY POSTURES TO IMPROVE SWALLOW FUNCTION

Disorder Seen on MBS	Posture Utilized	Rationale
Impaired oral tongue function (reduced manipulation/propulsion of the bolus) resulting in prolonged oral transit times and oral residue	Head back	Utilizes gravity to propel material into the pharynx
Delayed triggering of the pharyngeal motor response (aspiration before the swallow)	Chin tuck	(a) Narrows the airway entrance (i.e., arytenoids are situated closer to epiglottic base); (b) situates the tongue base closer to the PPW, providing extra airway protection; and (c) widens the vallecular space, allowing the bolus to sit in this space rather than enter the airway before the swallow triggers
Reduced tongue base posterior motion (resulting in oropharynx residue and potential aspiration after the swallow)	Chin tuck	Situates the tongue base more posteriorly and closer to the PPW, improving bolus clearance past this region
Unilateral laryngeal dysfunction (aspiration during the swallow)	Head rotation to the impaired side of the larynx	Improves glottic closure, as extrinsic pressure is applied to the thyroid cartilage
Reduced laryngeal closure (aspiration during the swallow)	Head rotation to the damaged side combined with chin tuck	Places epiglottis in more protective position, narrows airway entrance and improves glottic closure
Reduced pharyngeal contraction—bilateral (resulting in residue and aspiration after the swallow)	Side-lying posture	Allows pharyngeal residue to collect on the lateral pharyngeal wall rather than near the glottis, so it reduces risk of subsequent aspiration
Unilateral pharyngeal paresis/paralysis (resulting in aspiration after the swallow)	Head rotation to the damaged side	Closes damaged side of pharynx and channels bolus through undamaged side, as well as improves pressure generation on bolus
Unilateral oral weakness (impaired bolus control, manipulation and propulsion through oral cavity resulting in oral residue)	Head tilt to stronger side	Improves bolus control and facilitates improved oral transit of bolus into pharynx by channeling bolus through stronger side of oral cavity
Cricopharyngeal dysfunction	Head rotation	Pulls cricoid cartilage away from PPW, improving opening and reducing intralumen UES pressure

rotation is also useful for those patients who are aspirating during the swallow due to vocal cord paralysis or following hemilaryngectomy. The patient rotates the head toward the paretic/surgical side, improving glottic closure (1,9). Combinations of postures are frequently used, particularly head rotation and chin tuck. These are particularly effective for those individuals who demonstrate a unilateral pharyngeal weakness as well as reduced airway closure (1,9).

Side-lying posture is used when pharyngeal clearance is reduced, resulting in residue that enters the airway after the swallow (1,2). In this posture, the patient is lying down on his side with his head propped up slightly. Residue will still be present after the swallow when using this maneuver, but the residue will remain on the lateral pharyngeal wall and will be cleared on subsequent dry swallows.

Head tilt posture is useful when a patient exhibits a unilateral oral and/or pharyngeal weakness (1,2). The head is tilted toward the unimpaired or stronger side, to allow the bolus to clear the oral cavity and pharynx on the stronger side. This posture is useful after hemiglossectomy and also for patients who are dysarthric with hemiparesis of the tongue, as this posture allows for improved oral control and propulsion of the bolus into the pharynx, resulting in improved oral phase swallow functioning. Head tilt is also useful to improve clearance of the bolus through the pharynx for those patients with unilateral pharyngeal paresis or paralysis (Table 58.1).

Sensory Enhancement Techniques

Therapy techniques that utilize sensory enhancement are helpful for those patients who have reduced sensory awareness, delayed initiation of lingual activity (often seen in patients with oral apraxia), and delayed triggering of the pharyngeal swallow. These techniques involve providing a preswallow sensory stimulus to improve initiation of lingual activity and/or triggering of the pharyngeal swallow. These techniques can include downward pressure on the tongue with a spoon, introducing boluses with other tastes, such as sour, or changing temperature and texture of the bolus (1,2,13,14). Carbonated boluses have been found to improve the oropharyngeal swallow, specifically, reducing pharyngeal transit time, percent pharyngeal residue, and aspiration (15). Another technique includes the use of thermal/tactile stimulation to improve triggering of the pharyngeal swallow (16,17). Slightly larger bolus volumes may provide increased sensory input and may result in improved oral initiation, as can boluses that require chewing. A slightly firmer bolus (i.e., pastes vs. liquids) can have the same effect.

Modifying Bolus Volume and Speed of Feeding

The ideal volume of food or liquid that will initiate triggering of the pharyngeal swallow will vary among patients. In addition, for those patients who demonstrate pharyngeal phase motility disorders resulting in pharyngeal residue, two to three repeat dry swallows are often needed to clear the pharynx. Thus, often taking smaller bolus volumes and eating at a slower pace, allowing time to reswallow to clear residue will reduce the risk of aspiration in these patients.

Bolus Consistency (Diet) Changes

Eliminating specific food consistencies is the last resort in compensatory diet modification. It is often unpleasant for the patient to be told that thin liquids must be eliminated from the diet. However, if other compensatory or direct therapy strategies do not eliminate aspiration or improve swallow efficiency, certain consistencies must be eliminated from the diet. In general, if a patient demonstrates reduced oral tongue control, delayed triggering of the pharyngeal swallow, or reduced airway closure, thin liquids might need to be eliminated, whereas slightly thicker consistencies would be indicated. For those patients who demonstrate reduced lingual strength or reduced bolus clearance through the pharynx, the latter impairment due to reduced tongue base posterior movement, reduced pharyngeal wall contraction, reduced hyo-laryngeal elevation and anterior motion, and cricopharyngeal dysfunction, thinner bolus consistencies are indicated, such as thin and thick liquids.

Intraoral Prosthetics

Intraoral prosthetics can help compensate for anatomic deficits, such as resection of a portion of the tongue, resection of part or all of the soft palate, neurologic damage that results in reduced lingual range of motion, or neurologic damage that results in palatal paresis. A *palatal lift* aids in velopharyngeal closure by lifting the paralyzed soft palate. A *palatal obdurator* seals off the velopharyngeal port for those patients who undergo soft palate resection, preventing material from entering the nasopharynx and improving intraoral pressure (18,19). A *palatal augmentation* prosthesis lowers the palatal vault for those patients who have undergone oral cancer resection. This prosthesis allows the remaining lingual tissue to contact the augmentation so that the tongue can control, seal, and propel a bolus of food through the oral cavity. A palatal augmentation prosthesis can benefit patients who have had a significant portion of the oral tongue resected, resulting in improved transport of the bolus through the oral cavity and reduced oral residue (19,20). The speech-pathologist works collaboratively with the maxillofacial prosthodontist to construct the prosthesis. For patients undergoing oral cancer surgery, construction of the prosthesis should begin 4 to 6 weeks postoperative. For those patients undergoing radiotherapy, construction typically begins at least 6 to 8 weeks after completion of treatment. In those patients with total glossectomy, the palatal augmentation prosthesis is typically fairly large because the augmentation portion needs to be

near the remaining muscles comprising the floor of mouth in order to assist with bolus control and clearance through the oral cavity. Additional swallow exercises are provided and should be practiced with the prosthesis in place to maximize its use for swallowing and speech.

THERAPY PROCEDURES

Direct therapy procedures are designed to change the swallow physiology by altering specific components of the oral and/or pharyngeal phases of swallowing. These can include exercises to improve or increase muscle strength, range of motion, and control. They can also improve the sensory-motor integration of the swallow or alter the timing and coordination of various aspects of the swallow (1,21,22).

RANGE OF MOTION, RESISTANCE, AND CONTROL EXERCISES

Exercise programs are designed to improve function of the target muscle or muscle groups to improve swallow physiology. Range of motion exercises are designed to increase range of the target muscle (23,24) and can include the jaw, lips, oral tongue, tongue base, pharyngeal constrictors, larynx, and hyoid-related musculature. They are often prescribed for head and neck cancer patients and stroke patients with dysarthria and dysphagia. They are also prescribed for those patients with dysphagia due to generalized weakness and deconditioning, particularly older patients who have been hospitalized for prolonged periods. Changes in the timing, coordination, and degree of muscle activity for swallowing occur with normal aging and with bolus volume and viscosity (5,13,25–34) and can place older, medically debilitated patients at risk for developing swallowing problems. Tongue range of motion exercises have been found to improve swallow function, specifically, oropharyngeal swallow efficiency in surgically treated oral cancer patients (23). Lingual range of motion exercises have also been prescribed for patients with progressive neurologic impairment, such as Parkinson disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS). However, it is commonly believed that tongue range of motion and strengthening exercises are not indicated for these patients, as active lingual exercise programs are thought to fatigue the muscles, resulting in poorer function for speech and swallowing. There are little data, however, to refute or support this theory.

Strengthening exercises involve active resistance to increase muscle strength and often target the tongue, lips, jaw, and suprahyoid muscles. Tongue strength has been found to be reduced in the elderly healthy population (35–37) and in patients with stroke, traumatic brain injury, ALS, PD, and oral cancer treated with radiotherapy (35,38–42). Lingual strengthening/resistance exercises have been found to increase tongue strength in young and elderly healthy individuals (43,44) and have been found to improve tongue strength and swallowing function in the stroke population (45).

The *pharyngeal squeeze maneuver* is also designed to improve pharyngeal contraction for swallowing (46) In this maneuver, the patient says a forceful "eee" in order to effect increased pharyngeal muscle contraction. Change/improvement in pharyngeal constrictor motion when using this maneuver can be easily visualized with fiberoptic laryngoscopic examination

Lingual control exercises can improve bolus control for chewing (1,3). These exercises involve manipulation of material such as a piece of licorice within the oral cavity to work on bolus seal, lateral trafficking of the bolus, bolus retrieval from the teeth, and sealing and propelling the bolus posteriorly through the oral cavity.

The Shaker exercise is a strengthening exercise program to improve upper esophageal sphincter (UES) opening for swallowing (47,48). This rehabilitation exercise involves a program of head-raising to strengthen the suprahyoid muscles involved in UES opening. In healthy asymptomatic elderly individuals, the Shaker exercise program resulted in increased UES opening diameter and a decrease in hypopharyngeal intrabolus pressure (47). In dysphagic patients with reduced UES opening, the Shaker exercise program resulted in significantly increased UES opening, increased anterior laryngeal excursion, reduction of pharyngeal residue, and elimination of postdeglutitive aspiration (48). There is evidence that respiratory strength training can have a positive impact on swallowing by training expiratory, suprahyoid, and velar muscles. Sapienza (49) reported that respiratory strength training improved swallowing in dysphagic Parkinson patients, with a reduction in pharyngeal delay time, improvement in speed and extent of hyolaryngeal motion during the swallow. In addition, subsequent studies have shown improved respiratory driving pressure in PD and MS patients employing respiratory strength training (50). This could lead to improved vocalization and decreased rates of aspiration in neurologically impaired patients (51,52). There is also evidence that the Lee Silverman Voice Training (LSVT), a voice exercise program designed to improve voice and speech in the Parkinson patient, can improve swallowing, specifically, by improving oral transit times, triggering of the pharyngeal swallow, and reducing percentage oral residue (53). In addition, the LSVT program has been found to improve tongue strength and quality of life (54), as measured by the SWAL-QOL, a swallowing quality of life measure (55).

SENSORY-MOTOR INTEGRATION PROCEDURES

Thermal-tactile stimulation has been used as a preswallow alerting mechanism for the central nervous system. This technique involves rubbing the anterior faucial arches with a size 00 cold laryngeal mirror and instructing the patient to swallow (1). It has been found to improve triggering of

the pharyngeal motor response in patients with delayed triggering of the pharyngeal swallow (16,17). Thermal/tactile stimulation combined with a sour stimulus has been found to result in a similar reduction in swallow latency (56). This technique can be performed in isolation (i.e., dry swallows or.5mL amounts of water for those patients who are nonoral) or intermittently during meals, as appropriate.

MANEUVERS

Maneuvers are designed to alter the physiology of the swallow, specifically, the pharyngeal phase, placing specific aspects of the pharyngeal swallow under voluntary control (Table 58.2). The *supraglottic swallow* is designed to improve airway closure before and during the swallow at the level of the glottis (2,57). Patients are instructed to hold their breath, swallow, and cough. The super supraglottic swallow is designed to improve airway closure before and during the swallow at the level of the airway entrance (i.e., laryngeal vestibule) and glottis (2,57,58). The *super supraglottic swallow* involves a tighter breath hold than that used with the supraglottic swallow and is designed to achieve arytenoid to epiglottic base contact for closure of the laryngeal vestibule (57,58). In patients having undergone supraglottic laryngectomy, the super supraglottic swallow is designed to achieve arytenoid to tongue base contact for vestibular closure. The patient is instructed to: (a) hold your breath very tightly while bearing down with the abdominal muscles, (b) swallow, and (c) cough. This maneuver has also been found to increase extent of laryngeal elevation during the swallow (22). Patients are often taught to exhale slightly before holding their breath tightly, as most individuals swallow during an exhalation, which may increase subglottic pressure during the swallow and reduce the risk of aspiration (59,60). The super supraglottic swallow maneuver requires a fair degree of cognitive functioning, attention, sequencing, and memory.

The *effortful swallow* is designed to improve tongue base posterior motion during the swallow and improve pressures to clear the bolus past the tongue base (1,3,24,61–63). This maneuver is helpful for those patients who demonstrate reduced tongue base posterior motion, a disorder that can result in residue on the tongue base, valleculae, and upper pharyngeal wall. The patient is instructed to squeeze hard with the tongue and throat muscles during the swallow. This maneuver can result in improved bolus clearance past the tongue base and through the upper pharynx. This maneuver is often combined with chin tuck posture, the latter places the tongue closer to the pharyngeal wall to maximize bolus clearance past the tongue base.

The *Mendelsohn maneuver* is designed to increase the extent and duration of laryngeal elevation and anterior motion during the swallow, thereby increasing the width and duration of cricopharyngeal opening during the swallow (22,64) (Fig. 58.1). This maneuver can also improve the coordination of the pharyngeal events occurring during the pharyngeal swallow (22). The patient is instructed to swallow normally, and in the middle of the swallow, when the larynx is felt to elevate, the patient is instructed to keep his larynx elevated for 2 seconds, then relax (Fig. 58.1).

The *tongue-hold maneuver* (also called the Masako maneuver) is designed to increase the extent of anterior motion of the PPW (65) (Fig. 58.2). This maneuver involves anchoring of the tongue tip between the teeth (or gums in edentulous patients), which places the tongue base in a more anterior position. This results in greater

TABLE 58.2 RATIONALE FOR USE OF SWALLOW MANEUVERS TO ALTER SWALLOW PHYSIOLOGY AND IMPROVE SWALLOW FUNCTION

Disorder Seen on MBS	Swallow Maneuver	Rationale
Impaired or delayed glottic closure; delayed triggering of the pharyngeal motor response	Supraglottic swallow	Breath hold improves glottic closure before and during the swallow
Impaired airway entrance closure	Super supraglottic swallow	Effortful breath hold facilitates arytenoid anterior motion to epiglottic petiole and maintains early airway entrance closure
Reduced tongue base posterior motion	Effortful swallow	Effort increases tongue base posterior motion
Reduced motion of the pharyngeal constrictors	Masako (tongue-hold) maneuver	Slightly anterior position of tongue base results in compensatory increase in anterior motion of pharyngeal constrictors
Reduced laryngeal motion and reduced cricopharyngeal opening	Mendelsohn maneuver	Increases extent and duration of laryngeal elevation, resulting in increased width and duration of UES opening
Discoordinated swallow	Mendelsohn maneuver	Effort improves timing and coordination of muscular events during pharyngeal swallow

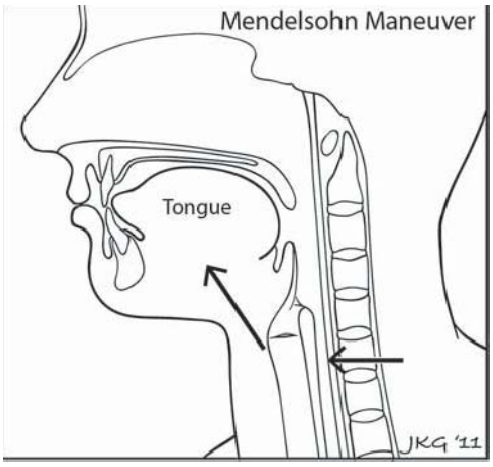


Figure 58.1 The Mendelsohn maneuver.

anterior motion of the PPW in order to make contact with the tongue base during the swallow (65). This technique is useful for those patients with reduced tongue base to pharyngeal wall contact and resultant reduction in bolus clearance past the tongue base. This exercise is designed to be a range of motion exercise for the pharyngeal constrictors and should be practiced with saliva or very small (1/2 mL) amounts of water. This exercise should not be practiced with food or liquid boluses, since anchoring of the tongue tip might result in reduced bolus control and aspiration.)

Surface electrode electromyography and electroglottography have been used as biofeedback tools when teaching swallow maneuvers, providing visual feedback of muscle activity during maneuver attempts. These maneuvers include the effortful swallow and the Mendelsohn swallow maneuvers, designed to improve tongue base posterior motion, laryngeal elevation, and UES opening for swallowing. These biofeedback techniques have resulted in improved swallow functioning, with increased muscle activity, improved temporal coordination of the swallow, and resumption of oral intake in stroke patients with chronic dysphagia and patients with MS (66–68). Nasendoscopy can provide biofeedback for patients when learning airway protection maneuvers, such as the supraglottic and super supraglottic swallow, as vocal fold motion and arytenoid to epiglottic base contact can be easily visualized with this technique (57).

Some patients must always use swallow maneuvers and postures during meals and, therefore, observation of fatigue when using maneuvers should be noted on fluoroscopy and during the course of therapy. Swallow functioning should be reevaluated with instrumental assessment, including VFSS or fiberoptic endoscopic examination of swallowing after a course of swallow therapy, to determine whether function has improved such that some type of oral diet can be implemented, a diet upgrade can be implemented, or to determine the need for continued use of postures and/or maneuvers during meals (2,69).

Neuromuscular electrical stimulation (NMES) is a technique that has traditionally been used for the limbs, but has only recently been introduced to improve swallowing. This technique involves the delivery of therapeutic electrical stimulation to facilitate muscle contraction through surface electrode placement in the region of the submental or thyrohyoid muscles (70,71). Stimulation of either region is believed to contribute to hyolaryngeal elevation for swallowing. Few studies examining the effects of NMES on swallowing, however, have been conducted in a systematic, quantitative, and methodologically replicable fashion. Burnett et al. (72) systematically examined differential stimulation of muscles to augment laryngeal elevation at rest and found that combined stimulation of the mylohyoid and thyrohyoid muscles resulted in greater degree of laryngeal elevation than single muscle stimulation. Power et al. (73) found that electrical stimulation can have a negative effect on swallowing, with lengthened swallow response time following stimulation at certain stimulation frequencies. Transcutaneous delivery of electrical stimulation, in recent studies, has not been shown to consistently target the submental or strap muscles responsible for anterosuperior movement of the larynx during swallowing (74). When muscles other than the mylohyoid or thyrohyoid are innervated, the larynx will actually be depressed which, in theory, could increase the likelihood of aspiration. Authors attempting to observe physiologic changes in

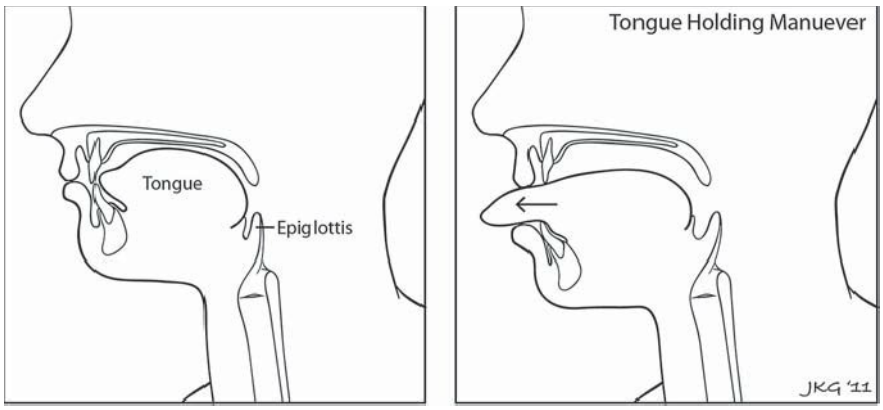


Figure 58.2 The tongue-hold maneuver.

swallow in normal patients receiving NMES have shown a propensity for patients to experience hyo-laryngeal depression and incomplete false vocal fold closure (75–77). NMES for swallowing remains a controversial treatment technique that requires additional research to examine the physiologic basis for and use in swallowing treatment.

Not all patients are candidates for direct swallow treatment, such as those with severe cognitive impairment. However, management decisions should be made based on the results of the instrumental evaluation, including compensatory strategies to be used during meals, for those patients taking some type of an oral diet. Compensatory strategies are also typically prescribed for patients with progressive neurologic disease, such as ALS, and can include modifying posture, diet type, bolus volume, and adding sensory enhancements, such as carbonation (78) (Table 58.2).

Therapy Considerations

Effects of Tracheotomy Tubes

Historically, presence of tracheotomy tubes has been believed to impair swallow functioning, including reduced laryngeal elevation, reduced tracheal sensitivity, reduced glottic sensation and closure function, and, in cuffed tracheotomy tubes, esophageal obstruction (78–81). Further, reduced ability to generate positive subglottic air pressure has been implicated as a cause of aspiration in tracheotomized patients (59,82). Presence of speaking valves, such as the Passy-Muir valve have been found to improve swallow function, with improved expiratory airflow, reduction in oropharyngeal secretions, and reduced aspiration (15,83–86). Digital occlusion and capping of tracheostomy tubes have also been found to be effective in improving swallow function (72,81,87). However, others have found no impact on swallow functioning with the presence of tracheotomy tubes, speaking valves, or tracheal occlusion, including digital and capping (88–91). In addition, others have found no impact of tracheotomy cuff inflation on swallowing (86). However, tracheotomy tubes are typically left in place during instrumental evaluations and swallow therapy. Cuffs are typically deflated during the swallow evaluation and, if medically able, during swallow therapy, as aspiration is likely to be detected via expectorated material through the tracheotomy tube.

Preventative Exercise Programs

Active exercise programs are often prescribed for patients who will undergo organ preservation protocols of chemoradiotherapy (92). These programs are designed to maintain swallow functioning during and following the chemoradiotherapy treatment. They are also used for those patients who will undergo primary radiotherapy and radiotherapy following surgery for head and neck cancer. Programs include range of motion exercises for the jaw, oral tongue, tongue base, pharyngeal constrictors, and hyolaryngeal muscles and strengthening exercises for the oral tongue, tongue base, and hyolaryngeal muscles. Patients are instructed to practice these exercises as able during the course of treatment, as swallowing problem can develop during and after radiotherapy as primary treatment, postsurgical treatment, and as concurrent treatment with chemotherapy (93–98). Patients are also instructed to continue practicing these exercises once daily following completion of treatment, as tissue fibrosis can occur long after completion of radiotherapy treatment (99,100), with resultant swallowing problems (4,21,101).

Swallow therapy, including compensatory and direct therapy procedures can improve swallow functioning in patients with oropharyngeal dysphagia, reducing the risk of aspiration pneumonia associated with dysphagia, and improving nutritional status (69,102–105). The speech–language pathologist plays a key role in performing the instrumental examination; including the VFSS and fiberoptic endoscopic evaluation of swallowing (3,69). In addition, the speech–language pathologist plays a major role in developing and implementing the swallowing rehabilitation program, in collaboration with the patient's attending physician, other health care professionals, and the patient and his/her family.

Subspecialists in laryngology can take charge in the management of patients with swallowing disorders. They must create working relationships with patients while stressing the value of multidisciplinary approaches to dysphagia. Being trained to recognize pathology and implement the armamentarium of medical and surgical tools, laryngologists must help make key decisions regarding escalation of care from conservative to aggressive while counseling the patient regarding the differing merits of each treatment option. Furthermore, tracheotomy placement, management, and possible decannulation should be spearheaded by trained physicians.

MEDICAL MANAGEMENT

Medical management of dysphagia is often ignored in favor of what are often perceived as more "interventional" approaches to improving swallow function. However, there is most certainly value in treating specific issues related to swallow dysfunction with medical treatment. Below we discuss several categories of medications and other treatments that should be considered in patients with dysphagia. Some of these treatments directly target patients' symptoms, while others are designed to prevent adverse consequences and complications associated with swallowing dysfunction.

MOTILITY DRUGS

The management of impaired esophageal motility poses a substantial challenge to the otolaryngologist. A handful of medications have garnered interest for their apparent

TABLE 58.3 ESOPHAGEAL MOTILITY DRUGS

Medication	Receptor Targeting	Adverse Reactions
Macrolides (i.e., erythromycin and clarithromycin)	Motilin, preganglionic Ach receptor targeting	Intravenous dosing, bacterial resistance
Cisapride	Increase acetylcholine release	Cardiac arrhythmias, drug interactions
Domperidone	Blocks dopamine receptors	Inconsistent results, stimulates prolactin secretion
Metoclopramide	Blocks dopamine receptors	Inconsistent results, extrapyramidal symptoms, increased prolactin secretion
Bethanechol	Acetylcholine agonist	Contraindicated in asthma, coronary artery disease, and Parkinsonism, epilepsy
Pyridostigmine	Acetylcholinesterase inhibitor	

clinical benefit in promoting esophageal contraction and lower esophageal sphincter (LES) tone, but few have shown physiologic or practical efficacy in research trials. Recently, new classes of drugs have shown promise in alleviating symptoms of esophageal dysphagia.

Previously employed drugs that have fallen out of favor include medications such as cisapride, macrolide antibiotics, metoclopramide, and domeperidone. Macrolide antibiotics, specifically erythromycin and clarithromycin, have shown efficacy in increasing duration, velocity, and strength of peristalsis in the esophagus, but primarily by intravenous delivery of the drug (106,107). These drugs are theorized to stimulate esophageal contractility by activating motilin receptors in smooth muscle and preganglionic cholinergic neurons (108,109). This subclass clinically has its long-term impracticalities owing to its inability to produce similar effects with oral dosing (110) and likely promoting bacterial resistance. Similarly, cisapride has been unpopular due to its safety profile and drug interactions. The oral form of cisapride showed efficacy in enhancing pressure at the LES and increasing esophageal peristalsis (111,112), but evidence showing an increased potential for cardiac arrhythmias led to its loss of Food and Drug Administration approval. Lastly, metoclopramide and domeperidone showed early success as prokinetic medications (52,113), but more recent studies have not been able to reproduce these results (114).

Recently, some medications have been found to be effective in increasing esophageal motility in their oral form. Comparison of three such drugs (bethanechol, pyridostigmine, and buspirone) found that all three agents cause increased motility and peristaltic amplitude after oral administration (115). Though previous works have described each medication alone as being effective in improving esophageal motility (116–118), they all work by increasing cholinergic activity on the esophageal smooth muscle (119); bethanechol as a direct cholinergic agonist, pyridostigmine as an Ach inhibitor, and buspirone acting on 5-HT1A and 5-HT2A receptors. Buspirone, by being an agonist at serotonergic receptors, can theoretically facilitate Ach release as shown in animal models (120). As efficacy of these drugs is being established, they could soon represent an option for medical management of dysphagia (Table 58.3).

REFLUX CONTROL

It has been shown that gastroesophageal reflux disease (GERD) can commonly lead to changes in esophageal motility (121). Mucosal injury and edema can lead to changes in peristalsis amplitude, bolus transit times, and LES tone and competence (122) In recent studies, duration and frequency of reflux episodes significantly correlated with esophageal dysmotility (122,123), but this has not been universally accepted due to confounding results from other authors (124). Sensation of the larynx can also be affected as seen by differences in Functional Endoscopic Evaluation of Swallowing with Sensory Testing in those with and without laryngopharyngeal reflux (LPR). This can lead to globus sensation, incoordinated swallow, and possible increased aspiration risk.

Treatment for reflux disease-related dysphagia is usually initiated with a trial of proton pump inhibitors (PPIs). Though some authors advocate for definitive diagnosis with pH probe monitoring, empiric treatment of LPR/GERD can be initiated with PPIs. Further investigation is warranted when there are nontraditional clinical presentations or refractory symptoms after therapy. Several authors have noted significant improvement in symptoms of dysphagia and globus sensation after trials of therapy with PPIs (125,126). While on maintenance therapy, these patients' symptoms were often alleviated

regardless of degree of severity of GERD. Others have also endorsed surgical control of reflux (i.e., Nissen Fundoplication, etc.) as an alternative to failed medical management or, in some centers, as a primary modality (127–130).

DRYING AGENTS

Often, dysphagia can stem from the inability to handle one's own secretions. Unmitigated pooling of saliva in the oral cavity, pharynx, or piriforms can lead to aspiration into the trachea. Commonly affected persons include those with neurologic limitations (Down Syndrome, ALS, cerebral palsy [CP]), PD, mental retardation) or anatomic abnormalities that do not allow proper management of oral secretions. Surgical therapy has focused on resection of major salivary glands or ligation of their ducts (131), but conservative options still are the mainstay of treatment. Team approaches with speech and language pathologists, neurologists, otolaryngologists, and occupational therapists can provide numerous options to a patient and family. Positioning techniques along with oral appliances can show benefit from directing saliva toward the pharynx safely (132–134). Furthermore, they can create proper closure of the oral commissure allowing for improved bolus formation and manipulation. In conjunction with these modalities, biofeedback therapy has shown some efficacy (135,136).

In more severe cases, medical management can be used in concert with other nonsurgical measures. These drying agents encompass medications whose mechanism of action affects the cholinergic stimulation of saliva in the upper digestive tract. Glycopyrrolate bromide, classified as an anticholinergic drug, has a quaternary ammonium structure that prevents it from crossing the blood–brain barrier. Recently, randomized prospective trials have shown glycopyrrolate to be a clinically effective method of sialorrhea management in adults and children (137–139). Within these trials, varying degrees of clinical failure due to side effects were demonstrated, though, in the adult PD patients, the adverse outcomes were minimal. Scopolamine and benztropine are anticholinergic drugs known to cross the blood–brain barrier avidly, which can limit their effective use due to dose-related effects. Some common complaints after the use of anticholinergic medications include pupil dilation, urinary retention, constipation, dizziness, blurred vision, and worsening of glaucoma. Proper patient selection and dose adjustments are key to effectively using this class of drugs.

Lastly, numerous authors have used botulinum toxin injections into the salivary glands as an adjunct therapy to medical management (140–144). Commonly, injections of Botox are targeted at the parotid and submaxillary glands with the aim of significantly reducing salivary flow into the oral cavity. Ultrasound guidance can be used to visualize infiltration of the drug into the salivary tissue and to prevent complications of toxin delivery to surrounding tissue (145–147). A recent review demonstrated a wide variability in duration of efficacy ranging from over 1 to 6 months before the need for repeat medication injections (148).

NUTRITION

An oftentimes ignored part of the care of the dysphagic patient is management of nutrition. Patients with dysphagia are often prescribed altered diets based on results of swallow studies. In addition, they often eat slowly and eating becomes a chore; as a consequence, they are unable to complete meals. These factors combine to lead to poor nutrition. Unfortunately, this often compounds the problem as patients become weak and dehydrated. The care provider must work with the nutritionist and speech pathologist to formulate a plan for adequate caloric intake in order to prevent the downward spiral that can lead to a permanent loss of swallow function.

PULMONARY STATUS

Often overlooked is the neurologic and functional codependency of the upper respiratory system and the digestive tract. Swallowing is not only composed of coordinated movement of the oral cavity and pharynx, but also of orchestrated laryngeal movement (149). It is known that laryngeal elevation and vocal fold adduction are key to swallowing action, but carefully timed apnea is also crucial (150,151). Studies aimed at understanding the natural physiology of aerodigestive tract coordination have found that during swallowing there is a reproducible apneic episode in the expiratory phase of respiration (103,152). Small bolus changes would produce similar periods of apnea, but large-volume swallowing necessitated extended apnea. This clearly poses a problem for those with pulmonary disease where shortness of breath or cough could restrict apnea times. This could lead to uncoordinated swallowing and possibly aspiration of food contents. An example of this occurs in chronic obstructive pulmonary disease (COPD) patients who can be prone to tachypnea and often unable to tolerate cessation of respiration while swallowing. In one author's experience, penetration/aspiration scores were significantly higher in stable COPD patients compared to controls (153). Pulmonary pathology often also coincides with GERD, which can lead to worsening of pulmonary status, globus sensation, and dysphagia (153–155). In some cases such as idiopathic pulmonary fibrosis, standard medications such as PPIs can be less effective at acid suppression when compared to normal adults (154). Rehabilitation of chest muscle strength with physical therapy and incentive spirometry use can often be implemented in concert to improve cough effectiveness and tidal volumes (50,156–158).

IMMUNOCOMPROMISE

Those with a nonfunctioning immune system may fall victim to opportunistic infections of the upper aerodigestive tract leading to dysphagia and pulmonary compromise. Oral candidiasis and herpes infection along with bacterial and fungal pharyngitis can lead to odynophagia (159). Tuberculous involvement can be seen often in the larynx, but can also been found in the esophagus and oral cavity (160–163). Similarly Cytomegalovirus, candida, and herpes simplex virus infection are a relatively common pathology in the upper aerodigestive tract and must be ruled out in cases of persistent odynophagia in immunocompromised patients. Some less common but reported causes of infection include aspergillus and actinomyces. HIV infection, transplant-recipients, and those suffering from blood-borne cancers can make patients prone to opportunistic infection. Care must be taken to address underlying causes of immune dysfunction while treating pain, encouraging nutritional supplementation, and treating infections appropriately.

ORAL CARE

Especially in the elderly and debilitated, dental hygiene is crucial to the prevention of aspiration pneumonia. These patients often can become immunocompromised due to chronic disease, develop oral biofilms, and have reduced salivary flow swaying the balance toward overgrowth of pathogenic microflora (164,165). Respiratory pathogens isolated from the oral cavity have been cultured from the pulmonary secretions of chronic aspiration patients (164,166). With proper mechanical cleaning and oral decontamination by patients or caregivers, potential pathogens for pneumonia can be decreased greatly (167–170). Though more research is needed, significant reductions of aspiration pneumonia and death with attention to proper oral care have been revealed in recent studies (171,172).

SUMMARY

The role of nonsurgical management of swallowing disorders can include various modalities from medications to rehabilitation. Without a strong knowledge of anatomy and neurophysiology, targeted treatment cannot be delivered. Careful history taking combined with thorough head and neck examination and the diagnostic radiographic findings can elucidate the etiology of improper swallow function. Once identified, pathologic insults to the upper aero–digestive tract can be first handled conservatively with the techniques outlined in this chapter reserving more aggressive management for refractory cases. Evolving imaging technology and new potent medications will soon expand the clinician's armamentarium.

HIGHLIGHTS

- Identification of the site(s) of swallowing pathology can be accomplished with careful history taking, indirect laryngoscopy, and radiologic imaging such as MBS.
- Compensatory postures are an important measure to redirect food boluses safely into the esophageal inlet. Commonly used postures include chin tuck, head back, head tilt, head rotation, and side-lying positions.
- Improving preswallow sensory stimulus through diet changes can improve lingual activity and trigger appropriate pharyngeal swallow.
- Unlike postures, maneuvers alter the physiology of swallowing by placing certain aspects under voluntary control.
- There are a myriad of esophageal promotility agents available that can be used with careful attention to mechanism of action and side effect profile.
- Those with neurologic disorders (i.e., PD, CP, and ALS) can sometimes pose a challenge to physicians due to poor mental status, uncoordinated swallow, sialorrhea, and aspiration risk.
- In the treatment of sialorrhea, a multidisciplinary approach can provide numerous options to a patient and their family including medications, oral appliances, and salivary gland botulinum toxin injection.
- Compromised pulmonary status can disrupt the necessary balance of respiration, namely coordinated apneic episodes, with swallowing leading to aspiration.
- Immunocompromised patients are at increased risk for infection with opportunistic pathogens leading to odynophagia, dysphagia, and pneumonia.

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59 Esophageal Disorders

Catherine Rees Lintzenich

Esophageal disorders are commonly encountered in the evaluation of throat pain, dysphagia, reflux, and globus pharyngeus. Knowledge of the motility, inflammatory, and neoplastic disorders is an essential component in the diagnosis and management of these common otolaryngologic complaints.

ESOPHAGITIS

Infectious Esophagitis

Infectious causes of esophageal inflammation include fungal pathogens, viral pathogens and, much less commonly, bacterial pathogens. The most common cause is *Candida albicans* fungal infection (Fig. 59.1). Risk factors include human immunodeficiency virus (HIV), systemic and inhaled steroids, and antibiotic use. However, esophageal candidiasis is frequently encountered in healthy immunocompetent individuals without risk factors. Pain and dysphagia are the most common presenting symptoms. The appearance of white to yellow plaques on an erythematous base is quite characteristic but may be confirmed with biopsy. It is important to recognize that esophageal candidiasis can be present without findings of candidiasis in the oral cavity or pharynx. Treatment options include topical antifungal solutions or oral antifungals, such as fluconazole.

Viral esophagitis may be caused by herpes simplex virus, cytomegalovirus, or HIV. Typically, multiple shallow ulcerations are seen in the esophageal mucosa. Biopsy is necessary to confirm the diagnosis.

Noninfectious Esophagitis

Pill-Induced Esophagitis

Medications can cause esophageal inflammation and injury via a systemic or local reaction. Systemic medications that relax smooth muscle may increase the incidence of reflux and its sequelae, including esophagitis, dysmotility, and stricture. Examples of drugs causing esophageal effects include alcohol, nicotine, and smooth muscle relaxants.

Alternatively, pills that become lodged in the esophagus can cause direct injury to the mucosa, resulting in stricture, pain, and dysphagia. Large pills, pills taken in the supine position, xerostomia, dehydration, and motility disorders are risk factors for esophageal pill injury (1). Doxycycline, tetracycline, alendronate, and potassium chloride frequently cause such direct esophageal injury. Symptoms include dysphagia, odynophagia, and heartburn. It is important to consider pill-induced esophagitis even when there is no known history of pill becoming lodged in the throat or esophagus. Endoscopic removal of the pill impaction and conversion of medications to liquid forms may be necessary. In severe cases, medications may need to be administered via a nasogastric tube until the esophagus heals. Sequelae of pill-induced esophagitis may include ulceration, stricture, and even perforation of the esophagus.

Eosinophilic Esophagitis

Eosinophilic esophagitis is increasingly diagnosed in both children and adults. This disorder is characterized by eosinophilic infiltration of the esophageal mucosa. Adults typically present with solid food dysphagia, reflux symptoms, and recurrent food impactions (2). Fluoroscopy and endoscopy may reveal a small caliber esophagus with a ringed appearance (trachealization) or esophageal strictures. Small white submucosal lesions may be noted on endoscopy (Fig. 59.2). The mucosa is typically friable and prone to tearing with instrumentation. Alternatively, the esophagus may appear normal. Food and/or inhalant allergies typically coexist with eosinophilic esophagitis. Biopsy confirms the diagnosis, requiring greater than 15 to 20 eosinophils per high power field. Treatments include topical esophageal steroids, allergy treatments, and elimination diets.



Figure 59.1 Candida esophagitis with white and yellowish plaques.

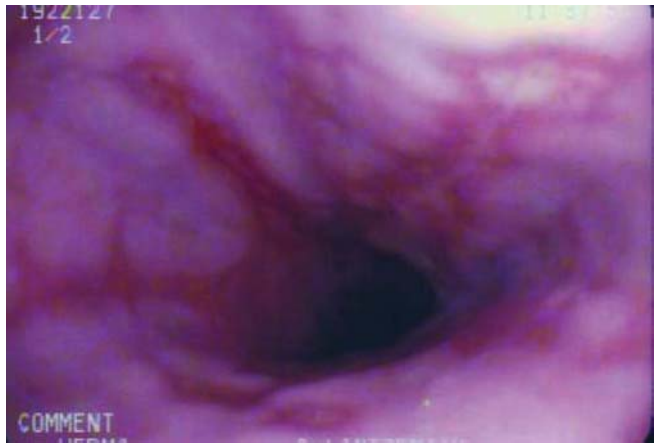


Figure 59.3 Circumferential erosive esophagitis from reflux.

GASTROESOPHAGEAL REFLUX DISEASE

Reflux refers to the backflow of gastric contents in a retrograde fashion into the esophagus and sometimes into the pharynx (laryngopharyngeal reflux is discussed in detail in Chapter 66) (3). Gastroesophageal reflux disease (GERD) occurs when reflux is excessive or symptomatic. Refluxate from the duodenum, containing bile acids, may also contribute to esophageal injury. Typical symptoms of GERD include heartburn and regurgitation, with less typical symptoms being cough, globus, and belching.

GERD is probably associated with inappropriate relaxations of the lower esophageal sphincter (LES) and poor esophageal clearance. The endoscopic appearance of the esophagus in GERD may be normal, or esophagitis with erosion and mucosal breaks may be present (Fig. 59.3). The most commonly used classification system for the endoscopic appearance of reflux esophagitis is the L.A. Classification, which takes into account the length, width, and number of mucosal breaks. Strictures can occur with chronic or prolonged esophageal acid exposure.



Figure 59.2 Small white lesions sometimes seen in eosinophilic esophagitis (guidewire for dilation is seen in the picture).

Ambulatory pH monitoring can aid in the diagnosis of pathologic reflux. When reflux esophagitis is present, proton pump inhibitor therapy is initiated to allow healing of the esophageal injury. Endoscopy may be repeated 3 to 6 months after initiation of therapy to confirm healing.

Reflux is a risk factor for Barrett metaplasia, the presence of which increases the risk of esophageal adenocarcinoma (4). To identify Barrett metaplasia, it is necessary to understand the normal gastroesophageal junction anatomy. The squamous epithelium of the esophagus interfaces with the columnar gastric epithelium at the gastroesophageal junction in the normal setting. This is visualized with a change from a lighter pink to a darker salon-pink in the stomach. Normally, this squamocolumnar junction (SCJ) coincides with the gastroesophageal junction, best identified by the termination of the gastric rugae. When the gastroesophageal junction extends more than 2 cm above the diaphragmatic compression, a hiatal hernia is present. When the SCJ extends proximal to the perceived gastroesophageal junction, Barrett metaplasia is suspected. Suspected areas of Barrett metaplasia must be biopsied to confirm the diagnosis and evaluate for dysplasia. Biopsy-confirmed Barrett metaplasia will include intestinal metaplasia and goblet cells on histopathology. The presence of no dysplasia or low-grade dysplasia indicates low risk for neoplastic transformation. However, high-grade dysplasia represents a significant risk of neoplasm and is usually treated as esophageal adenocarcinoma.

ESOPHAGEAL MOTILITY DISORDERS

Disorders of esophageal motility may be classified as hyperkinetic and hypokinetic. Both classes of motility disorders can lead to dysphagia, globus pharyngeus (feeling of lump in throat), regurgitation, and/or noncardiac chest pain. The mainstay of esophageal function testing is esophageal manometry. The recent advances of high-resolution manometry have allowed for assessment of esophageal pressure along the entire pharynx, upper esophageal

sphincter, esophageal body, and LES (5). High-resolution manometry catheters have pressure sensors at approximately 1-cm intervals. Impedance technology has also added to assessment of esophageal motility. Impedance determines the comparative resistance of air, the bolus, and the esophageal mucosa and therefore indicates bolus transit along the esophagus (6).

Hyperkinetic Esophageal Motility Disorders

Nutcracker Esophagus

Nutcracker esophagus is a disorder typically associated with noncardiac chest pain. This condition typically coexists with reflux disease, and there may be a causal relationship between nutcracker esophagus and reflux. Manometric assessment reveals normal peristalsis and high amplitude esophageal contractions during swallowing, with the average distal esophageal amplitude being greater than 180 mm Hg. Bolus transit is typically normal (7), as is fluoroscopy of the esophagus. Treatment for nutcracker esophagus usually involves antireflux treatment and/or pH testing. Surgical esophageal myotomy is generally not effective for this disorder (8). Nitrates and calcium channel blockers may be beneficial in decreasing the intensity of the esophageal contractions.

The etiology of nutcracker esophagus is still unclear, but it may be related to coordination between the longitudinal and circular muscle layers of the esophagus (9). Jung et al. performed high-frequency intraluminal ultrasound in 5 healthy volunteers and 10 subjects with nutcracker esophagus. In the healthy volunteers, the peak contraction of the circular and longitudinal muscles was nearly synchronous. In nutcracker esophagus, there was asynchrony in contraction between these muscle layers in the distal esophagus.

Distal Esophageal Spasm

Distal esophageal spasm (DES) is a nonperistaltic motility disorder, which may or may not be associated with high amplitude esophageal contractions. In manometric terms, greater than 20% but fewer than 100% of wet swallows produce simultaneous contractions, with onset velocity of the peristaltic wave being greater than 8 cm/s. This disorder is also highly associated with reflux disease and is more likely to produce dysphagia and impaired bolus transit. Chest pain is typically associated with higher distal esophageal amplitudes (10). Esophagram may be normal or may show a "corkscrew" pattern during a swallow (Fig. 59.4). The etiology of DES is likely related to alterations in nitric oxide metabolism.

Treatment of DES usually begins with pH testing and/or antireflux therapy. Other treatment modalities are not well supported by controlled studies, but they have shown some possible efficacy in case series. These therapies include phosphodiesterase inhibitors (11), calcium channel blockers (12), peppermint oil (13), visceral analgesics, and botulinum toxin injections (14). Esophageal dilation may be helpful (15), and surgical myotomy is considered in severe cases (16,17).

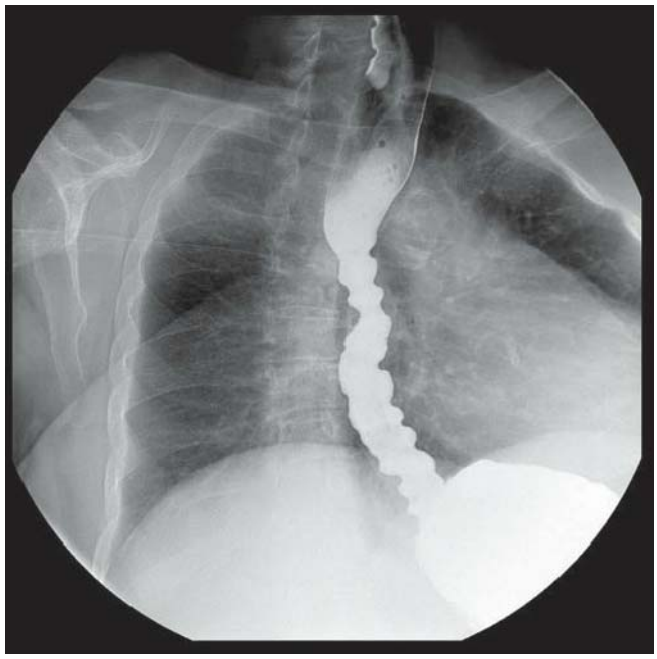


Figure 59.4 Fluoroscopic esophagram showing corkscrew appearance occasionally seen in diffuse esophageal spasm.

Hyperkinetic Disorders of the Lower Esophageal Sphincter

The LES normally relaxes at the initiation of a swallow to allow passage of the bolus into the stomach. When the LES resting pressure is found to be greater than 45 mm Hg on manometry, the sphincter is hypertonic. This disorder does not typically cause dysphagia as long as esophageal peristalsis is normal (7). However, when the LES does not relax completely (resting pressure greater than 8 mm Hg), regardless of the LES resting pressure, dysphagia may result, particularly for solid foods. This disorder can be treated with botulinum toxin injections or surgical myotomy.

Hypokinetic Esophageal Motility Disorders

Ineffective Esophageal Motility

Ineffective esophageal motility (IEM) disorder is a common hypokinetic disorder that may cause dysphagia or globus pharyngeus symptoms. On manometry, 50% or more swallows have amplitudes less than 30 mm Hg in distal esophagus (18). About half of patients with IEM have impaired bolus transit on impedance testing. This disorder often coexists with reflux disease and is difficult to treat effectively. Aside from antireflux treatment, bethanechol, a muscarinic receptor agonist, may improve distal esophageal contractility (19).

Achalasia

Esophageal achalasia is a rare disorder defined by complete absence of peristalsis, usually accompanied by poorly relaxing LES (7). Classic achalasia demonstrates

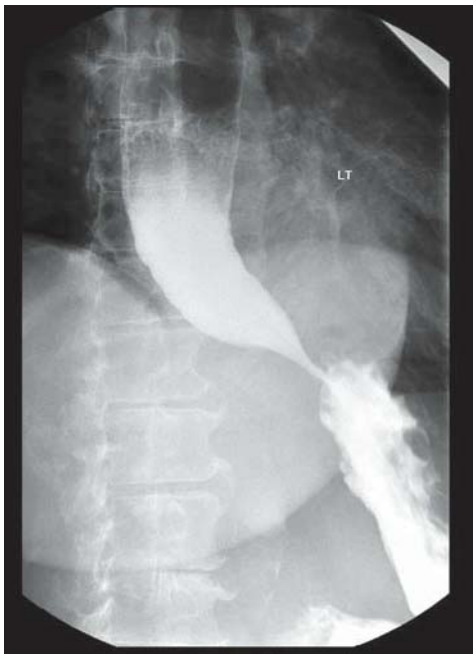


Figure 59.5 Fluoroscopic esophagram showing the "bird's beak" appearance of achalasia, caused by a dilated esophageal body and poorly relaxing LES.

manometric contractions less than 30 mm Hg, and the more uncommon vigorous achalasia may have higher esophageal pressures. Bolus transit is severely impaired in achalasia, and patients are generally present with dysphagia for all consistencies, regurgitation, cough, chest pain, and/or weight loss. Achalasia is thought to be related to ganglion cell degeneration in the myenteric plexus of the distal esophagus. Nitric oxide metabolism is significantly altered at the LES.

Esophagoscopy is essential to rule out pseudoachalasia from an obstructing lesion at the LES, such as a malignancy. Additionally, achalasia is a risk factor for development of esophageal squamous cell carcinoma. Fluoroscopy may show a dilated aperistaltic esophagus with a "bird's beak" pointed appearance at the LES (Fig. 59.5). Treatment options include botulinum toxin, pneumatic dilation with the intent of disrupting the muscularis propria layer, and surgical myotomy (20).

PROGRESSIVE SYSTEMIC SCLEROSIS

Progressive systemic sclerosis (PSS) is historically known as scleroderma. PSS is a multisystem collagen vascular disease with vascular damage contributing to fibrosis and atrophy of smooth muscle. Gastrointestinal involvement is present in 90% of PSS, with the distal esophagus being the most common site of involvement. Since the upper esophageal sphincter and proximal esophagus comprise skeletal muscle rather than smooth muscle, only the distal two-third of the esophagus and the LES are affected in PSS. Manometry reveals poor peristalsis and weak contractions in the distal esophagus, or aperistalsis. The LES is incompetent, putting PSS patients at high risk for reflux and its potential sequelae, including Barrett metaplasia, strictures, candida esophagitis, and neoplasm (21). Treatment of PSS includes antireflux therapy and possibly immunosuppressive agents.

ESOPHAGEAL WEBS, STRICTURES, AND RINGS

The normal esophageal lumen is 20 mm in diameter. When the diameter of the lumen is narrowed to 13 mm or less, symptomatic dysphagia may occur, particularly for solids. However, in the presence of esophagitis, larger diameter strictures may be symptomatic. Narrowing of the esophagus is best assessed with esophagram, although these abnormalities may also be seen on esophagoscopy.

Strictures most commonly result from reflux disease (peptic strictures). Impaired peristalsis, prolonged refluxate exposure, and transient LES relaxations contribute to the development of peptic strictures. These are typically treated with antireflux therapy and dilation of the affected esophageal area. Strictures may also develop in the setting of weakly acidic or alkaline reflux, despite appropriate antisecretory reflux therapy (22). In refractory cases, antireflux surgery or esophageal stents are considered (23).

Esophageal dilation may be undertaken with general anesthesia, conscious sedation, or topical anesthesia only. Bougie-type tapered dilators can be used with or without wire-guidance and/or fluoroscopy. Controlled radial expansion balloons allow for precise dilation at a specific site, rather than diffuse esophageal dilation. For tight strictures or complicated strictures, wire-guidance is safest. Endoscopic evaluation of the esophageal mucosa is always advisable before or during dilation to identify infections, esophagitis, and neoplasms.

Esophageal webs are thin membranous narrowings of the esophageal body that respond well to dilation. Cervical esophageal webs may be incidental or may contribute to solid food and/or pill dysphagia. These are quite thin and may not be well visualized with fluoroscopy.

Plummer-Vinson syndrome is the clinical triad of dysphagia, upper cervical esophageal web, and iron deficiency. This syndrome is also known as the Patterson-Kelly syndrome and may include glossitis, cheilitis, and koilonychia (24). The syndrome typically causes intermittent dysphagia for solids with possible esophageal food impaction. Treatment of Plummer-Vinson syndrome is correction of the iron deficiency with dilation of the web if symptoms persist.

Esophageal rings are limited to the lower esophagus, and clinically significant rings are classified as A or B (25). The A ring represents muscular hypertrophy at the most proximal limit of the LES. This is rarely symptomatic. In the event that a hypertrophic A ring is symptomatic,

chemical or surgical myotomy are the most effective treatments. Esophageal dilation is not helpful for symptomatic A rings.

The B ring is also known as Schatzki ring. This occurs at the SCJ, usually with squamous mucosa covering the superior surface and gastric mucosa on the inferior surface. A hiatal hernia is very frequently found with a B ring. B rings are considered to be reflux-related and are more likely to occur without reflux treatment. Indeed, reflux treatment is a critical aspect of treating a B ring. Fluoroscopy is the best way to visualize a B ring. Schatzki rings generally present with solid food dysphagia and possibly food impaction. Symptomatic B rings are treated with dilation.

ESOPHAGEAL DIVERTICULA

Outpouchings, or diverticula, may occur anywhere along the esophagus but are most commonly seen in the pharyngoesophageal segment. Diverticula are best evaluated with fluoroscopy. If a modified barium pharyngeal function study is performed rather than an esophagram, the shoulder may block visualization of a pharyngoesophageal diverticulum and an anterior view may be necessary.

A pharyngoesophageal diverticulum is a pulsion diverticulum, also known as a Zenker diverticulum. This occurs at Killian dehiscence, a natural weakness in the esophageal wall between the inferior constrictor muscle and the cricopharyngeus. The etiology of Zenker diverticulum is not clear, but it is likely related to reflux disease (26) and/or long-standing cricopharyngeal dysfunction (27). It is most common in the elderly population and usually presents with dysphagia with regurgitation of food that does not appear to have been digested. More subtle symptoms include halitosis, cough, or weight loss. Rarely, aspiration pneumonia may be the presenting sign of Zenker diverticulum.

Symptomatic Zenker diverticula, or those causing silent aspiration, are treated surgically with either open diverticulectomy or endoscopic diverticulotomy with cricopharyngeal myotomy (28). Open diverticulectomy is approached from a left oblique cervical incision or collar incision at the level of the cricoid cartilage. Identification of the diverticulum may be facilitated by packing of the pouch endoscopically. The entire diverticulum is removed via surgical stapling or excision with primary layered closure of the defect. Cricopharyngeal myotomy is usually performed in association with this procedure to help prevent recurrence and residual symptoms. Repositioning of the diverticulum to a more superior position (diverticulopexy) so that it does not collect food has been described for poor surgical candidates, since it purportedly takes less time than a diverticulotomy.

Endoscopic diverticulotomy is an alternative to the open approach. Specially designed bivalve diverticuloscopes have been designed to endoscopically expose the common wall between the esophagus and the pouch, which contains the cricopharyngeus muscle. Carbon dioxide laser or endoscopic stapling (29) is performed to cut the common wall between the esophagus and diverticulum. The diverticulum is not removed, but rather it is opened into the esophagus so that the pouch no longer collects food or liquid. Success rates and incidence of esophageal perforation are similar between the endoscopic and open approaches to Zenker diverticulum.

Traction diverticula occur in the middle third of the esophagus and are associated with scarring external to the esophageal lumen, for example, from chest irradiation or tuberculosis. These are rarely symptomatic. Epiphrenic diverticula are pulsion-type diverticula in the distal esophagus, associated with esophageal dysmotility. When symptomatic, epiphrenic diverticula may result in regurgitation and dysphagia.

ESOPHAGEAL EMERGENCIES

Esophageal Perforation

Violation of the esophageal wall results in perforation of the esophagus with possible mediastinal spillage. This may occur from trauma or, more commonly, from iatrogenic causes during esophageal procedures. Traumatic perforations may be due to blunt or penetrating chest trauma, severe vomiting (known as Boerhaave syndrome), caustic injury, or foreign body ingestion. Mediastinal malignancies, such as lymphoma, may lead to esophageal perforation from erosion of the tumor or from radiation necrosis. Procedures such as esophagoscopy, esophageal dilation, and nasogastric tube placement have all been associated with esophageal perforation. In the setting of esophageal diverticula or malignancies, the risk for iatrogenic perforation increases.

The most important concept in management of esophageal perforation is early recognition, since fulminant mediastinitis has a dismal prognosis. Ideally, an iatrogenic perforation is identified when it occurs, by visualization of transmural tearing, excessive bleeding, or mediastinal fat. After esophageal procedures, chest pain, fever, and subcutaneous emphysema are warning signs that a perforation has occurred. Water-soluble contrast, such as gastrografin, should be used in fluoroscopy whenever a perforation is suspected. Barium is irritating to the mediastinum and persists for years on imaging, making subsequent fluoroscopic evaluation difficult.

Small esophageal perforations may be managed medically with endoscopic feeding tube placement and *nil per os* status. Broad-spectrum antibiotics are usually initiated, to include anaerobic coverage. Fluoroscopy may be used in 5 to 7 days to evaluate for persistent leakage from the esophagus. Alternatively, surgical closure of the defect may be undertaken. Muscle flaps may be used to separate the defect from the trachea, particularly when there is risk for erosion into the trachea and creation of a tracheoesophageal fistula.

Esophageal Foreign Body

Foreign body ingestion is most prevalent in the pediatric population. Three natural compressions of the esophagus are the most common site for a foreign body to become impacted: the cricopharyngeus (most common), the compression from the aortic arch, and the LES. Drooling and dysphagia are the most common symptoms of esophageal foreign body. Compression of the trachea with subsequent respiratory distress may also occur. In children, the most commonly ingested foreign body is a coin, followed by obstructing food boluses and toys. Large food items, such as hot dog pieces, can completely compress the trachea and lead to death. Coin-shaped watch batteries are a dangerous foreign body, causing caustic alkaline injury with possible perforation. When a history or suspicion of battery ingestion occurs, endoscopic removal should be undertaken immediately. Adults have a wider variety of esophageal foreign bodies, with food bolus being the most common. This typically occurs in the setting of esophageal stricture, esophagitis, or neoplasm. Dentures are sometimes ingested during trauma or intubation. The sharp edges of dental appliances make extraction difficult and risk of perforation high.

History is the most important tool in diagnosing foreign body ingestion. Coins and other radiopaque items are readily identified on plain films. Food and plastic items, such as toys, are not typically seen on plain films and may require contrast fluoroscopy. Endoscopy is ultimately the best method for identifying esophageal foreign bodies.

Foreign bodies or food impactions are usually managed under general anesthesia with rigid endoscopy. This method helps to eliminate the potential of a foreign body dropping into the airway during extraction from the pharynx. Optical forceps are used often for extraction, allowing for simultaneous visualization and grasping of the object. The entire esophagus needs to be evaluated after the foreign body is removed to rule out esophageal injury, stricture, neoplasm, or multiple foreign bodies.

CAUSTIC INGESTION

Caustic ingestion has fortunately decreased in the past few decades in the United States because of laws regulating hazardous material labeling and improved community education. Small children who accidentally encounter caustic substances usually only ingest a small amount because the substance is so distasteful. Suicidal adults may swallow more of a caustic substance and sustain more serious injuries. Careful history and description of the substance ingested is critical in the management of patients with suspected caustic ingestion. Alkaline substances, with pH 7, are the most dangerous, including lye and laundry detergents. Strongly alkaline substances lead to deep, transmural esophageal injury from liquefaction necrosis. Acidic substances tend to cause a more superficial esophageal injury.

Examination of the lips, mouth, pharynx, larynx, and esophagus is recommended in the evaluation of caustic ingestion. Gastric lavage and emetics should not be used because further injury may occur. If esophageal injury is suspected, esophagoscopy should be performed. In the setting of significant esophageal injury, a feeding tube may be necessary.

ESOPHAGEAL NEOPLASMS

Malignant Esophageal Neoplasms

Most esophageal masses are malignant, and the gold standard for evaluating esophageal neoplasms is esophagoscopy. Larger lesions may be seen on fluoroscopy, but esophagoscopy is necessary to rule out neoplasm when suspected. Unfortunately, esophageal neoplasms are often asymptomatic until they are advanced enough to cause esophageal obstruction. Solid food dysphagia is the most important symptom. Other symptoms include weight loss, hematemesis, cough (30), and vomiting.

Adenocarcinoma of the esophagus is the most common esophageal malignancy in the United States, with its incidence increasing rapidly over the last three to four decades (31). Adenocarcinoma is found in the distal esophagus, frequently arising in the setting of Barrett metaplasia. Reflux, central obesity, middle age, and male gender are risk factors for adenocarcinoma. Squamous cell carcinoma of the esophagus is highly associated with tobacco and alcohol abuse. This neoplasm may occur anywhere along the esophagus and is most frequently found in the middle third.

Benign Esophageal Neoplasms

Benign lesions in the esophagus are rare and usually slow-growing. They are infrequently symptomatic and are usually an incidental finding on fluoroscopy or endoscopy. The most common benign esophageal neoplasm is leiomyoma, an intramural lesion covered by smooth mucosa (32). Esophageal cysts are also intramural and may be congenital. Fibrovascular polyps may originate from the postcricoid region and may become "giant." Asphyxiation from a regurgitated fibrovascular polyp can cause sudden death (33). Surgical excision via esophagotomy or endoscopy is typically performed (34). Esophageal papillomas may occur, caused by the human papilloma virus. These are usually sessile and asymptomatic but they may degrade to squamous cell carcinoma in a small percentage.

HIGHLIGHTS

- Esophageal disorders may present with head and neck symptoms, such as dysphagia, globus pharyngeus, or throat pain.
- Esophagitis due to infectious, caustic, medical, or irritant causes should be evaluated in cases of throat pain.
- Esophagoscopy is required when esophageal neoplasm is suspected, particularly in the instance of solid food dysphagia.
- Candida esophagitis is the most common type of infectious esophagitis and may be seen in immunocompetent individuals. Throat pain is a common symptom.
- Reflux may cause erosive or nonerosive esophagitis, with sequelae of strictures, motility disorders, and intestinal metaplasia.
- Eosinophilic esophagitis commonly presents with food impaction. Biopsy is necessary to confirm the diagnosis.
- Esophageal masses are predominately malignant. Benign neoplasms of the esophagus are typically incidental findings.

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Management of Intractable Aspiration

60

David E. Eibling

Aspiration pneumonia accompanies a wide variety of disease states, and often contributes substantially to the impact on the patient. Inhalation of food and liquid into the lower airways is recognized as a contributing factor in the death of many patients, and is frequently the terminal event. Stroke is a well-known example, in that although aspiration risk is transitory in most stroke patients, a considerable percentage of those with persistent dysphagia (20% to 50%) will eventually succumb to aspiration pneumonia (1–3). Mitchell et al. reviewed the clinical course of 323 nursing home patients with advanced dementia and noted that more than 50% had died within 18 months, and that the combination of dementia and aspiration was particularly deadly. The *6-month mortality rate* for patients with advanced dementia who had eating difficulties was 38.6%; if they developed pneumonia the figure rose to 46.7% (4). Despite the prevalence of aspiration in many disease states, and its often grave impact on the patient, (not to mention the cost to the health care system) the evaluation and management of aspiration remain enigmatic to many, if not most, health care providers. Most aspirating patients are managed by nonsurgical means, addressed in Chapter 58. This chapter focuses on surgical management of aspiration unresponsive to conservative measures.

IDENTIFICATION OF ASPIRATION

One might suspect that clinically significant aspiration would be readily apparent to the patient's caregivers. However, the signs of aspiration are frequently attributed to the primary disease, and aspiration may remain unrecognized until the terminal phase of the disease process. Neurologic impairment masks the usual symptoms of aspiration, particularly by facilitating so-called *silent aspiration*. Common manifestations of aspiration are enumerated in Table 60.1.

Aspiration pneumonia entails substantial costs for the health care system (not to mention the patient) hence most health care facilities have introduced standard screening procedures to identify patients at risk for aspiration. These are most commonly developed and overseen by a *dysphagia team*, typically organized and led by a senior speech–language pathologist (SLP). Screening is usually performed by admitting nursing staff. Patients determined to be at risk are then evaluated by the multidisciplinary dysphagia team headed by a SLP with expertise in dysphagia who makes recommendations for further evaluation and/or intervention. In some facilities, an otolaryngologist is an integral part of the team (5); however, in others the team functions effectively without physician oversight. The Joint Commission removed the requirement for universal dysphagia screening of all stroke patients in 2010; however, other performance-monitoring organizations continue to include screening for aspiration risk in their bundles (2). High-level evidence exists that improved outcomes (reduced episodes of pneumonia) are correlated with the presence of a dysphagia team, but no clear evidence exists to guide the team activities. In other words, *paying attention* in and of itself seems to be the most critical factor in promoting improved outcomes in hospitalized patients with swallowing disorders!.

ETIOLOGY OF ASPIRATION

Otolaryngology trainees encounter aspirating patients most often on the head and neck cancer service; however, the majority of patients suffering severe aspiration are those with neuromuscular dysfunction. A retrospective review of patients with intractable aspiration who required laryngotracheal separation revealed that more than two-thirds had suffered devastating neurologic disease, such as amyotrophic lateral sclerosis, multiple sclerosis, or brainstem stroke (6). The aging baby boomer population

TABLE 60.1 DIAGNOSIS OF ASPIRATION

Aspiration pneumonia
Recurrent pneumonia of unknown causation
"Bronchorrhea" after tracheotomy
Coughing, choking with eating
Dysphagia and prolonged time for eating
Weight loss

and attendant increases in the numbers of patients with dementia predict that otolaryngologists practicing in the second and third decades of the 21st century will encounter an epidemic of aspirating elderly patients. Decision making for this group of future patients will challenge today's trainees.

Increased numbers of patients with head and neck cancer will survive their disease only to suffer from long-term dysphagia and aspiration. Treatment-induced acute inflammation and mucositis, as well as long-term fibrosis, xerostomia, web formation, and stenosis (or even obliteration) of the cricopharyngeal lumen, result in severe dysphagia and often frank aspiration for many cancer survivors. Acute radiation-induced dysphagia abates several weeks following completion of therapy, only to be replaced with chronic dysphagia as fibrosis develops. This dysphagia typically increases in severity with the passage of years due to progressive fibrosis and muscle weakness (7). If recent trends in the incidence of human papilloma virus—associated oropharyngeal (OP) cancer continue, otolaryngologists can anticipate growing numbers of OP cancer survivors presenting to their offices with progressive dysphagia, possibly many years after treatment. Although recent alteration in radiation fields and dose de-escalation may reduce dysphagia rates for patients treated in coming years, for the short term at least, standard doses of combined chemotherapy and radiotherapy will likely lead to increasing prevalence of posttreatment dysphagia and even morbid aspiration.

PHYSIOLOGY OF SWALLOWING

Aspiration is a sequella of disordered deglutition, so a basic knowledge of the physiology of normal swallowing is required to understand the pathophysiologic underlying etiologies of aspiration. The reader is referred to Chapters 56 to 58 and to the classic references on the topic (7,8). Some indication of the primacy of airway protection can be seen by examining the phylogeny of the larynx (9). Humans are at particularly high risk for soilage of the lower airways during deglutition due to the caudal location of the human larynx. This location facilitates vocalization by enlarging the resonance cavity, but increases the risk of aspiration associated with relatively minor abberations in swallowing function. Effective swallowing requires that food and liquid be formed into a finite bolus and then moved rapidly and completely past the closed glottis. Failure to form a finite bolus, premature leakage of bolus material into the pharynx, delay in moving the bolus through the pharynx or incomplete emptying of the pharynx at the completion of deglutition permits material to be aspirated into an open glottis. Glottic incompetence during swallowing can lead to aspiration, particularly when accompanied by sensory changes or pharyngeal weakness. Aspiration pneumonia, therefore, is the end result of laryngopharyngeal dysfunction, and typically is due to neuromuscular disease.

Glottic Closure

Glottic closure is required for effective swallowing. Closure occurs rapidly (the glottic closure reflex is less than 25 ms in duration) and is reflexively triggered by the presence of bolus material in the pharynx. Interruption of the afferent limb through loss of sensation of the larynx and pharynx causes loss of this reflex and can lead to clinically significant aspiration. Aspiration often is associated with the effector limb of the reflex through vocal cord paralysis, atrophy, or other causes of inadequate glottic closure (Fig. 60.1). Sasaki et al. (10) have demonstrated that glottic closing pressure also impacts effectiveness of closure, and may be reduced following thyroplasty even if the glottis is anatomically closed. Surgical procedures designed to improve glottic closure can have a dramatic effect in the care of some patients (11).

Upper Esophageal Sphincter Relaxation

Relaxation of the cricopharyngeal muscle allows opening of the upper esophageal sphincter, facilitating passage of the bolus from the pharynx into the esophagus. The upper

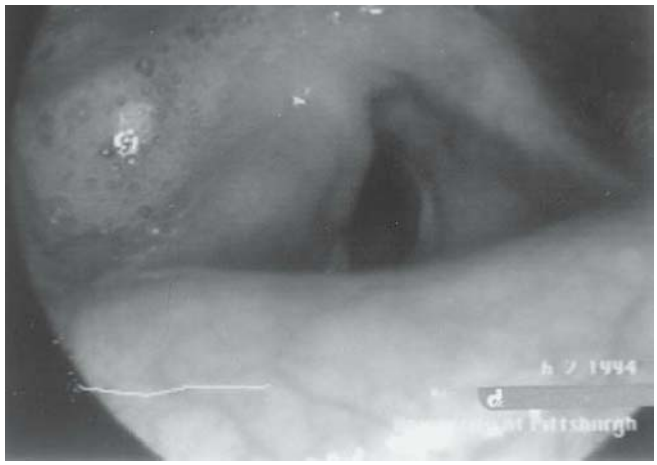


Figure 60.1 Right vocal cord and ipsilateral pharyngeal paralysis cause hoarseness and aspiration in a patient with a large glomus jugulare tumor. Saliva has pooled in the right pyriform sinus. Medialization thyroplasty was performed before tumor excision to facilitate pulmonary toilet in the postoperative course.

esophageal sphincter is actively dilatated by anterio–superior elevation of the laryngeal cartilage immediately before arrival of the bolus. Failure of either relaxation of the muscle or of hyo-laryngeal elevation will result in retained food and bolus in the pharynx.

TRACHEOSTOMY AND ASPIRATION

Aspiration has been noted in patients with a tracheostomy for nearly 50 years (12); however, controversy exists as to whether a cause-and-effect relationship exists. Sasaki (9) noted loss of the glottic closure reflex in the presence of a tracheostomy and Muz et al. (13) noted aspiration, which varied in extent depending on whether the tube was open or plugged. Several investigators (13–15) noted that plugging or placing an expiratory valve on a tracheostomy tube appeared to benefit swallowing and reduce aspiration, suggesting that subglottic air pressure played a role. Others (16) have been unable to duplicate these findings, suggesting that the specific relation between tracheostomy and aspiration varies based on patient comorbidities, age, and underlying disease.

SENSORY LOSS

Aviv et al. (17) found that stroke patients have marked reductions in pharyngeal and supraglottic sensation and that these reductions correlate with aspiration risk. Pharyngeal sensation can be measured utilizing a puff of air directed against the supraglottic structures while the larynx is observed with a flexible laryngoscope, although most examiners utilize other findings as surrogates for sensory loss (Chapter 57).

EVALUATION OF A PATIENT EXPERIENCING ASPIRATION

Once aspiration has been identified as a source of morbidity for a particular patient, additional evaluation is needed to find the cause and extent of aspiration, to assess the risk to the patient's health, and to select the optimal therapeutic course. Evaluation to identify the etiology and severity of the underlying dysphagia is integral to decision making and is discussed in detail in Chapter 57. In the past, blue dye routinely placed in tube feedings was to detect, and to some extent quantify, aspiration in patients with a tracheostomy; however, due to the risk of systemic toxicity, it is no longer utilized in this manner.

Radiographic examination (Fig. 60.2) or flexible endoscopic laryngopharyngeal examination (described in detail in Chapter 57) is the usual strategy employed to identify the etiology and evaluate the severity of dysphagia and accompanying aspiration. These studies permit real-time testing of compensatory strategies and dietary modification, which may be effective in some patients. If these strategies are not successful, then surgical approaches many be required.

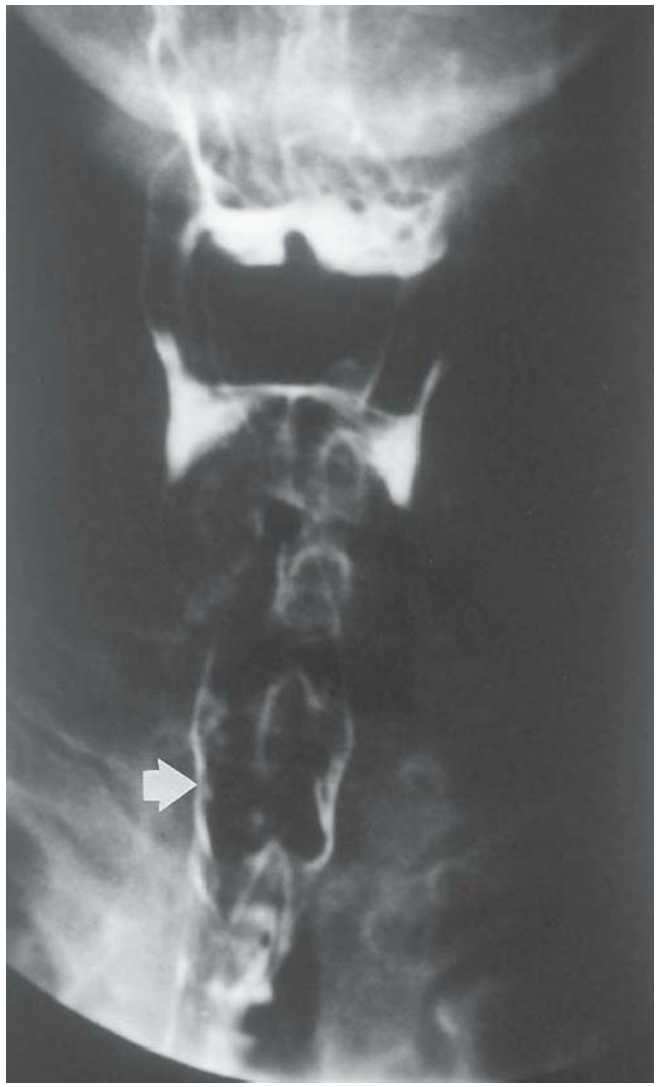


Figure 60.2 Photograph shows tracheal aspiration (*arrow*) identified during a barium swallow examination.

DECISION MAKING

Decision making in the management of intractable, morbid aspiration is typically the most complex challenge faced by the otolaryngologist. Many patients who have undergone conservation partial laryngeal surgery for cancer can be shown to aspirate on barium studies, however, actively compensate and avoid pneumonia while maintaining adequate oral intake. An understanding that the clinical effect of aspiration varies dramatically from patient to patient is required for optimal decision making in the evaluation of aspirating patients. Overall functional reserve, pulmonary status, activity level, and underlying disease processes must be considered in addition to the assessment of the extent of aspiration. The patient's overall goals and the wishes and expectations of the patient's family, as well as the role aspiration plays in the patient's overall medical status must be considered. For example, most would consider the performance of a

laryngotracheal separation on a hospice patient with terminal lung cancer who has developed severe aspiration to be inappropriate. On the other hand, there is no clear consensus on tube feeding in this setting, and decision making for each patient must be individualized. Should the same patient have glottic incompetence due to vocal cord paralysis, most surgeons would recommend performance of medialization thyroplasty, which may dramatically improve the quality of the patient's remaining life by improvements in voicing as well as reductions in aspiration. A patient who has suffered a brainstem stroke may benefit from tracheostomy and short-term placement of a laryngeal stent. This maneuver may facilitate rapid extubation and transfer out of an acute care hosptial to a skilled nursing facility merely by reducing the extent of aspiration. An understanding of the patient's disease process, the etiology of aspiration, and a knowledge of the wide range of possible solutions is essential in selecting the optimal therapeutic course. In this regard, the otolaryngologist often assumes the role of educator and facilitator in discussions with the patient and their family and care team.

THERAPEUTIC OPTIONS

Nonoral Feedings and Airway Management

Nonsurgical strategies for mild aspiration are addressed in detail in Chapter 58. Initial treatment of a patient experiencing severe aspiration is supportive and includes steps listed in Table 60.2. Elimination of oral feeding and alternative enteral access via either nasogastric tube or percutaneous endoscopic gastrostomy (PEG) are the usual initial steps in management. Surprisingly, the risk of aspiration pneumonia is not eliminated with alternative feeding. Langmore et al. (1) observed that patients who were tube-fed had a higher risk of pneumonitis (probably due to selection bias). Oral care has been shown to impact the risk of aspiration pneumonia in intubated patients (18), probably through reductions in the bacterial load contained in aspirated secretions, and should be standard in all hospitalized patients (Table 60.3).

Aspiration may become apparent in association with intubation, and often may be the trigger for placement of an endotracheal tube in a decompensating patient.

TABLE 60.2 INITIAL MANAGEMENT OF SEVERE ASPIRATION

Nothing by mouth
Nasogastric or gastrostomy tube
Intubation for respiratory failure
Tracheostomy with cuffed tube
Laryngeal stent in some instances

TABLE 60.3 MANAGEMENT STRATEGIES FOR ASPIRATION

Adjunctive measures
Alternative feeding techniques
Removing, plugging, or valving tracheostomy tube
Reduction of gastropharyngeal reflux
Adjunctive surgical procedures
Vocal cord medialization
Cricopharyngeal myotomy or chemodenervation
Esophageal dilatation
Partial supraglottic closure
Laryngeal stenting
Total laryngectomy
Laryngotracheal separation

Moreover, intubated and ventilated patients are at high risk for ventilator-associated pneumonia (VAP), at least in part due to aspiration of OP secretions through the open glottis. An evidence-based VAP—prevention bundle is now standard of care for Ventilator patients (19) (Table 60.4). Another strategy is subglottic secretion drainage utilizing an endotracheal tube designed to remove secretions from above the cuff. A recent (epub ahead of print April 2011) work demonstrates that VAP can be reduced by nearly 50% with this strategy (20).

Conversion to a tracheostomy, or elective tracheostomy with insertion of a cuffed tracheostomy tube, facilitates pulmonary toilet, although does not eliminate the risk for VAP. The presence of an inflated tracheostomy tube cuff inflation reduces but does not altogether prevent aspiration into the distal airways. Decannulation, or downsizing, plugging, or valving the tracheostomy tube after resolution of the acute process may reduce aspiration in some patients (Fig. 60.3) (14,15). The effect of these maneuvers can be assessed with either fluoroscopy (modified barium swallow) or flexible endoscopic evaluation of swallow. Employment of subglottic secretion strategies as utilized in the VAP bundle can occasionally be beneficial for patients with persistent aspiration despite use of a cuffed tracheostomy tube (20).

Procedures to Enhance Glottic Closure

Glottic closure is an integral component of normal swallowing, hence surgical procedures that enhance closure represent a critical adjunct in the management of aspiration in the patient with inadequate glottic closure. The procedures most commonly used are vocal cord augmentation or medialization with a variety of techniques, or arytenoid adduction. Evaluation of laryngeal function and performance of these procedures are discussed in detail in Chapters 69, 70, and 73. Augmenting or medializing a paralyzed cord does not completely restore glottic closing

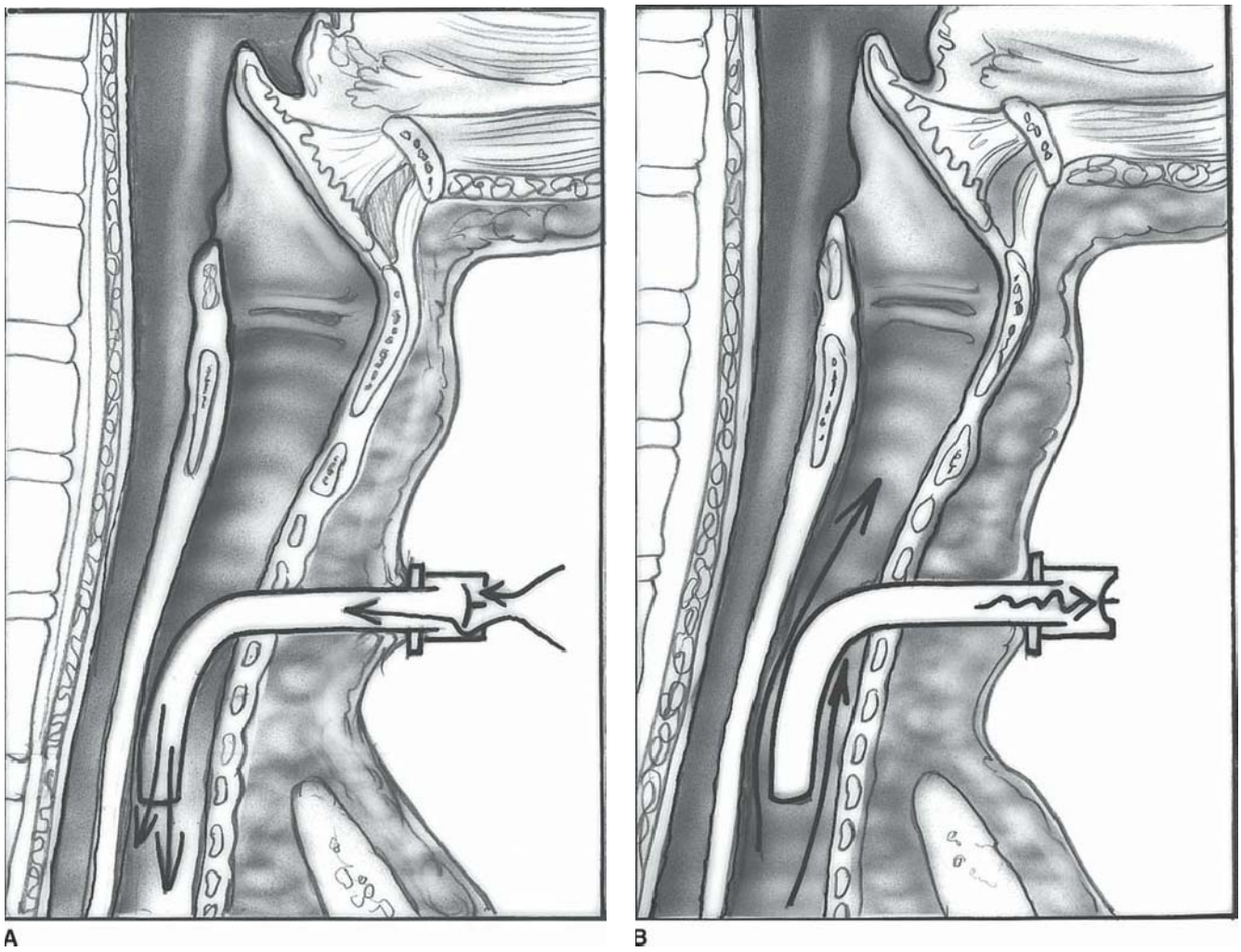


Figure 60.3 Function of expiratory speaking valve. The valve opens to allow inspiration but closes immediately to divert the inspired air out through the larynx, enabling vocalization. Use of this valve reduces aspiration for some patients with tracheostomy (10,14,15).

force since there is no active adduction on the paralyzed side (10), but typically is sufficient to thwart aspiration in cases of unilateral isolated paralysis.

Occasionally a patient experiencing severe aspiration due to severe neurologic impairment will benefit from bilateral medialization and tracheotomy. This technique can markedly diminish aspiration while maintaining vocalization, but necessitates a permanent tracheostomy.

TABLE 60.4 VENTILATOR-ASSOCIATED PNEUMONIA PREVENTION BUNDLE

Elevation of head of bed
"Sedation vacation"
Reduction of gastroesophaeal reflux
Oral care
Possible subglottic secretion suction

Procedures to Enhance Esophageal Run-Off

Persistent pharyngeal residue following an otherwise intact swallow positions the airway for entrainment of food and liquid when the glottis opens for the following breath. As a result, esophageal diseases (see Chapter 59) may also contribute to intractable aspiration. Strategies to improve esophageal run-off may be the most critical management strategy for some patients.

Management of Esophageal Strictures

More than 50 years ago most esophageal strictures encountered by otolaryngologists were due to accidental ingestion of lye. Changes in product availabilty and labeling, as well as public awareness, have dramatically reduced the incidence of this devastating injury. By the end of the 20th century suicide attempts had largely replaced accidental ingestion as the cause of caustic esophageal burns.

However, the declining incidence of caustic strictures is now being replaced with stenoses secondary to organ-sparing treatment for head and neck cancer, primarily OP cancer. The average otolaryngologist can expect to encounter several in the coming decades, and most head and neck treatment centers are developing considerable experience with their management. Ongoing controversy exists as to whether the presence of a PEG during therapy contributes to the development of a stricture within the radiation field. Many Head and Neck surgeons postulate that by eliminating the need for swallowing during therapy, the repeated effective dilatation by food boluses is eliminated, permitting the raw mucosal surfaces to stenose. Esophageal dilatation has traditionally been performed in the operating suite under general anesthesia using bougies. However, many surgeons are now using balloon dilatation in an outpatient setting, and this technique seems poised to become the standard for affected patients in future years.

UPPER ESOPHAGEAL SPHINCTER

The upper esophageal sphincter is opened during the pharyngeal phase of swallowing by both passive relaxation of the cricopharyngeal muscle and active displacement of the larynx. Failure of opening results in obstruction or delay in passage of the bolus into the esophagus. Evaluation of upper esophageal sphincter dysfunction is challenging, in that failure of dilatation may be due to reduced laryngeal displacement, failure of muscle relaxation, or fibrosis. Often multiple factors contribute, and identifying the relative contribution of each may be challenging. Careful examination of the region during modified barium swallow is often instructive, but as many as one-third of elderly patients will have a persistent cricopharyngeal bar visualized on radiographic studies. Typical evaluation requires careful frame-by-frame examination of videofluoroscopic images. Occasionally the benefit of intervention can only be determined by therapeutic trial.

Cricopharyngeal myotomy may be efficacious for some aspirating patients with failure of upper esophageal sphincter dilatation during passage of the bolus, particularly when hyolaryngeal elevation is normal. An alternative to surgical division is to chemodenervate the cricopharyngeus (CP) with botulinum toxin, which may provide long-term benefit (21). The procedure can be performed as an outpatient office procedure utilizing electromyographic monitoring (Chapter 73), or can be performed in the operating suite under general anesthesia with direct visualization. Forty to fifty units of botulinum toxin are injected, with care being taken to avoid injecting too close to the postcricoid region to reduce the likelihood of posterior cricoarytenoid muscle denervation and resultant airway obstruction. Endoscopic laser division of the cricopharyngeal muscle is effective, and safe if performed in a judicious manner (22). Care must be taken to avoid entering the mediastinum in using this technique. External approaches to the CP muscle are well described elsewhere and are not reviewed in this chapter.

ZENKER DIVERTICULUM

Long-standing cricopharyngeal dysfunction may be associated with Zenker diverticulum. Large Zenker may be associated with substantial dysphagia, failure of cricopharyngeal relaxation, and resultant pooling in the hypopharyngeal pouch. Although typically not considered in the differential diagnosis of aspiration, occasionally a Zenker diverticulum will be demonstrated on radiographic studies requested to evaluate dysphagia, aspiration, and inition. Treatment of Zenker is now most commonly performed via endoscopic diverticulotomy, dividing the septum separating the pouch from the esophagus with laser, stapler device (23), or even direct incision and suture. Stapler-assisted techiques require that the pouch be larger than 2 cm, since smaller pouches do not permit complete division of the cricopharyngeus muscle. Open procedures in which the cricopharyngeal muscle is divided and the pouch either resected or inverted are also effective.

LARYNGEAL CLOSURE PROCEDURES

A number of procedures to close the larynx have been employed in reducing or preventing aspiration when more conservative strategies fail. Partial supraglottic closure converts the laryngeal introitus into a narrow tube, reducing aspiration while maintaining an aperature for phonation (24). These procedures are technically difficult, their case selection is difficult, and are probably useful in only a very small subset of patients with intractable aspiration.

Laryngeal stenting is a useful technique for severe aspiration and likely to be limited to a relatively brief period, such as in brainstem stroke. Eliachar et al. (24) reported successful control of aspiration with acceptable complications utilizing prolonged larynx stenting. Clinical experience suggests that 2 to 3 months is the typical maximum time that the laryngeal stent can remain in place. Various stents are available, as are various means for securing the stent (Fig. 60.4).

Total laryngectomy is an effective management strategy for intractable aspiration. The role of laryngectomy in the care of the aspirating patient whose larynx is nonfunctional due to prior chemoradiation, tumor destruction, or partial laryngectomy is well known. Complete laryngectomy may be required many years following successful partial laryngectomy due to aging or changes in pulmonary fuction, such as subsequent to lung surgery for a second primary lung cancer. Despite its effectiveness, the

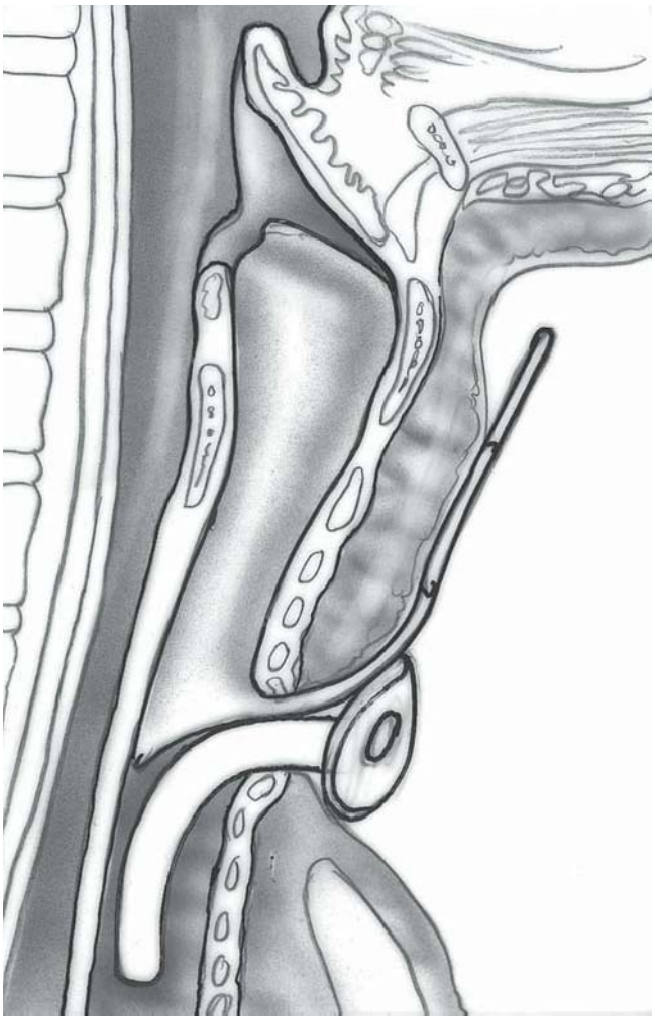


Figure 60.4 Eliachar stent in place. The stent is maintained in position by a strap that passes through the tracheostomy above the tracheostomy tube. (From *Understanding and treatment of aspiration.* SIPAC, American Academy of Otolaryngology—Head and Neck Surgery, Alexandria, VA 1993, with permission.)

procedure typically is unacceptable to patients (or their families) with intractable aspiration due to neurologic disease, even if all concerned are aware of the hopelessness of the situation, the morbidity of ongoing aspiration, and the availability of alternative techniques for voicing. The risk of wound breakdown with pharyngocutaneous fistula in the debilitated patient with poor nutritional status is not insignificant, so that preoperative nutritional support may be indicated. Alternative forms of separating the airway from the food passages are feasible and are often more acceptable to patients.

Laryngotracheal Separation

Lindeman (25) described surgical division of the trachea as a strategy for the management of intractable aspiration more than 35 years ago. As performed most commonly, the proximal tracheal stump is not anastamosed to the esophagus but is closed in a pouch (Fig. 60.5). The procedure is

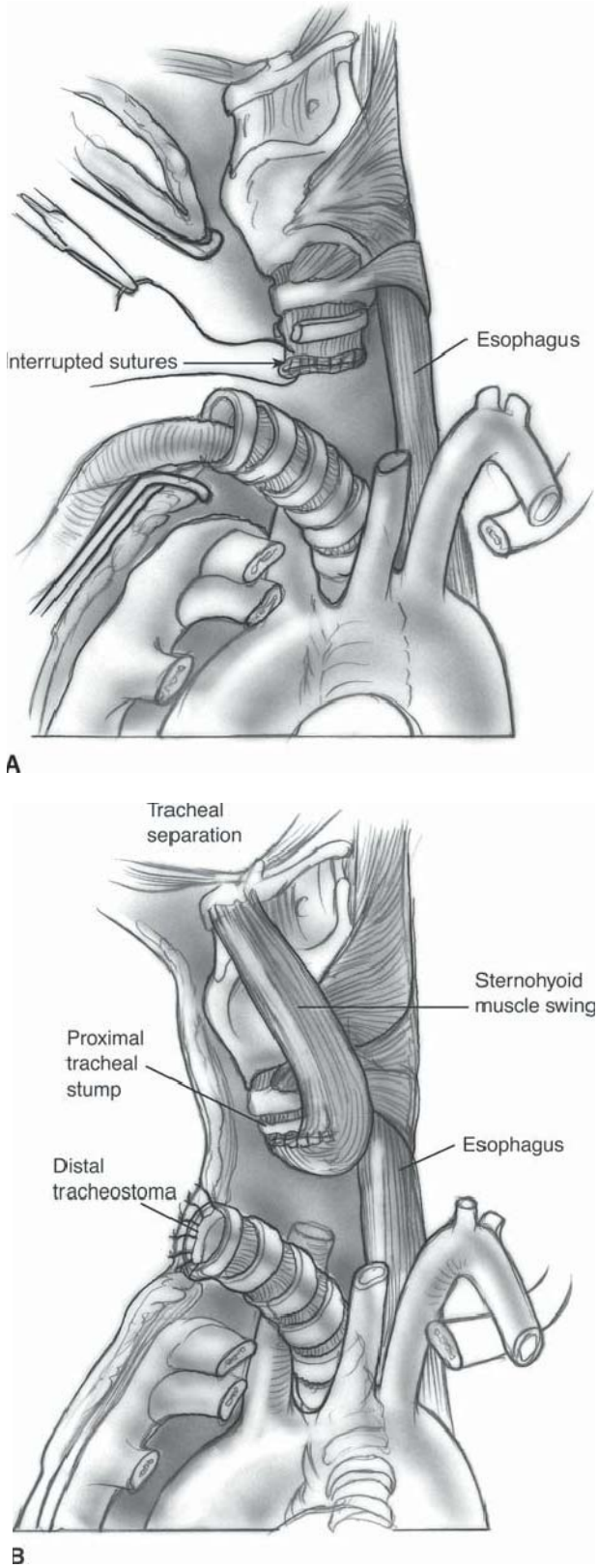


Figure 60.5 A,B: Laryngotracheal separation. The trachea is divided, and the proximal stump is closed in two layers to form a watertight subglottic pouch. The distal end of the trachea is sutured to the skin as it is in total laryngectomy. (Modified from *Understanding and treatment of aspiration.* SIPAC, American Academy of Otolaryngology–Head and Neck Surgery, Alexandria, VA 1993, with permission.)

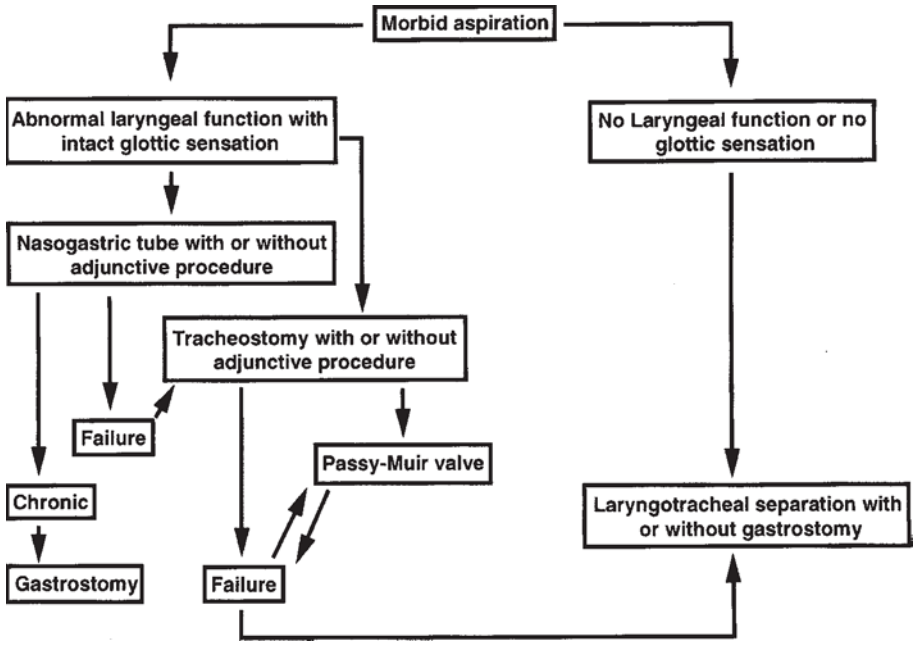


Figure 60.6 Algorithm for the management of aspiration. Adjunctive procedures, such as medialization and thyroplasty or tracheostomy tube valving, are used only in the care of patients who have a sensate functional larynx. It is more expedient to proceed directly to laryngotracheal separation if the larynx is not functional. (From Snyderman CH, Johnson JTJ, Eibling DE. Laryngotracheal diversion and separation in the treatment of massive aspiration. *Curr Opin Otolaryngol* 1994;2:63–67, with permission.)

technically easy, can be performed after tracheotomy, and is at least theoretically reversible. It has become the standard at most institutions for the management of intractable aspiration unresponsive to more conservative measures or adjunctive surgical procedures.

Laryngotracheal separation is most commonly performed following prior tracheostomy. The previous tracheostomy site is excised, the trachea dissected free, and the proximal end closed to form a blind pouch. Temporary leakage from the stump closure occurs among more than one-third of patients due to technical difficulties encountered from prior scarring, but most leakage resolves within several days with conservative therapy alone. Wound complications do occur, but tend to be self-limited. Because the larynx remains in place and is not affected by the procedure, reanastomosis of the divided trachea is feasible for the rare patient whose neurologic function returns. Tracheal reanastomosis has been reported by several authors, although the procedure can be technically challenging.

CONCLUSIONS

A decision tree useful for the management of intractable aspiration is based on whether the larynx is sensate and whether return of glottic or pharyngeal function is likely (Fig. 60.6) (26). The prognosis of the primary disease process and goals of the patient and family must take precedence over physiologic functional status. Nevertheless, if return of function is unlikely in a patient with intact cognition and otherwise acceptable quality of life, early laryngotracheal separation may provide maximal benefit. Intervention is most likely to progress in a stepwise fashion, however, with initial trials of alternative strategies prior to resorting to laryngotracheal separation. Active participation by the otolaryngologist in assisting the patient, family, and care team in difficult decision making is often invaluable in optimizing outcomes.

HIGHLIGHTS

- Morbid aspiration is a sequella of severe dysphagia.
- Aspiration accompanies many illnesses, primarily head and neck cancer and neuromuscular disease processes.
- Detection of patients at risk for aspiration is facilitated by the presence of a dysphagia team.
- Evaluation of aspirating patients should include endoscopic examination of the laryngopharynx.
- Management of aspiration should be based on assessment of the patient disease process, prognosis, swallowing physiology, and goals of care.
- A stepwise progression of theraputic interventions optimizes patient benefit while minimizing undesirable consequences.
- Procedures to enhance glottic closure and improve esophageal run-off often benefit patients with aspiration.
- Laryngectomy and laryngotracheal separation are effective interventions for aspiration, but should be considered "last resort" and utilized rarely.

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61 Upper Airway Anatomy and Function

Gayle E. Woodson

The upper airway includes the nasal and oral cavities, the pharynx, and the larynx. The functional design is far from ideal because ingested food and water must traverse the upper airway to reach the alimentary tract. The pharynx must serve two conflicting functions. It must rapidly constrict to propel material into the esophagus during swallowing, yet maintain patency during the negative pressure generated by inspiration. The close proximity of the orifices into the esophagus and the lower airway present a significant risk of aspiration; therefore, the larynx has a major protective function, and breathing and speech must be interrupted during a swallow. The precarious arrangement of the airway is a product of its evolution and embryology. The trachea and lungs evolved as an offshoot of the digestive tract, and this origin is reflected in the development of human embryos. The lung buds arise from the lower pharynx.

In all nonhuman mammals, the common upper chamber for eating and breathing poses little problem, because there are functionally separate channels for breathing and eating, formed by the interdigitation of the epiglottis and the soft palate. The central channel, leading from the nose to the larynx, is for breathing, with a pathway for swallowing on either side, leading from the mouth to the esophagus. This configuration persists in human infants and explains why neonates experience such respiratory distress with nasal obstruction. In the second year of life, the larynx descends in the neck, associated with pharyngeal elongation, so that the soft palate and larynx are no longer in contact, but separated by a significant gap (1). This results in a larger hypopharyngeal space, which confers greater vocal power and diversity in articulation. But the separation of the uvula from the epiglottis abolishes the separation of air and alimentation pathways, which makes the process of swallowing considerably more complex. The purpose of this chapter is to provide the anatomic and physiologic basis for understanding the processes of breathing and speech. Because nasal and oral anatomy are covered in other parts of this text, the following section focuses primarily on the larynx and pharynx.

PHARYNGEAL ANATOMY

The pharynx is an irregularly tubular structure, extending from the base of the skull to the esophageal inlet (Fig. 61.1). The posterior and lateral walls of the pharynx are composed of three pharyngeal constrictor muscles attached to the cervical vertebrae posteriorly. The pharynx has anterior openings into the nasal and oral cavities, and inferiorly it opens into the larynx and esophagus. There are three segments: the nasopharynx, the oropharynx, and the hypopharynx. The nasopharynx can be sealed off from the oropharynx by simultaneous elevation of the soft palate and formation of a fold in the pharyngeal walls, known as Passavant ridge. Complete physical examination of the pharynx requires a mirror or endoscope, because only the posterior wall of the oropharynx is visible by transoral inspection.

The superior constrictor is suspended from the base of the skull, the medial pterygoid plate, the pterygomandibular raphe, the mylohyoid line of the mandible, and the lateral tongue. The anterior attachments of the middle constrictor are the hyoid bone and the stylohyoid ligament. The inferior constrictor attaches to the thyroid and cricoid cartilages. Activation of these muscles constricts the pharynx; there is no evidence to support the concept that they contribute to stability of the airway. Pharyngeal patency during the negative pressure generated with inspiration is maintained by muscles that dilate the lumen by pulling the base of the tongue or hyoid bone anteriorly. These muscles include the genioglossus, the geniohyoid, and the anterior belly of the digastric muscle.

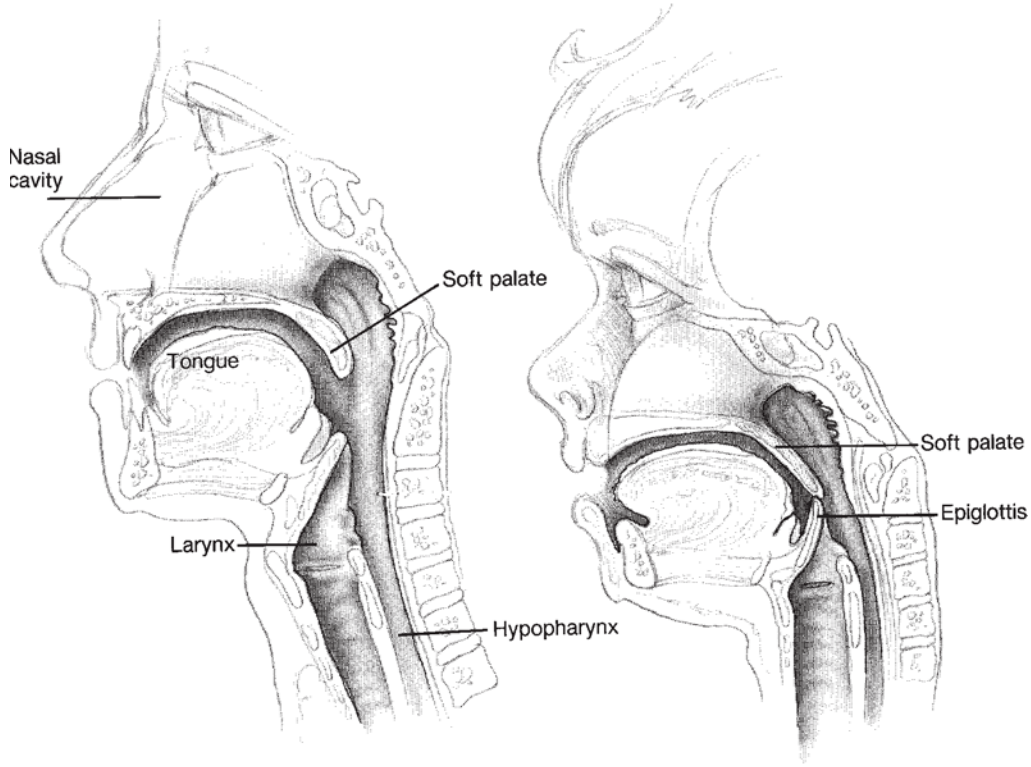


Figure 61.1 Sagittal view of upper airway.

PHARYNGEAL AIRWAY PHYSIOLOGY

Maintenance of upper airway patency is a peculiarly human problem. Some degree of airway collapse occurs during sleep in all humans, and obstructive sleep apnea (OSA) is extremely common. But sleep disordered breathing is extremely rare in any other animal (2). The instability of the human pharyngeal airway is a byproduct of the inferior displacement of the larynx during development (3). The pharyngeal walls, suspended from the base of the skull and mandible, are pliable. Some skeletal support is provided by the hyoid bone. Because its walls are collapsible, the pharynx acts as a Starling resistor. Flow through such a resistor is not determined solely by the difference between the upstream and downstream (i.e., intrapleural) pressures, but is critically influenced by the difference between the upstream pressure and the collapsing forces. In other words, if the pressure of the air inspired through the nose is not high enough to keep the throat from collapsing, no air can reach the lungs, no matter how hard the inspiratory muscles contract, and obstructive apnea results. Snoring occurs when the collapsing pressure is less than upstream pressure, but greater than downstream pressure. The airway intermittently closes, but is reopened by increased upstream pressure (2).

As mentioned above, muscles that connect the hyoid bone and tongue base to the mandible provide the force to open the pharynx. These dilating muscles are activated by the negative airway pressure generated during inspiration in the presence of upper airway obstruction. During the Mueller maneuver, which generates negative pressure in the pharynx, the dilating muscles should maintain patency. A significant decrease in the cross-sectional area of the pharynx during the Mueller Maneuver is highly predictive of OSA (4). Thus, inadequate force of pharyngeal dilating muscles is implicated in the pathogenesis of OSA.

Patients with OSA have a higher than normal activity of phasic inspiratory activity of upper airway dilating muscles during wakefulness. This suggests that these individuals require more force than normal to keep the airway patent. They are able to compensate while awake, but during sleep, airway muscle activity decreases and is inadequate to prevent collapse during inspiration. Pharyngeal patency at end expiration is also a major factor. Endoscopic observations in patients with sleep apnea demonstrate a decrease in airway cross-sectional area before an actual obstructive event. At end-expiration, with no flow, the pharyx can collapse completely. When inspiration is attempted through an already obstructed airway, the result is an obstructive apnea. Continuous positive airway pressure can stent open the collapsed segment during end-expiration. This may be one mechanism by which continuous positive airway pressure (CPAP) therapy is effective. CPAP causes a decrease in genioglossus muscle activity during wakefulness in patients with sleep apnea, but not in normals, suggesting that the increased activity in the waking OSA syndrome patient represents compensation for a mechanically obstructed airway, not defective reflexes.

LARYNGEAL ANATOMY

The most superior portion of the larynx is the epiglottis, which projects posteriorly into the pharynx. The vallecula is the pouch between the base of the tongue and the epiglottis. Interiorly, the glottis is seen as a roughly triangular opening during inspiration and a narrow slit during phonation. The true vocal folds comprise the anterior edges of the glottis. Superior and lateral to the true vocal folds are the false vocal folds. The ventricle is a narrow space between the true and false folds. The posterior glottis is formed by the two arytenoid cartilages and the intervening mucosa. The arytenoids are the posterior attachments of both the true and false vocal folds. Opening and closing of the glottis is accomplished by action of muscles that move the arytenoids. There is a mucosal bridge between the epiglottis and the arytenoid on each side, known as the aryepiglottic fold. These folds serve as levees between the esophagus and airway, by separating the piriform fossae from the glottis. The piriform fossae are mucosal-lined spaces lateral to the aryepiglottic folds but medial to the laryngeal skeleton (Figs. 61.2 to 61.4), and are the pathways by which ingested food and liquid are conveyed to the esophagus.

Skeleton

The laryngeal skeleton is made up of several cartilages and one bone strung together in series and suspended from the skull base and mandible (Fig. 61.5). Laryngeal motion can be caused by both intrinsic muscles, which arise and insert onto laryngeal cartilages, and extrinsic muscles, which connect the larynx to other structures. Also, descent of the trachea during inspiration produces widening of the glottis. This phenomenon is a result of the ligamentous interconnections of the laryngeal skeleton.

The hyoid, which supports the larynx and stabilizes the hypopharynx, is roughly U shaped, with the two free ends projecting posteriorly as the greater cornua. The lesser cornua are two small bumps on the superior anterior surface. The hyoid is connected to the thyroid cartilage by the broad thyrohyoid membrane. A bursa in this membrane enhances vertical mobility of the larynx. Laterally, the edges of the membrane thicken to form the thyrohyoid ligaments.

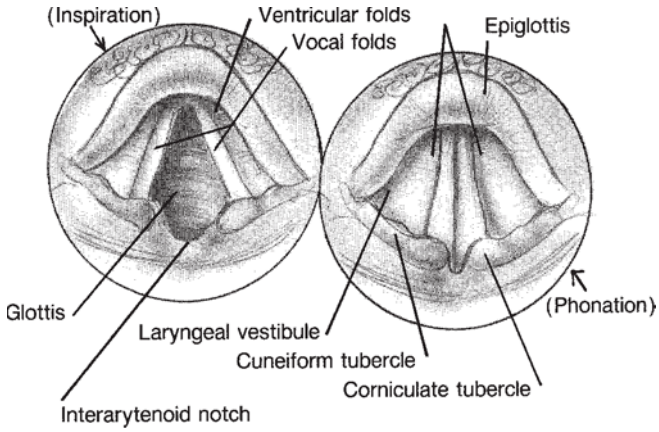


Figure 61.3 Endoscopic view of the larynx.

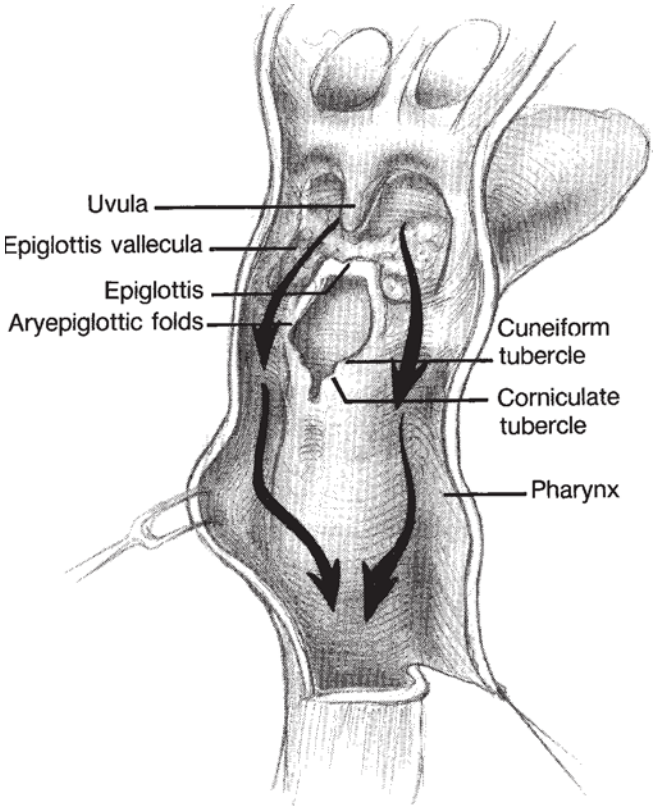


Figure 61.2 Posterior view of anterior airway.

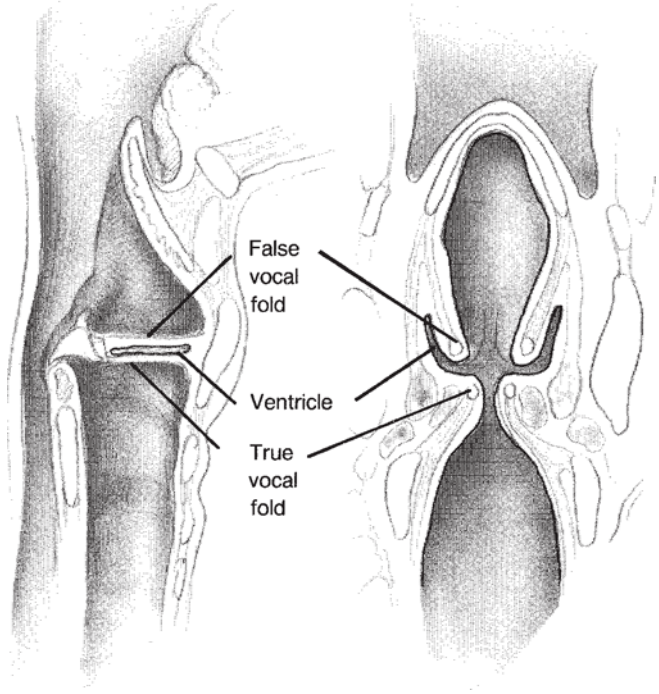


Figure 61.4 Vertical section through the larynx.

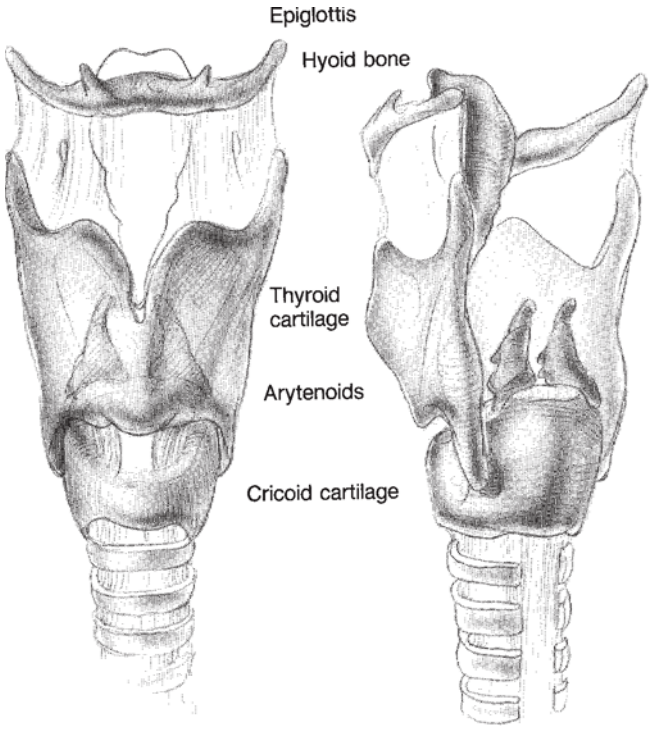


Figure 61.5 Laryngeal skeleton.

The thyroid cartilage is composed of two halves fused anteriorly at a sharp angle (90 degrees in males and 120 degrees in females). The posterior border has superior and inferior cornua. The superior cornu attaches to the thyrohyoid ligament, whereas the inferior articulates with the cricoid cartilage. The thyroid cartilage begins to gradually ossify after the age of 20. This process accounts for many age-related changes in pitch and resonance of the voice.

The epiglottis is a fibroelastic cartilage, attached anteriorly in the midline to the inner surface of the thyroid cartilage and supported by the hyoepiglottic ligament. The free end of the epiglottis projects into the hypopharynx.

The cricoid cartilage is the skeletal support of the subglottis, which is the portion of the larynx below the vocal folds. The subglottis is the only point in the airway with a completely rigid diameter. It has a smaller cross-sectional area than the trachea, so that a single foreign body that is small enough to pass through the subglottis does not cause total airway obstruction. Anteriorly, the cricoid is about 1 cm high, with a smooth curved surface. Posteriorly, it is 2 to 3 cm high, and the superior surface is flattened centrally to provide an area of articulation for the arytenoid cartilages. Posterolaterally, on each side, the cricoid articulates with the inferior cornu of the thyroid cartilage to form a visorlike apparatus, allowing rotation in a sagittal plane, which opens or closes the anterior cricothyroid space.

Each arytenoid cartilage is a somewhat pear-shaped mass. The broad base articulates with the cricoid in a complex synovial joint, which is essentially a shallow ball and socket, allowing multiaxial rotation but minimal translation (5). The vocal process, an anterior and medial projection of the arytenoid, is the posterior segment of the vocal fold (Fig. 61.6). Two other small sesamoid cartilages, the corniculate and the cuneiform, are located superior to the arytenoid and support the aryepiglottic fold.

Two fibroelastic membranes are important components of the larynx. The conus elasticus provides support to the vocal fold. From its lateral attachment to the cricoid, it extends anteriorly to the midline lower edge of the thyroid cartilage and posteriorly to the vocal process of the arytenoid. Its free edge forms the vocal ligament. The quadrangular membrane supports the supraglottis. It connects the epiglottis with the arytenoid and the corniculate cartilages. The superior free edge is draped in mucosa to form the aryepiglottic fold, whereas the inferior edge is a part of the false vocal fold (Fig. 61.7).

Muscles

Motion of the vocal folds is affected primarily by the intrinsic laryngeal muscles. It should be noted that each laryngeal muscle exerts a unique torque on the arytenoid. Physiologic motion results from the net effect of all muscles activated at any point in time (6). Thus, the vocal folds do not just open and close, but move in three-dimensional space and change shape.

The posterior cricoarytenoid muscle (PCA), the only abductor of the glottis, originates from the posterior surface of the cricoid and inserts onto the muscular process of the arytenoid. Contraction of this muscle externally rotates the arytenoid, displacing the vocal process superiorly and laterally, resulting in abduction of the glottis. However, the PCA is also activatated during phonation, presumably to stabilize the arytenoid and resist the anterior traction exerted by adductor muscles. Actually, the PCA consists of two compartments, which are innervated separately, and differ in fiber-type composition (7). The two compartments also differ in their action on the arytenoid. The horizontally oriented compartment causes rotation around a more vertical axis than does the oblique compartment (5). Potential differences in the physiologic function of the two compartments remains to be elucidated.

The lateral cricoarytenoid muscle is the primary adductor of the larynx. It originates on the lateral aspect of the cricoid and inserts onto the muscular process of the arytenoid. This muscle pulls the muscular process forward, rotating the vocal process medially. The thyroarytenoid muscle arises from the anterior inner aspect of the thyroid cartilage to insert on the vocal process of the arytenoid. The human thyroarytenoid muscle contains at least two compartments: the medial thyroarytenoid (vocalis) and the lateral muscular thyroarytenoid. The lateral portion has significant adductor action; however, isolated

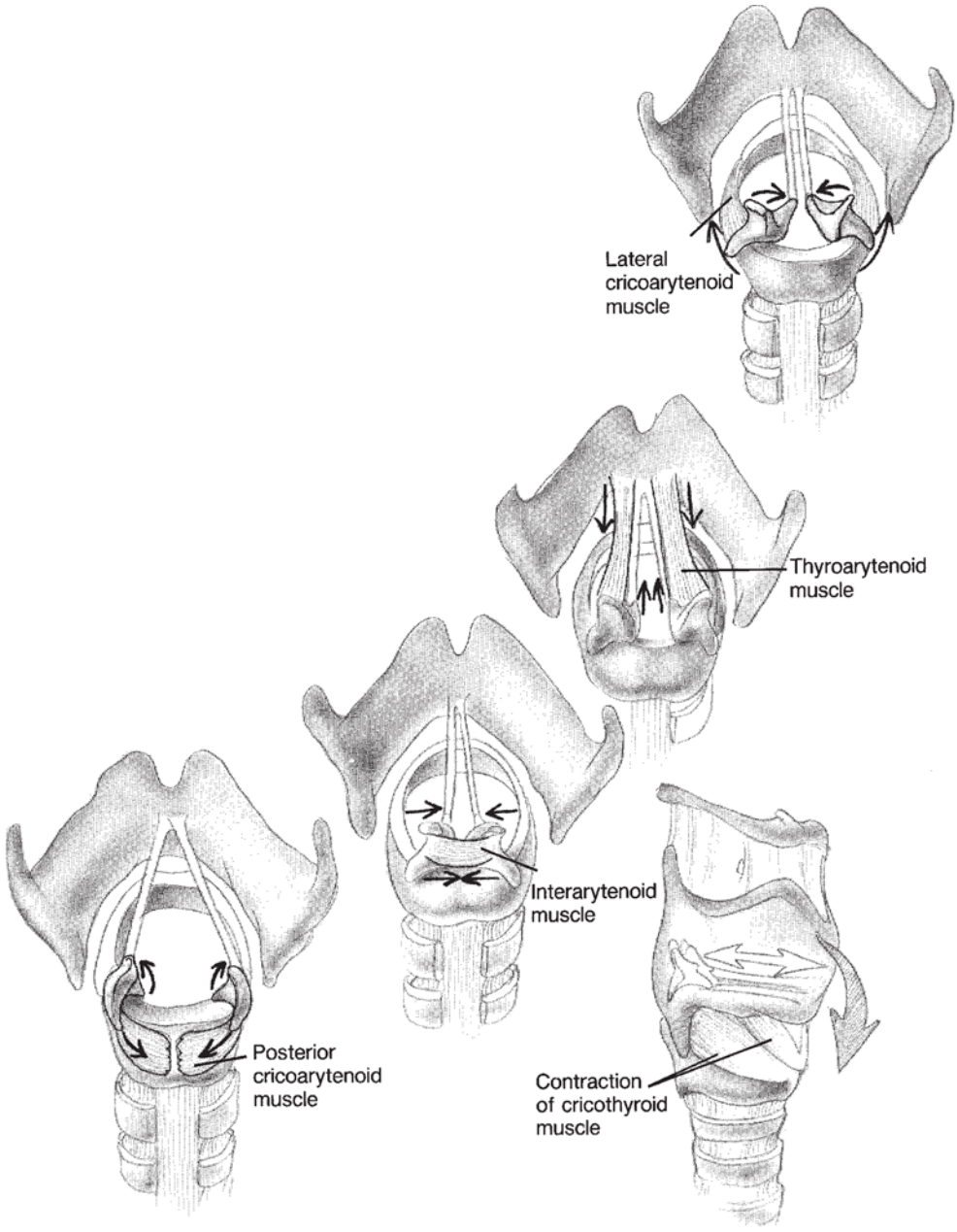


Figure 61.6 Laryngeal muscles.

contraction of the vocalis does not adduct the vocal fold, and actually produces slight abductor force (6). The vocalis does exert anterior traction on the vocal process, increasing vocal fold tension, thickness, and stiffness. In the absence of cricothyroid muscle contraction, it also reduces tension in the mucosal cover. The cricothyroid muscle pulls the cricoid and thyroid cartilages together anteriorly to increase the length and tension of the vocal folds. The interarytenoid muscle, the only unpaired laryngeal muscle, rocks the arytenoids together posteriorly (Fig. 61.6). Electromyography (EMG) studies indicate that it participates in adduction (8); however, a recent study indicated that isolated contraction of the IA abducts the vocal folds (6). The smallest laryngeal muscle, a very small band of muscle fibers between the epiglottis and arytenoid, constricts the supraglottic inlet and is probably responsible for false vocal fold adduction in functional and compensatory hyperfunction (9).

Extrinsic laryngeal muscles include the mylohyoid, digastric, and stylohyoid muscles, which suspend the larynx superiorly, and the cervical strap muscles: the omohyoid, sternohyoid, sternothyroid, and thyrohyoid. The extrinsic muscles elevate or depress the larynx or move it anteriorly or posteriorly. The extrinsic muscle activity can indirectly adduct, abduct, or tense the vocal folds or constrict the supraglottis.

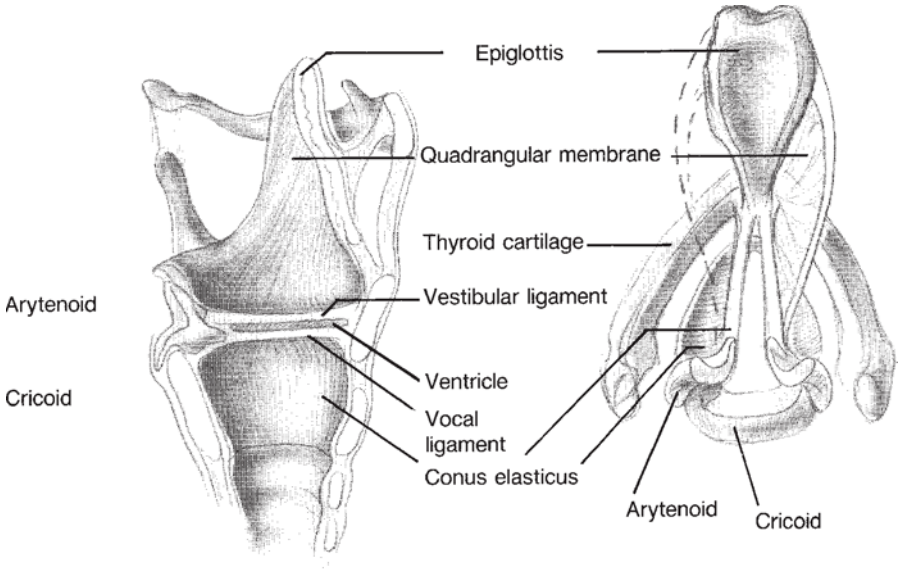


Figure 61.7 Fibroelastic membranes.

Nerve Supply

The vagus nerve supplies the larynx through two branches, the superior laryngeal nerve (SLN) and the recurrent laryngeal nerve (RLN). The SLN exits the vagus below the nodose ganglion and branches into two divisions, the internal branch, which enters the larynx laterally through the thyrohyoid membrane, and the external branch, which travels to the cricothyroid muscle. The RLN does not travel straight from the vagus to the larynx but first descends into the upper mediastinum. The right RLN curves back upward around the subclavian artery, whereas the left descends to the ligamentum arteriosum, a fibrous band connecting the aortic arch to the pulmonary artery. The nerves then ascend in or near the tracheoesophageal groove to enter the larynx. The development of the branchial arterial arch and nerve system during embryogenesis is responsible for the circuitous route of these nerves. The RLN and SLNs both contribute branches to form Galen loop, a nerve that runs submucosally along the posterolateral surface of the larynx (10).

Laryngeal mucosal sensation is mediated by both the SLNs and RLNs. The internal branch of the SLN is primarily sensory, carrying fibers from the supraglottis and vocal folds. The RLN mediates sensation from the subglottis and trachea.

A simplified view of motor innervation of the larynx is that the external branch of the SLN supplies the cricothyroid muscle, while the RLN supplies all other intrinsic laryngeal muscles. The interarytenoid muscle is bilaterally innervated, receiving motor fibers from both RLNs. However, there is a long-standing controversy regarding the possible contribution of internal SLN fibers to the motor innervation of the interarytenoid muscle. In 1929, nerve fibers from the SLN were reported to pierce the interarytenoid muscle (11). But it has been generally believed that these were sensory fibers that passed through the muscle to reach the mucosa (12). Detailed dissection using Sihler stain has provided stronger evidence that SLN fibers as well as RLN innervate the muscle and that the muscle received bilateral innervation (13). Detailed dissections have also documented that besides Galen loop, there are numerous other connections between the SLN and RLN that are variable, yet pervasive, which raise the possibility that motor control is not neatly compartmentalized between the two nerves (14). Support for this was provided by a recent EMG study in patients undergoing laryngectomy (15). In 7 of 13 patients, stimulation of the RLN resulted in a compound action potential of the cricothyroid muscle in response to stimulation of the RLN in 7 patients and in 3 patients, stimulation of the external SLN activated the posterior cricoarytenoid muscle. The variations in intralaryngeal neural connections may have significance in laryngeal paralysis and reinnervation.

Extralaryngeal branching of the RLN is also common and variable. A recent study in 579 patients undergoing thyroid or parathyroid surgery found branching on at least one side in nearly half the patients and bilateral branching in nearly 10%. Intraoperative stimulation indicated that all motor supply, both adductor and abductor, was contained within the anterior branch (16). Within the larynx, the terminal branch of the RLN supplies the transversus abdominis (TA) muscle. But the nerve supply to the PCA is not discrete and is highly variable. A recent anatomic study in 43 cadaver larynges found 1 to 5 direct branches to the PCA from the RLN and usually at least one branch from the nerve to the interarytenoid muscle. All PCA muscles received nerves arising from the anterior division of the RLN, while less than half received some innervation from the posterior branch (17). This fragmented and variable nerve supply to the PCA muscle is likely one reason why spontaneous reinnervation of this muscle is poor in comparison to that of adductory muscles (18).

Mucosal Cover

The mucosal cover of most of the upper airway is respiratory epithelium, with numerous mucous glands

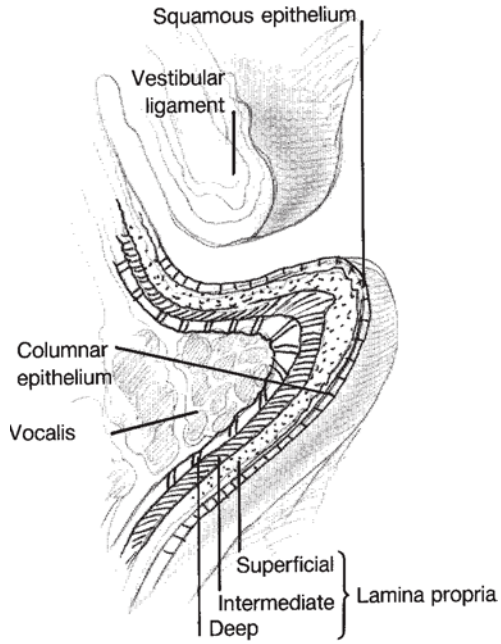


Figure 61.8 Vocal fold mucosa.

(Fig. 61.8). Over the free edge of the vocal fold, however, mucosa is adapted for periodic vibration with squamous epithelium and no mucous glands. A highly specialized lamina propria separates the epithelium from underlying muscle (19). The lamina propria serves as a shock absorber, or impedance matcher, so that the epithelium can vibrate freely, without restriction by the bulky underlying muscle. The lamina propria of the vocal fold contains three layers: superficial, intermediate, and deep. Each layer has unique mechanical properties because of varying densities of elastic and collagenous fibers. The deep layer of the lamina propria contains densely organized band of collagen fibers that penetrate superficially into the vocalis muscle. This layer is about 36% of the lamina propria. The intermediate layer occupies about half the thickness of the lamina propria. Collagen fibers are less dense and there are numerous elastic fibers. The superficial layer, immediately below the basement membrane of the epithelium, contains loosely orgainzed collagen fibers and accounts for about 13% of the lamina propria. The superficial layer of the lamina propria is often referred to as Reinke space, although it is not actually a potential space.

RESPIRATORY PHYSIOLOGY OF THE LARYNX

The most primitive function of the larynx is that of a sphincter, preventing the ingress of anything other than air into the lungs. Other functions include coughing, Valsalva maneuver, and the regulation of airflow in and out of the lungs. The larynx also serves as a sensory organ and contains receptors that influence the control of breathing and even affect cardiovascular function.

Cough

Cough ejects mucus and foreign matter from the lungs and helps to maintain patency of the pulmonary alveoli (20). Cough may be voluntary but more often occurs in response to stimulation of receptors in the larynx or lower respiratory tract. A greater stimulus is required to produce a cough during sleep, and in deep sleep a stimulus must first result in arousal to a lighter level of sleep before cough occurs.

A cough has three phases: inspiratory, compressive, and expulsive. First, the larynx opens very widely to permit rapid and deep inspiration. If the cough is voluntary, the degree of glottal abduction and inspiratory effort is proportional to the intended strength of the cough. The compressive phase is produced by tight closure of the glottis and strong activation of expiratory muscles. During the expulsive phase, the larynx suddenly opens widely, with a sudden outflow of air in the range of 6 to 10 L/s.

Valsalva Maneuver

The true vocal folds offer more resistance to inspiratory than to expiratory airflow. However, very tight closure of both true and false vocal folds enables the larynx to resist very strong expiratory forces. Forced expiration against a tightly closed glottis is known as the Valsalva maneuver. It is important in defecation because the pressure is transmitted to the abdominal cavity. Valsalva also serves to stabilize the thorax during heavy lifting by the arms.

Regulation of Airflow

The larynx is ideally located to regulate the flow of air in and out of the lungs and is better adapted than any other portion of the respiratory tract for producing sudden alterations in resistance to airflow. Observations of laryngeal movement demonstrate that the glottis widens during inspiration and narrows during expiration, and this movement with breathing varies with respiratory demand. Opening, or abduction of the larynx, facilitates breathing by decreasing resistance to airflow. Two forces contribute to inspiratory opening of the larynx: longitudinal tension on the laryngeal skeleton, caused by the descent of the trachea, and contraction of the posterior cricoarytenoid muscle. Both these forces increase during hyperpnea. Active laryngeal abduction is a primary action of breathing, because the posterior cricoarytenoid muscle consistently begins to contract before the diaphragm with each inspiration. The larynx opens more widely during inspiration with increasing effort of breathing and in response to negative upper airway pressure.

Under most conditions of breathing, respiratory rate is primarily controlled by varying the rate of exhalation. During quiet breathing, exhalation is mostly a passive phenomenon, as inspiratory muscles, including the diaphragmatic and intercostal muscles relax, and the

diaphragm and ribcage relax and recoil. The posterior cricoarytenoid muscles also relax during expiration resulting in expiratory adduction of the vocal folds, which prolongs the expiratory phase. The TA muscle is usually quiet during sleep and basal breathing. But during conscious breathing, the TA regulates the duration of expiration and the pattern of expiratory airflow. Expiratory adduction of the vocal folds also increases transglottic resistance, and can therefore provide positive end expiratory pressure in the lower airway.

As respiratory demand increases, expiratory muscles in the abdominal wall and rib cage are recruited to force air out of the lungs, accelerating the rate of expiration. Expiratory activity of the posterior cricoarytenoid muscle is also recruited during labored breathing. With increasing respiratory drive the PCA continues to contract during expiration, after the diaphragm has relaxed. This results in decreased glottic resistance and faster outflow of air, which shortens the duration of expiration and increases the rate of breathing.

In addition to dynamic control of airflow, the configuration of the static larynx exerts mechanical influences on airflow. At any given glottic aperture, resistance to airflow in the inspiratory direction is much greater than resistance to expiratory flow. Because of this, conditions that cause laryngeal obstruction, such as edema, papillomas, or laryngeal paralysis, usually produce inspiratory stridor before expiration is impaired.

Sensory Input to Respiratory Control

The larynx is not only an effector organ; it is also richly supplied with a variety of sensory receptors that exert influences on breathing and cardiovascular function. There are several times more sensory fibers from the larynx than from the lungs, which have internal surface areas of several square meters. Some responses to laryngeal stimulation are appropriate and beneficial; however, some responses such as laryngospasm and cardiovascular collapse appear maladaptive. These reflexes can be produced experimentally by electrical stimulation of the SLN. Such extreme responses probably represent an oversaturation of pathways that serve a useful function at lower levels of input. Three major types of laryngeal receptors are activated by the process of breathing and have an influence on the central control of breathing: negative pressure receptors, airflow (cold) receptors, and "drive" receptors, which are probably proprioceptors that respond to respiratory motion of the larynx (21). Laryngeal receptors also respond to touch and chemical stimuli.

Negative upper airway pressure increases the inspiratory activation of upper airway dilating muscles, including the genioglossus, the geniohyoid, the ala nasi, and the posterior cricoarytenoid muscle. Negative pressure sensation is primarily mediated by the SLN and is believed to be an important stimulus for maintaining upper airway patency.

Airflow receptors have been identified in the nose and the larynx and appear to modulate central respiratory drive. Stimulation can decrease respiratory rate or even cause apnea. Airflow receptors behave as thermistors, responding to the temperature drop induced by air flowing through. Thus, laryngeal flow receptors do not respond to air that has been warmed and humidified by the nose but are activated by air that comes in through the mouth, particularly in cold and dry weather.

A number of responses can be elicited by mechanical stimulation of the larynx, including apnea, laryngospasm, and cardiovascular collapse. Because the larynx is in a very protected position, such responses do not usually occur naturally. Laryngospasm, the forceful and prolonged closure of the larynx, is most often seen in the operating room in response to endotracheal intubation. It is most likely to occur when the patient is well oxygenated and under light anesthesia. It occurs in the conscious state under certain pathologic conditions such as upper respiratory infection. Sometimes a decreased threshold for laryngospasm can persist for many months after an infection, resulting in frequent episodes of frightening total airway obstruction. Mechanical or chemical stimulation of the larynx can produce prolonged bronchoconstriction.

The laryngeal adductor reflex is a rapid brief closure of the true vocal folds in response to appropriate stimulation of the mucosa innervated by the SLN. Sensory deficits in the laryngopharyngeal region can result in dysphagia and aspiration. Recent studies have shown the importance of sensory testing in this region, especially in predicting aspiration pneumonia risk in patients with dysphagia (22).

Apnea is a prominent response to laryngeal stimulation, prevents the aspiration of the stimulating material into the lower airway. Apnea may occur in response to such diverse chemical agents such as ammonia, phenyl diguanide, and cigarette smoke. Water in the larynx can also inhibit inspiration under certain conditions, such as general anesthesia, and during upper respiratory infections. In infants, water in the larynx can produce prolonged apnea. The typical response to water, however, in the normal conscious adult is vigorous coughing. It has been suggested that laryngeal reflexes may be implicated in the pathogenesis of sudden infant death syndrome, because respiratory reflex pathways go through a process of maturation in infancy that make laryngospasm and reflex apnea much more likely to occur during the interval of peak incidence of sudden infant death syndrome (23).

CIRCULATORY REFLEXES

Stimulation of the larynx can produce changes in heart rate and blood pressure. This effect is most noticeable during induction of general anesthesia in response to endotracheal intubation. It may also occur in natural circumstances such as OSA. When upper airway patency is not maintained

during sleep, the resulting increase in negative airway pressure can stimulate receptors in the larynx so strongly that cardiac arrhythmias occur. The direct result of laryngeal stimulation on blood pressure is hypertension. However, if laryngeal stimulation produces significant bradycardia or ectopy, the indirect result can be hypotension.

The pathways responsible for mediating cardiovascular responses to laryngeal stimulation are not clearly understood. The afferent limb is the SLN. Transection of the SLN abolishes cardiovascular responses to laryngeal stimulation, and electrical stimulation of this nerve affects heart rate and blood pressure. The efferent limb for bradycardia is clearly the vagus nerve, but the efferent limb for blood pressure elevation is not known. Intervening central connections have yet to be identified, but there is evidence that sympathetic response to laryngeal stimulation may be mediated through central respiratory control mechanisms. Recordings from cervical sympathetic roots in the neck have documented phasic activity with breathing, and this activity is suppressed by electrical stimulation of the SLN.

SPEECH

The human voice results from the coordinated interaction of the larynx, lungs, diaphragm, abdominal muscles, throat, neck muscles, lips, tongue, buccinators, and soft palate. Speech consists of three component processes: phonation, resonance, and articulation. Phonation is the generation of sound by vibration of the vocal folds. Resonance is the induction of vibration of the rest of the vocal tract to modulate and amplify laryngeal output. Articulation is the shaping of the voice into the words that characterize human speech.

Phonation

Sound is produced by the larynx when expiratory airflow induces vibration of free edges of the vocal folds as a result of the interaction of aerodynamic and myoelastic forces. Five conditions must be met to support normal phonation: appropriate vocal fold approximation, adequate expiratory force, sufficient vibratory capacity of the vocal folds, favorable vocal fold contour, and volitional control of vocal fold length and tension. Just before phonation, the vocal folds are approximated in the midline. Exhalation then causes subglottic pressure to rise until the vocal folds are pushed apart. This separation produces a rapid decrease in subglottic pressure. The vocal folds then return to the midline as a result of sudden decrease in pressure, elastic forces in the vocal fold, and the Bernoulli effect. Pressure in the trachea builds once more, and the cycle is repeated. During modal phonation, the vocal fold essentially vibrates as two masses, with the upper edge lagging behind the lower edge. This results in a traveling wave, from caudal to rostral, known as the mucosal wave. In falsetto mode, the vocal fold is thinner and vibrates as a single mass; therefore, the mucosal wave is absent.

Vocal fold position is a critical factor in phonation. When the vocal folds are loosely approximated, the mucosa can easily swing open to produce wide fluctuations in pressure. If the vocal folds are tightly compressed, more expiratory effort is required to initiate and sustain phonation. If a gap exists between the vocal folds, efficiency is markedly reduced and a higher airflow is required to induce vibration. The resulting voice is breathy, and duration of phonation is shortened. With a wide gap, the airflow requirement exceeds the expiratory capacity, and the voice may dwindle to a whisper.

In normal conversational speech, the driving force for phonation is passive exhalation, the release of energy stored in the rib cage and diaphragm. Deeper inspiration stores more energy and therefore permits louder and longer phonation. Contraction of abdominal and intercostal muscles provides additional expiratory force during greater phonatory efforts such as singing or shouting. An increase in perceived loudness of phonation during singing can be achieved by a technique known as vibrato: Expiratory effort is usually cyclically varied to superimpose slower frequency pressure changes in the vocal output.

The capacity of the vocal folds to vibrate periodically depends on the homogeneity and flexibility of the mucosa and on the integrity of the lamina propria. Edema, which increases the impedance of the submucosa, impairs vibration. Trauma, infection, or surgery can produce scars that tether the epithelium to the underlying muscle and block the normal propagation of mucosal waves.

The surface contour of the vocal folds determines the shape of the glottal tract. To support normal phonation, the medial surfaces of the vibratory portions of the vocal folds must be roughly parallel. If the vocal muscle is atrophic, then the medial surface is concave rather than convex, resulting in a convergent glottis, which is unfavorable for phonation.

Changes in vocal fold length and tension influence the fundamental frequency of vibration of the vocal folds to produce dynamic inflections of the voice. Frequency can also be controlled by changing the thickness of the fold or by limiting the length of the vocal fold segment that participates in vibration. The physical properties of a larynx determine the range of pitches it can produce. The small larynx of a child has a higher pitch range than the larger larynx of an adult. Young adult males, with longer and heavier vocal folds and a deeper supraglottis, produce the lowest human pitches. In males during puberty, the rapid increase in the size of the larynx often outstrips the capacity for adaptation, resulting in frequent sudden pitch changes. Size is not the only determinant of pitch range, however, because ossification of the thyroid cartilage with increasing age contributes to elevation of pitch.

Resonance

The sound output of the isolated larynx in no way resembles the human voice. Phonatory output is modulated by resonance, the induction of vibration in the chest, pharynx,

and head with selective amplification of certain component frequencies. Resonance not only gives the voice its characteristic acoustic pattern but can also amplify the voice. Vocal training, for singing and acting or public speaking, concentrates heavily on refining and maximizing resonance, so that the loudest and most pleasing sound can be produced with the least amount of strain or pressure on the larynx. Resonance is controlled by altering the shape and volume of the pharynx, by raising or lowering the larynx, by moving tongue or jaw position, or by varying the amount of sound transmission through the nasopharynx and nose.

Articulation

The formation of consonants and vowels is largely controlled by the lips, tongue, palate, and pharynx. The larynx also participates in articulation, by coordinating the beginnings and endings of phonation to coordinate with upper articulators, producing voiced and unvoiced sounds.

Sensory Input to Speech Control

One of the primary mechanisms for controlling phonatory output during speech is auditory feedback. However, when we speak or sing, we do not simply make a random sound and then adjust the pitch and quality; we preset the vocal tract for the intended sound. This skill, learned very early in life, uses cues that are largely unconscious. Other evidence for the involvement of nonauditory cues in voice control is the ability of deaf patients to maintain fairly normal speech patterns. Well-trained singers are able to perform with good control of pitch and loudness even when they cannot hear their own voices. Tactile sensation of induced vibration in the face, throat, and chest is important to the trained singer. The degree to which receptors in the larynx influence vocal control is not known. Stimuli such as contact of mucosal surfaces, air pressure, stretch of joint capsules, and tension in muscles are indicators of laryngeal posture and expiratory effort and can be important in speech control.

HIGHLIGHTS

- The human upper airway is distinguished from that of all other mammals by the descent of the larynx in early development, which abolishes the separation of channels for respiration and deglutition.
- Patency of the upper airway during breathing depends on active contraction of muscles that pull the hyoid and tongue base forward to dilate the pharynx.
- Vocal fold motion is controlled by muscles that act on the arytenoid.
- Tight laryngeal closure is required for the production of an effective cough.
- The mucosal cover of the vocal fold is highly specialized for phonation.
- Human speech has three components: phonation (sound production), resonance (amplification and filtering of sound), and articulation (formation of words).
- The mucosal cover of the vocal fold is highly specialized for phonatory vibration.
- The pitch of the voice is controlled by changes in length and tension of the vocal folds.
- The sound of the human voice is greatly determined by the resonance of the upper vocal tract.
- Sensation in the larynx and pharynx is very important in swallowing and deficits can lead to aspiration.
- Stimulation of the larynx can result in laryngospasm, breathing changes, bradycardia, or hypotension.

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Upper Airway Stenosis: Evaluation and Management

62

Philip A. Weissbrod *Albert L. Merati*

Upper airway stenosis is an umbrella term for scarring or cicatrix of the trachea, subglottis, glottis, or supraglottis that can lead to airway obstruction. Stenosis can be limited to soft tissue scarring and fibrosis, involve cartilaginous remodeling from chondritis, or be a combination of the two. On a patient level, symptomatic stenosis is debilitating leading to significant reduction of quality of life due to obstructed breathing patterns and voice alterations (1). For many patients, especially those with postintubation-related stenosis, the difficulty breathing that comes with an airway lesion can potentiate their medical condition or significantly hinder their recovery. For all patients with airway stenosis at any level, their road to a diagnosis can often be laborious, time-consuming, and at the expense of considerable personal and societal resources. Many of them have seen numerous physicians and traveled a road fraught with misdiagnosis and unclear answers. Often patients present having been misdiagnosed with asthma, vocal fold dysfunction, or other respiratory conditions (2,3). During this period of delay between onset of symptoms and diagnosis, especially if there is significant symptomatology, their function can be limited and both their physical and mental well-being impaired limiting capacity for work and normal daily living.

In this chapter, subsites of airway stenosis including supraglottic, glottic, subglottic, and tracheal are independently addressed. Common causes, staging systems, treatment methods, and outcomes are discussed in an effort to provide overview of the current state of medical and surgical management. Etiology and evaluation of airway stenosis are discussed in general terms for all subsites, as there is significant overlap between subsites. When appropriate, specifics for each subsite are also discussed. Discussion of pediatric and congenital stenosis is not included as it is covered elsewhere in the text.

ETIOLOGY

The etiology of airway stenosis is varied (Table 62.1). While certain sites are more prone to specific disease processes, many can cause scarring anywhere between the supraglottis and trachea.

The origin of airway stenosis encompasses a broad spectrum of disease processes. Inflammation is the common link between all the disease processes. Injury to the airway can occur acutely from trauma, intubation, infection, endoscopy, or any form of surgery to the intrinsic airway that can cause mucosal or cartilaginous injury. Systemic processes such as laryngopharyngeal reflux, autoimmune disease, and neoplasm can create an environment of acute and/or chronic insult, which ultimately leads to scar and stenosis. Injury that is circumferential, in particular, can lead to greater likelihood of airway stenosis as noted by Andrews and Pearson (4) in their 2-year prospective study of intubated patients.

A number of canine models of airway stenosis have been created using drills, surgical dissection, or endotracheal tubes as the mechanism of injury. Regardless of the origin of trauma, any mucosal disruption, ulceration, or chondritis can lead to the formation of intraluminal granulation tissue and subsequently damage to the underlying cartilaginous framework, mucosal thickening with submucosal fibrosis, and ultimately, scar formation (5–8).

Trauma

The most common inciting factor for airway stenosis is trauma, most frequently in the form of postintubation injury. An endotracheal tube can create injury at two levels: the glottis due to the rigid tube's wall and the trachea due to cuff pressure (9). An endotracheal or tracheotomy tube has the potential to create a circumferential injury within the

TABLE 62.1 ETIOLOGY OF UPPER AIRWAY STENOSIS

Trauma	Intubation injury
	External blunt trauma
	Penetrating trauma
	Chemical injury
	Iatrogenic/post surgical
Systemic	Wegener's
	Sarcoid
	Amyloidosis
	Relapsing polychondritis
	Pemphigoid/pemphigus
	Laryngopharyngeal reflux
Infectious	Tracheitis
	Ulcerative laryngitis
	Tuberculosis
	Diphtheria
Congenital	
Neoplastic	
Idiopathic	
Post radiation	

trachea (7). Injury can come from direct mucosal abrasion or from vascular compromise as a result of sustained cuff pressure (10). The vascular supply to the tracheal cartilage is derived from small intercartilaginous vessels that create a submucosal plexus (11). A number of these vessels originate from the inferior thyroid artery. Other vascular contributions to the cervical and thoracic trachea include the supreme intercostal, subclavian, right internal thoracic, and innominate artery (12,13). Increased cuff pressures, drops in systemic perfusion, cardiac bypass, and systemic vasculopathy, such as diabetes, can all contribute to local deprivation of blood supply. With ischemia come congestion, edema, and eventually ulceration (14,15). Ulceration can lead to chondritis and necrosis. Healing of necrotic compromised regions occurs by secondary intention leading to scar formation (16).

Size of endotracheal tube, length of intubation, cuff pressure, and traumatic intubation all potentially can increase the likelihood of airway stenosis (17). Postintubation stenosis arose as a frequent disease process in the mid-20th century after an increase in long-term intubation injury as related to poliomyelitis (18). It became clear that the increases in incidence of stenosis was due to injury at the tracheostoma site from surgical manipulation, the presence of a pressurized balloon, and irritation of the tip of the respiration device (19). Localized infection of the stoma and trachea also was found to be a significant risk factor in early animal studies (20).

Over time, a number of mechanisms to reduce injury of the tracheal wall were identified. Early cuff pressures were high: the balloons were initially small in size and required intraluminal cuff pressures of greater than 180 mm Hg to allow for adequate positive pressure ventilation at 20 to 25 mm Hg (21,22). By increasing the size and compliance of the endotracheal and tracheotomy tube balloon subsequently lowering the intracuff pressures, there are fewer tracheal lesions from postintubation trauma seen in the later half of the last century (23,24).

Stenosis, however, can occur with a brief intubation and small endotracheal tube. In addition to tracheal and subglottic stenosis, intubation injury can lead to trauma and scarring of the posterior glottis in the intra-arytenoid region and cricoarytenoid joints, the location within the glottis which receives the most pressure from the presence of an endotracheal tube (25).

Tracheotomy or tracheostomy is the most common form of surgical trauma causing airway stenosis. Stenosis can be at any level along the tracheotomy tube or above the stoma. Postintubation or posttracheotomy stenosis is not uncommon, ranging from 10% to 19%, but typically only is symptomatic in less than 1% of cases (26–28). It is unclear in the current literature if there are any differences in rates of stenosis between open and percutaneous dilational tracheotomy (29,30), however, conceptually, percutaneous tracheotomy may cause greater cartilaginous injury from less controlled entry into the airway leading to destabilization of the laryngotracheal framework (31,32).

Other forms of injury can include laryngotracheal trauma secondary to blunt or penetrating neck trauma, which can lead to cartilaginous framework disruption, mucosal lacerations, and tears, both of which can potentially lead to scarring at any level. Other forms of surgically induced injury along the course of the upper airway can come in the form of thyroidectomy, partial pharyngectomy, partial laryngectomy, tracheal and bronchial surgery, and any endoluminal airway procedure that can lead to inflammation and scarring.

Iatrogenic glottic stenosis can occur with bilateral de-epithelialization of the anterior commissure and anterior true vocal folds leading to anterior glottic web. Once formed, this can be difficult to treat, often requiring multiple procedures and stent or keel placement. Similarly, posterior glottic stenosis (PGS) can occur with excess manipulation of the posterior vocal folds and posterior glottis leading to scar formation and cricoarytenoid joint fixation; however, it should be restated that the most common cause is from endotracheal tubes. It has also been hypothesized that severe coughing can lead to telescoping of the cricoid cartilage over the first tracheal ring leading to vascular insult, which in the setting of poor wound healing can lead to airway stenosis (33).

Systemic Disease

Wegener's granulomatosis is a disease of unknown etiology that can involve the kidney, lungs, and upper respiratory tract. The frequency of airway stenosis in Wegener's, in particular subglottic stenosis varies depending on the series, but can

range from 8.5% to 50% (34–36). While the *subglottis* is the most commonly involved portion of the upper airway, glottic and supraglottic involvement has also been noted. Biopsy of the region can show noncaseating granulomas; however, biopsy is not always diagnostic. Antineutrophil cytoplasmic antibodies (c-ANCA) are greater than 90% positive during the active vasculitic phase of the disease and can be a useful adjunct in diagnosis (37). Adequate systemic control of disease is recommended prior to entertaining definitive treatment for stenosis. Systemic control can include medications such as methotrexate, cyclophosphamide, and in refractory cases rituximab (38).

Relapsing polychondritis is another systemic disease process that has consequences in the airway. Most commonly associated with inflammation of the cartilaginous structures of the ear, it can also involve the nose, joints, larynx, and tracheobronchial tree. In a large cohort series of patients, 31/145 patients (21%) with polychondritis had airway manifestations. Of the 31 patients with airway symptoms, 8 (26%) had subglottic stenosis, 8 (26%) had other foci of stenosis within the tracheobronchial tree, and the remainder had diffuse malacia. Forty percent required surgical intervention including tracheotomy and dilation (39).

Laryngopharyngeal Reflux

Laryngopharyngeal reflux was first suggested as a culprit of airway stenosis in the early 1980s (40,41). In recent years, there has been increasing evidence that chronic acid injury to the lining of the airway can be caustic and lead to, among other things, stenosis. There have been numerous studies aimed at teasing apart the causative role of reflux in subglottic and tracheal stenosis. Koufman (42), in 1991, studied 32 patients with laryngotracheal stenosis and noted laryngopharyngeal reflux in 78%. Others have identified similar trends in 24-hour pH probe results establishing laryngopharyngeal reflux as one of the many factors that play a role in the development of airway stenosis (43–45).

The intubated patient is at particular risk of acid-related injury given the presence of an endotracheal tube and its associated trauma. Supine position and the use of a nasogastric or orogastric feeding tube has been suggested to increase rates of reflux events, aspiration, and ventilator-associated pneumonia in the intubated patient (46,47). Currently, most ICUs place patients in a semirecumbent position (45 degrees), which has been shown to reduce ventilator-associated pneumonia and presumably gastric reflux events (48). Additionally, the widespread use of acid suppression medication in ICUs has likely further reduced acid-related injury in this patient population.

Idiopathic Stenosis

Idiopathic laryngotracheal stenosis occurs predominantly in childbearing aged women, ages 30 to 50. It is often a diagnosis of exclusion; patients usually have no history of airway trauma, systemic disease, or other identifiable etiology of stenosis. Typically, idiopathic stenosis involves a short segment of the subglottis and/or upper trachea; it manifests as a circumferential fibrous ring. These are usually isolated single level lesions as apposed to intubation injury-related stenosis, which often can have multilevel involvement (49). Interestingly, symptomatically, idiopathic stenosis patients tend to have less symptoms and individuals maintain normal respiratory effort until a critical stenosis has formed leading to relatively sudden onset of symptoms. Pathologically, idiopathic stenosis also behaves differently than stenosis from intubation trauma. Lacking is chondromalacia, a common factor seen in other forms of stenosis, and instead, there is a dense fibrotic process of the lamina propria (50).

Given the age and sex predilection, there is question as to the role of hormones in the development of idiopathic stenosis. Subglottic tissue has been evaluated for the presence of estrogen receptors; however, initial studies have failed to identify a link leaving the association still unfounded (51,52).

There is considerable debate of the role of laryngopharyngeal reflux as the underlying cause of idiopathic stenosis; however, to date there has been no definitive evidence to support this. Blumin and Johnston recently evaluated for the presence of pepsin in patients with idiopathic glottic stenosis. Pepsin serves as a highly sensitive and specific marker for the exposure of mucosal tissue to gastric contents (53). They noted 13/22 patients with idiopathic stenosis (59%) had evidence of pepsin in the stenotic tissue as apposed to controls that had no pepsin noted in biopsy specimens ($P = 0.041$) (54). Despite the relatively high rate of pepsin identified, there was not a statistically significant correlation between 24-hour pH probe and the presence of pepsin, which could relate to the deficiencies in acid testing alone or temporal limitations of testing methods.

It seems plausible that a certain percentage of patients with idiopathic stenosis may have stenosis from laryngopharyngeal reflux, but not all of this population tests positive leaving the underlying process, in many patients, still unknown. Grillo et al. (55) commented in their series of 72 patients with idiopathic stenosis, that only 5 (7%) required additional dilations despite cessation of antireflux medication further strengthening the argument that idiopathic stenosis and reflux-related stenosis are distinct entities.

Laryngitis and Tracheitis

Infection of the upper airway is a consideration in the development of tracheal stenosis. As mentioned previously, inflammatory lesions and ulcerations can lead to chondritis, granulation tissue, and scar formation. Theoretically, any intraluminal airway infection, whether viral or bacterial,

can incite an inflammatory reaction that can ultimately contribute to the development of airway stenosis, especially in cases where endotracheal intubation is necessary, as the results of multiple insults to the area could be additive. In a small but telling animal study, Squire et al. traumatized rabbit tracheas and inoculated them with *Staphylococcus aureus*. Animals were sacrificed at postoperative day 10. Those treated with antibiotics had significantly lower mean stenosis percentages as compared to those infected tracheas (50.8% vs. 85%) suggesting that infection, in the setting of airway trauma, can significantly worsen the rate and severity of stenosis (8).

Other specific infective processes have no associations with stenosis. In some tuberculosis (TB) endemic regions, TB-related airway stenosis is a common, if not the most common etiology of tracheobronchial stenosis (56). Tracheal lesions in TB can develop from lymphatic spread, direct infection of local tissue via infected sputum, or local extension from paratracheal or mediastinal lymph nodes (57).

EVALUATION

The most important component in understanding stenosis is a history that accounts for all associated risk factors and conditions. An accurate understanding of intubation history and sources of trauma can point toward a culprit etiology. In cases where there is no prior history of trauma, consideration of appropriate infectious, laryngopharyngeal reflux, autoimmune, and systemic diseases should be entertained. Other considerations should include details about the rapidity of symptom development, exercise intolerance, and the effects of airway inflammation such as upper respiratory infections. In patients who are operative candidates, special consideration should be paid to processes that could effect wound healing such as diabetes mellitus, collagen disorders, vascular disorders, history of smoking, and alcohol consumption. Patients can be followed over the time by their subjective respiratory symptoms. Self-assessment of dyspnea at rest or on exertion can be valuable clinical indicators of the need for intervention. The rapidity of symptom return can also help determine the urgency of intervention.

Physical Examination and Office Endoscopy

Physical examination should start with careful observation of both shallow and deep respiration. The presence of stridor indicates obstruction and can point toward the level of obstruction. Low pitch inspiratory stridor indicates supraglottic obstruction. High pitched inspiratory or biphasic stridor suggests laryngeal, subglottic, or tracheal obstruction. The utilization of accessory muscles, suprasternal retractions, or rapid breathing can suggest impending airway compromise and the necessity for intervention either with intubation or tracheotomy.

Examination of the airway is important for characterization as it can dictate treatment options. Flexible or rigid laryngoscopy should be an integral part of airway evaluation. For evaluation of the supraglottis, glottis, and immediate subglottis, transnasal flexible endoscopy with topical nasal anesthetic with 4% lidocaine should be sufficient. In most cases, with proper patient positioning, detailed evaluation as far distal as the subglottis is possible. For patients with heightened laryngeal sensitivity or suspected mid or distal tracheal stenosis, direct application of lidocaine to the glottis allows for transglottic views of the trachea with flexible transnasal laryngotracheobronchoscopy with relatively low risk (58). When assessing stenotic patients, all areas of stenosis and scar should be noted. Dynamic examination of the larynx is important to ensure there is no paralysis or paresis of the vocal folds, a potential source of additional obstruction. Evaluation for mucosal inflammation, edema, erythema, and other signs of laryngopharyngeal reflux should also be noted (59).

If a tracheotomy is present, careful study of the stoma in relation to the cricoid should be performed as this can have bearing on the available surgical options. Examination via trans-stomal flexible tracheoscopy is easily accomplished. If the patient is stable and has a well-established tracheotomy track, the tracheotomy should be removed and the scope retroflexed, to view the subglottis from below.

Imaging

If access to an otolaryngologist or flexible laryngoscope may be limited, plain radiograph can be helpful in outlining the silhouette of the airway. The level and length of the stenosis usually can be visualized with plain radiography, but more detailed information such as thickness of the tracheal wall, further characterization of the lumen, and presence of wall calcifications can only be identified with computer tomography (CT) (60). The presence of calcifications is often seen in cases of postintubation-related trauma; in idiopathic stenosis often there is no calcification evident (61). Noncontrast thin cut CT is a more revealing study and can be helpful in visualizing stenotic airway segments or extraluminal compression from tumors or aberrant blood vessels (62,63). In addition, in situations where there is glottic compromise, CT scan may represent a means of airway evaluation while avoiding the risk associated with transglottic endoscopy.

Despite its many benefits, CT does have limitations in airway evaluation. If the stenotic segment is thin and CT scan slice is thick, a thin stenotic segment can be missed on imaging. In addition, when compared to endoscopy, CT if significantly less accurate in predicting stenotic segment length, an important negative predictive factor in airway surgery (64).

A relatively new imaging technology, *virtual tracheobronchoscopy*, is gaining popularity. This technology takes advantage of CT spiral data acquisition and utilizes the contrast between airway and surrounding tissue to allow for virtual endoluminal navigation through the airway (65,66). In a review of 37 patients, flexible tracheobronchoscopy,

intraoperative endoscopy, CT, and virtual endoscopy all correctly estimated the Cotton-Meyer stenosis grade of stenosis in greater than 94% of cases (67). Considering this, virtual endoscopy may be of particular benefit in patients who have tenuous airways where endoscopic evaluation may be risky or in patients with severe stenosis where the airway distal to the obstruction may not be easily visualized.

Pulmonary Physiologic Testing

The use of physiologic objective testing of the airway can also be helpful. Flow volume loops (FVLs) are the standard method for assessing flow and volume characteristics of the upper airway by plotting the forced vital capacity against the rate of flow. Based on FVLs, airway obstruction can be differentiated into intrathoracic versus extrathoracic and fixed versus mobile obstruction. With a fixed obstruction, there is plateau of flow rates on both inhalation and exhalation as apposed to mobile extrathoracic obstruction which has a plateau on inspiration, and mobile intrathoracic obstruction with a plateau of flow on exhalation (68).

Despite the utility of FVLs, there are some limitations. It appears that they are a good qualitative instrument in determining obstruction but do not necessarily show the correlation between the degree of airway obstruction and severity of breathing symptom (69).

Reflux Testing

Objective reflux testing in patients with symptomatic reflux or idiopathic stenosis is also used by many practitioners (70). The gold standard for testing is dual probe 24-hour pH monitoring (71). More recently, esophageal manometry and impedance testing have been included in the diagnostic armamentarium to provide additional detail about the origin of reflux and the presence of both acidic and nonacidic reflux events. There is considerable debate regarding what represents positive testing. This discussion is outside of the scope of this chapter; however, many believe that any acidic (and even nonacidic) reflux event into the pharynx to be abnormal, especially when considering a patient with airway stenosis.

Direct Microlaryngoscopy and Operative Endoscopy

Operating room-based direct laryngoscopy is an integral part in evaluating all levels of airway stenosis. Careful preoperative planning with the anesthesia team is essential for safe administration of anesthesia and airway control. Aside from standard direct laryngoscopy techniques, advanced intubation techniques such as video-assisted endotracheal intubation and awake fiberoptic nasal intubation can be helpful in the appropriate patient. In cases of advanced glottic and supraglottic stenosis, intubation may be difficult. Rigid ventilating bronchoscopes for emergent intubation are a valuable tool in many cases. The surgical team should also be prepared for the possibility of an emergent tracheotomy if needed, preferentially at or just below the level of stenosis to limit the extent of additional airway injury. Ventilation in stenosis cases can be achieved via endotracheal tube, rigid bronchoscope, or supralesional jet.

Direct laryngoscopy and tracheobronchoscopy can serve as both a diagnostic and, when performed in conjunction with dilation, a therapeutic procedure. Diagnostic information attained from endoscopy should include the level, length, and severity of stenosis, as well as the mobility of the cricoarytenoid joints. Characterization of the stenosis is important. Multisubsite involvement complicates management considerably. Length of stenosis, granulation tissue, and thickness of stenosis are important to note as they can alter therapeutic decision making. In subglottic stenosis and tracheal stenosis, distance from the inferior margin of the vocal fold is important in ensuring that there is sufficient soft tissue proximally to perform a reanastomosis.

NONOPERATIVE MANAGEMENT

Nonoperative management is an important component of the long-term management of stenosis patients. This can include measures to prevent recurrence of stenosis or delay intervention with medical management.

Preventative measures include control of reflux, management of rheumatologic disease, and avoidance of chronic irritants that can cause an inflammatory response. For patients undergoing surgical intervention requiring intubation, the use of small caliber tubes reduces the incidence of intubation-related stenosis (14). For patients who require endotracheal intubation or tracheotomy, using low-pressure cuffs and keeping intracuff pressure less than 30 mm Hg greatly reduces airway injury (72,73). In addition, the use of lightweight swivel tracheal connectors and endotracheal tube support devices has been proven to be an effective resource in reducing incidence of intubation and tracheotomy-related stenosis in cases that require mechanical ventilation (4).

In symptomatic stenosis patients, oxygen supplementation, air humidification, systemic steroid application, and antibiotics when appropriate can all provide symptomatic relief in those who are acutely symptomatic. In patients with severe obstruction who are not candidates for dilation or resection, or who are symptomatic from an inflammatory exacerbation such as an upper respiratory infection, the use of heliox can be valuable in avoiding intubation, which could theoretically potentiate additional inflammation and worsen stenosis (74).

SUPRAGLOTTIC STENOSIS

Supraglottic stenosis leading to obstruction is most often in the region of the laryngeal inlet (Fig. 62.1). Postsurgical scarring, infection, caustic ingestion, and autoimmune diseases can lead to contractile scarring of the aryepiglottic folds, arytenoids, epiglottis, and intra-arytenoid region and

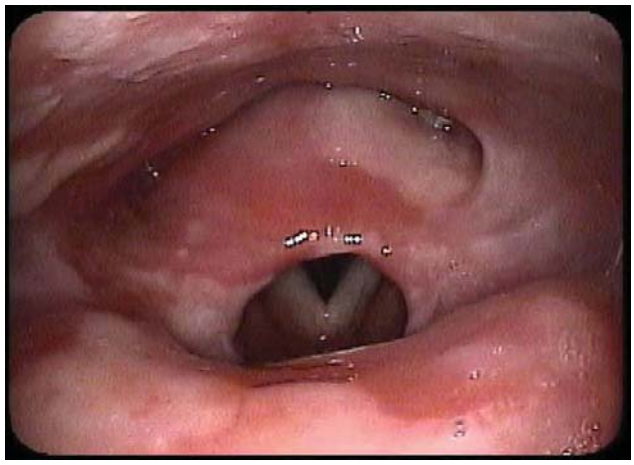


Figure 62.1 Flexible fiberoptic laryngoscopy of supraglottic stenosis in a patient with bullous pemphigus.

subsequent narrowing of the laryngeal inlet. Anterior cervical trauma that leads to injury of the thyroid cartilage and/or hyoid can displace the epiglottis posteriorly and narrow the supraglottic airway. Depending on the extent of involvement, symptoms can vary from stridor to severe airway obstruction.

Correction of supraglottic stenosis can be performed both endoscopically and via external neck incision with laryngofissure, and in extreme cases, in the form of supraglottic or suprahyoid laryngectomy (75,76). Endoscopic techniques focus on conservation of mucosa and lysis of scar via releasing procedures.

GLOTTIC STENOSIS

Glottic stenosis can be divided into three subtypes: anterior, posterior, and complete glottic stenosis. *Anterior glottic stenosis*, which includes laryngeal webs, can be congenital as seen in children and neonates, but also can form from bilateral anterior vocal fold trauma from surgery, caustic injury, infection, or malignancy (Fig. 62.2). Anterior glottic stenosis can be limited to a thin web between the anterior true folds or can be more extensive involving the false folds creating a thick web. Symptoms can range from hoarseness to varying degrees of dyspnea due to limitations of abduction.

Treatment of anterior glottic stenosis can be challenging. The technical aspects of treatment should focus on two components: division of the stenosis and prevention of restenosis. Simple web lysis with cold or laser techniques can be effective but has been associated with a high level or recurrence.

A number of techniques have been described to prevent restenosis. Most written about is placement of a keel in the anterior commissure to prevent regrowth of anterior-based scar. Initially described by McNaught (77), keels were placed through a laryngofissure and required a tracheotomy and repeat laryngofissure for removal. Keel placement was modified with the advent of endoscopic procedures. Today, silastic keels are placed endoscopically and secured to the external neck by various techniques (78–80).

Mitomycin-C can also be applied to the anterior commissure to prevent stenosis. In a canine model, Roh and Yoon showed that mitomycin-C significantly reduced the extent of web formation after vocal fold stripping procedures. Mitomycin-C–treated animals on average had stenosis that affected the anterior 31% of the vocal fold as compared to untreated animals who had a mean of 72% (81). Chitosan, a product derived from arthropod shells, has also shown promise as a topical agent in prevention of glottic stenosis in a canine laser injury model (82).

Posterior glottic stenosis is typically due to intubation injury, overzealous surgical manipulation of the posterior commissure, or relating to postinfectious scarring. Diagnosis can be difficult as scarring is not always easily visualized and signs and symptoms can mimic airway obstruction as seen with bilateral vocal fold paralysis. Fixation and ankylosis of the cricoarytenoid joint usually can only be appreciated by direct palpation under general anesthesia. While the typical finding is poor abduction, PGS has also been noted to be associated with poor adduction due to scar, a finding described as posterior glottic diastasis (83,84) (Fig. 62.3).

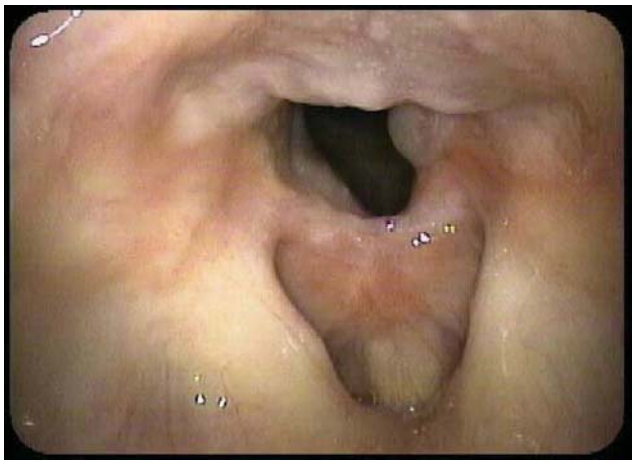


Figure 62.2 Flexible fiberoptic laryngoscopy of anterior glottic stenosis in a patient who previously underwent bilateral vocal fold polypectomy.

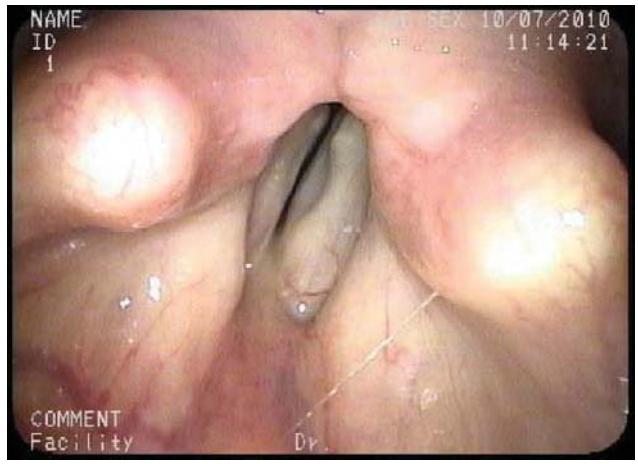


Figure 62.3 Flexible fiberoptic laryngoscopy of PGS. Note the bilateral adducted vocal folds which can be easily confused with bilateral vocal fold paralysis.

TABLE 62.2 BOGDASARIAN AND OLSON STAGING FOR PGS

Stage I	Vocal process adhesion
Stage II	Posterior commissure stenosis with scarring in the interarytenoid plane and internal surface of the posterior cricoid lamina
Stage III	Posterior commissure stenosis with unilateral cricoarytenoid joint ankylosis
Stage IV	Posterior commissure stenosis with bilateral cricoarytenoid joint ankylosis

The classic Bogdasarian and Olson staging of PGS incorporates concepts of stenosis, involvement of one or both sides, and cricoarytenoid joint fixation (Table 62.2). Electromyography can be helpful in differentiating neuromuscular paralysis from posterior glottic scarring and joint ankylosis.

A number of treatment options for PGS are available including local steroid injection, endoscopic techniques, and open techniques. For low-grade stenosis, steroid injection and endoscopic scar lysis is a reasonable first step with either laser or cold instrumentation. If the stenosis recurs, or is more advanced at the time of diagnosis there are a number of alternate endoscopic procedures available. Arytenoidectomy with or without stent placement and cordotomy (Fig. 62.4) are both options but at some expense of voice quality (85). In one of the only comparative studies of medial arytenoidectomy to cordotomy, Bosley et al. (86) reported similar postoperative voice outcomes in PGS patients treated with either technique. These procedures do not necessarily directly treat the stenosis, but rather aim to improve the symptoms of stenosis, that is, airway obstruction. There have also been a number of descriptions of endoscopic advancement flaps, which have been used over the past few decades sporadically with varying success (87,88). Langman et al. (89) describe success with endoscopic placement of a Teflon stent in the posterior glottis with decannulation in 6/9 patients.

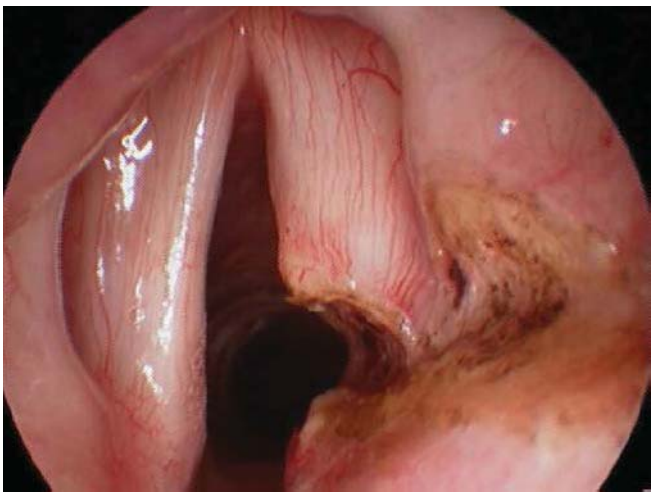


Figure 62.4 Intraoperative rigid 0-degree telescopic image of right cordotomy.

More advanced stage posterior stenosis may require open surgical intervention. In a series of 10 patients with advanced PGS, 9/10 were decannulated after laryngofissure removal of scar and skin grafting over the scar bed (90). Finally, posterior cartilage augmentation is another option for open management of PGS. Described extensively in children, costal cartilage is used to widen the posterior glottis (91). Rutter and Cotton in a series of 29 pediatric patients with isolated posterior stenosis had a 97% decannulation rate. Twelve of twenty-nine patients were treated with a single stage procedure. The 17 remaining patients had a suprastomal stent placed with a second stage required for stent removal (92). This is covered in greater detail in the pediatric airway chapter within this reference.

Complete glottic stenosis is an unusual entity that develops from severe laryngeal trauma or infection. Once the airway is secure, the larynx may be recannulated from a dual approach from both above and below the glottis if possible. Alternatively, a laryngofissure approach can be used and the stenotic region can be grafted with mucosal or skin grafting followed by stent placement (93).

SUBGLOTTIC AND TRACHEAL STENOSIS

The subglottis is found inferior to the vocal folds and includes the cricoid cartilage, a signet ring-shaped cartilaginous structure that is the only complete cartilaginous ring of the airway. In adults, the trachea is an 11 to 14 cm long by 1.6 to 2.4 cm wide tube. When cut in axial sections, it is D-shaped. It is comprised of a series of C-shaped cartilaginous tracheal rings, fibrous tissue, and smooth muscle. Most commonly associated with intubation injury (94), subglottic and tracheal stenosis are also associated with Wegener's, iatrogenic injury in the form of tracheotomy, and idiopathic subglottic stenosis. Symptoms can range from subtle hoarseness to severe dyspnea, in particular on exertion.

The Cotton-Meyer staging system (Table 62.3), while fundamentally meant for the pediatric airway is the most commonly used method of staging in the subglottis but

TABLE 62.3 COTTON-MEYER STAGING OF SUBGLOTTIC STENOSIS

Grade I	Obstruction of 0%–50% of the lumen obstruction
Grade II	Obstruction of 51%–70% of the lumen
Grade III	Obstruction of 71%–99% of the lumen
Grade IV	Obstruction of 100% of the lumen (i.e., no detectable lumen)

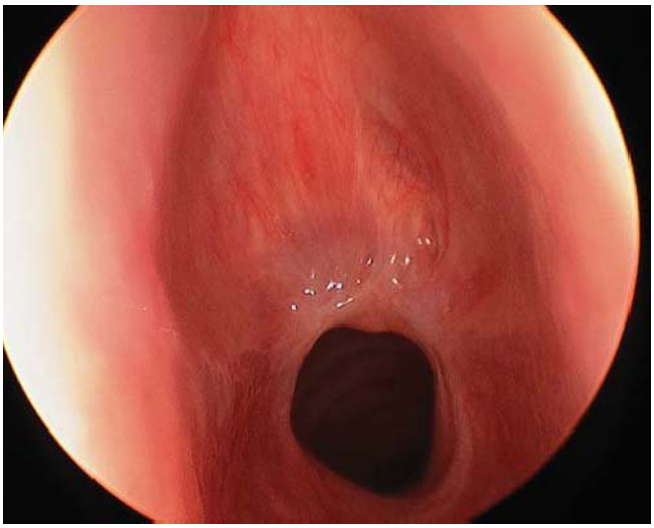


Figure 62.5 Intraoperative rigid endoscopic view of thin segment fibrous subglottic stenosis in a patient with idiopathic subglottic stenosis.

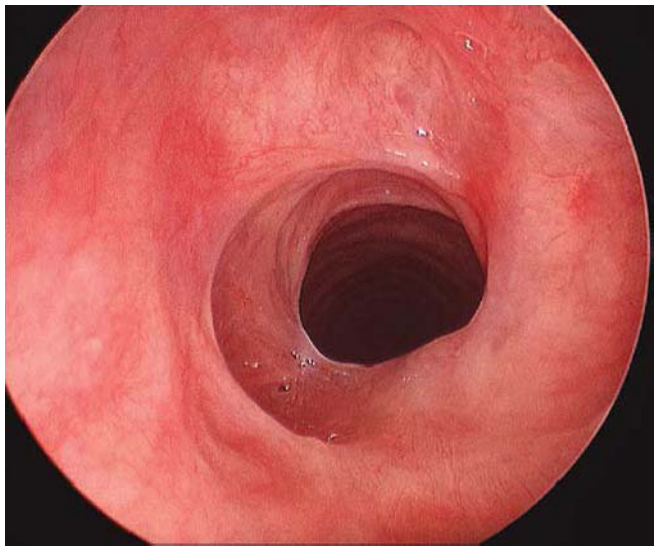


Figure 62.7 Intraoperative rigid endoscopic view of corkscrew subtype tracheal stenosis.

can be used descriptively to stage tracheal obstruction also (95). It was developed to describe subglottic stenosis in children but is easy to remember and a useful tool in characterizing adult subglottic stenosis as well. The utility of the Cotton-Meyer system in prognostication of outcomes in adult airway intervention has not been widely established. McCaffrey (96) proposed a more encompassing airway stenosis classification system that more closely reflects the challenges in treatment.

The appearance of stenosis can vary considerably: it can consist of a simple thin fibrous stenosis (Fig. 62.5), a long thick segment (Fig. 62.6), or have a "corkscrew" appearance (Fig. 62.7). There can be varying degrees of associated inflammatory tissue (Fig. 62.8) and cartilaginous collapse (Fig. 62.9).

For the purposes of this chapter, management of tracheal and subglottic stenosis will be discussed together when appropriate, given that there are many similarities and overlaps in treatment methods.

Endoscopic Management

Endoscopic management is a mainstay of treatment, which includes steroid injections, laser incisions of stenosis, dilation, and application of mitomycin-C. Many surgeons use a combination, if not all of the above procedures in treating airway stenosis patients. Endoscopic management, for most patients should be the initial surgical treatment offered as long as treatment does not further damage previously uninvolved mucosa. For many patients, an

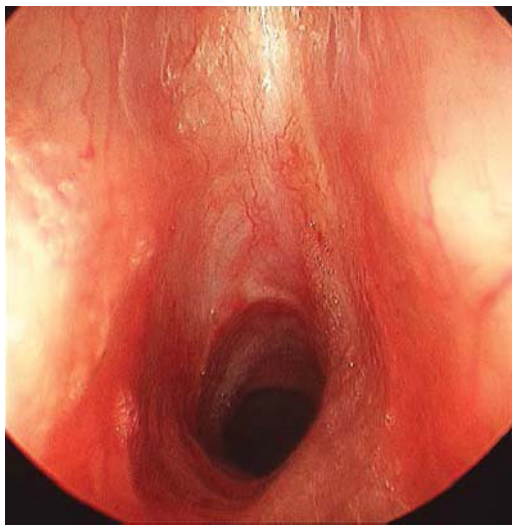


Figure 62.6 Intraoperative rigid endoscopic view of long thick segment subglottic stenosis in a patient with Wegener.

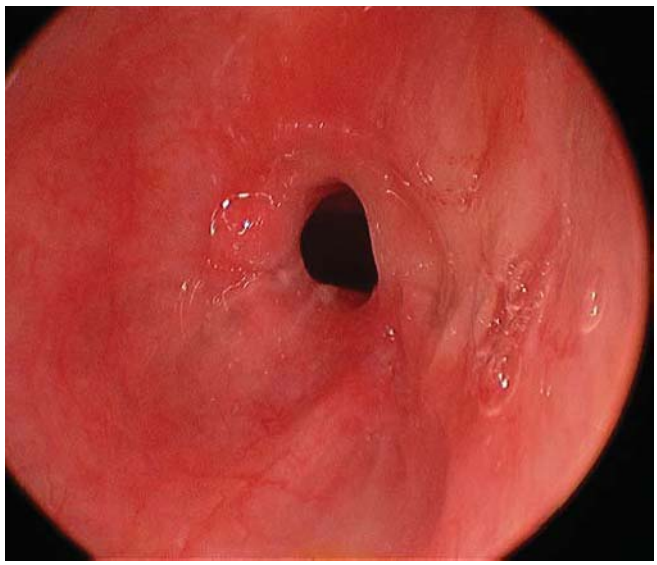


Figure 62.8 Intraoperative rigid endoscopic view of thick subglottic stenosis with associated granulation tissue.

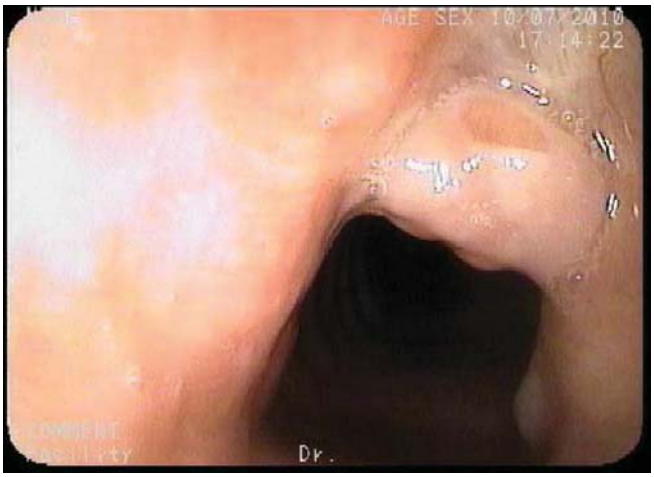


Figure 62.9 Flexible fiberoptic laryngoscopy of tracheal stenosis at a previous tracheotomy site. Note the lateral tracheal wall collapse and granulation tissue anteriorly.

endoscopic approach may be the only treatment necessary. Some may opt for multiple dilations in order to avoid surgical resection. Avoidance of open surgical repair or tracheotomy is attractive given the potential morbidity associated with open surgical complications.

Strong and Jako (97) first performed endoscopic laryngeal laser surgery in the early 1970s. A number of groups subsequently adopted using CO_2 laser to treat airway stenosis by creating radial incisions in stenotic segments with variable success (98,99). Simpson et al. (100), in a series of 60 patients with upper airway stenosis, 49 of whom who had laryngeal stenosis, determined that failure rates of endoscopic management were higher for patients with circumferential stenosis, stenosis greater than 1 cm in the vertical dimension, tracheomalacia or cartilage loss, PGS, and previous history of bacterial infection associated with tracheostomy. Valdez and Shapshay (101) also noted that length of stenosis greater than 1 cm was the most important factor in predicting failure of endoscopic management.

It is unclear how many patients who undergo endoscopic dilation require a second intervention. Recently, Roediger et al. (102), in a relatively small series of 15 patients, showed that tracheotomy can be avoided with the use of endoscopic dilation, CO_2 laser incisions, and mitomycin-C, and that only 60% of patients required repeat dilation at an average of 9 months.

Typically, following incision, kenalog is injected into the stenotic segment and then the region is dilated. There are a number of options for dilation including rigid bronchoscope, Jackson tracheal dilators, and balloon dilators. It remains unclear as to which, if any, type is superior to another in creating long lasting results.

Mitomycin-C

Mitomycin-C is an antiproliferative and antineoplastic agent produced by *Streptomyces caespitosus* that causes DNA cross-linking, suppresses inflammatory response, and prevents scar formation by inhibiting fibroblast proliferation.

Initially used as a topical medication in the eye to prevent postoperative fibrosis in pterygium surgery, it has been used over the past 15 years as an adjunct to reduce rates of restenosis (103–105).

Perepelitsyn and Shapshay in a retrospective cohort study identified 20 patients with idiopathic subglottic stenosis who underwent CO_2 laser incisions with rigid bronchoscopic dilation, laser dilation with steroid injection, or laser dilation with mitomycin-C. A successful procedure was defined as improvement of airway symptoms without recurrence of symptoms or clinical evidence of narrowing requiring intervention. The patient group with mitomycin-C was significantly more successful than the laser dilation group ($P = 0.001$) and the dilation with steroid injection group ($P \sim 0.015$) (106).

Similarly, Simpson and James, in a retrospective review, studied 36 patients with upper airway stenosis who underwent 67 procedures over a 6-year period. Patients underwent laser incision of stenosis with dilation, and a proportion, in addition, underwent topical application of mitomycin-C. Patients were followed at 2- to 4-month intervals and evaluated for dyspnea and stridor. Seven patients who underwent CO_2 laser incision plus dilation alone had a mean of 4.9 symptom-free months as apposed to 35 patients who underwent mitomycin-C application who had 23.2-month symptom-free interval ($P = 1 \times 10^{-11}$). Twenty four of 29 subjects (83%) who had mitomycin-C required only a single dilation procedure with an average of 38-month follow-up. There are a number of limitations of the study including a small sample size and no description of how it was determined which patients would receive mitomycin-C in addition to laser and dilation. Regardless, the evidence here suggests a significant advantage for patients receiving mitomycin-C (107).

In a prospective randomized double-blind placebo-controlled trial, Smith and Elstad enlisted patients with idiopathic subglottic stenosis into a treatment regimen that entailed dilation procedures every 3 months. All patients at the initial procedure underwent dilation and mitomycin-C application. The regimen varied at the second procedure in that one group had a second application of mitomycin after dilation as apposed to saline application. The third procedure was a dilation without any topical application. The recurrence rates were significantly lower at 1 and 3 years for patients who had multiple mitomycin applications, however, at the 5-year interval the benefit of mitomycin was lost suggesting that mitomycin delays but does not prevent restenosis. Ubell et al. (108) have also argued that the use of mitomycin offers a reasonable cost benefit.

Cricotracheal Resection

Most practitioners will pursue endoscopic dilation as an initial intervention for subglottic and tracheal stenosis. In patients who fail endoscopic management, open resection

is indicated for many patients. There are a number of applicable open techniques for management of subglottic stenosis. When considering open surgical resection for subglottic stenosis both *augmentation* of stenotic regions and *resection* of stenosis should be considered.

Cricotracheal resection is indicated when there is a circumferential scar within the subglottis. The entire anterior cricoid, inferior thyroid cartilage, and posterior cricoid inferior to the cricoarytenoid joints can be resected when necessary; in most cases, however, the anterior cricoid is the only part of the laryngeal complex that is removed. Anastomosis of the trachea directly to the inferior thyroid cartilage and posterior cricoid allows for reapproximation of the airway. Sufficient tissue inferior to the glottis must be present to allow for placement of anastomatic sutures.

In high subglottic stenosis, the mucosa overlying the inferior posterior cricoid plate often needs to be resected. In this situation, a sleeve of tissue can be included from the inferior tracheal segment as described by Grillo (109,110) (Fig. 62.10).

Outcomes using this single stage laryngotracheal and reconstruction technique have been impressive with a 90% success rate in regards to airway symptoms with a mean of 8-year follow-up. Despite the improvements in airway symptoms, voice suffers due to the resection of the cricothyroid muscle, which is responsible for lengthening of the vocal folds and pitch elevation. In Grillo et al.'s series of 72 patients, only 26% of patients reported no change in their voice and 64% noted changes in their singing voice and projection (52). Smith et al. measured voice frequency change in a series of 14 patients who underwent cricotracheal resection. In their paper, the mean fundamental frequency for their female patients lowered from 186 to 165 Hz, which is in the male range. Patients must be counseled about this expected change (111).

Alternatively, anterior augmentation of the cricoid cartilage via a laryngocricoid fissure can provide an option to performing an end to end anastomosis, especially in the presence of high subglottic involvement when a high anastomosis would make cricotracheal resection prohibitive.

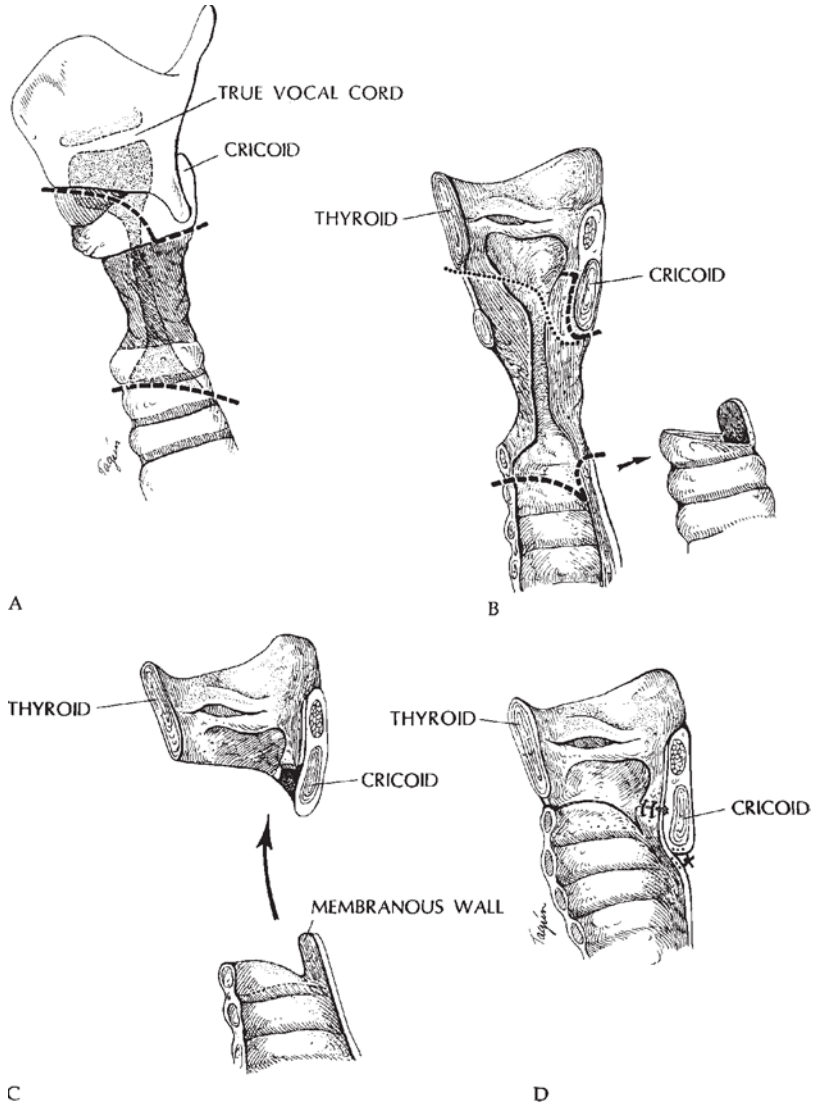


Figure 62.10 Technique of laryngotracheal resection in the presence of circumferential stenosis involving the subglottis. (Used with permission from Grillo H. Primary reconstruction of airway after resection of subglottic laryngeal and upper tracheal stenosis. *Ann Thorac Surg* 1982;33:3–18.)

Augmentation procedures with costal cartilage have been studied extensively in children with noted good success (112). In adults there have been few studies that address the efficacy of this procedure. Terra et al. describe a series of 20 patients who underwent anterior and posterior glottic/subglottic augmentation for highly advanced laryngotracheal stenosis. Fifteen of the patient had grade IV stenosis and six required simultaneous cricotracheal resection in addition to augmentation. All patients temporarily retained a tracheotomy and glottic stent postoperatively which was switched to a T-tube at 6 weeks post op. Ultimately, 80% of patients were decannulated at a mean of 23 months (113).

Cui et al. describes using thyroid cartilage as an alternative to costal cartilage in a series of adult patients. For patients with grade II Cotton-Meyer stenosis, no scar was removed, with grade III, the scar was removed submucosally, and with stage IV the scar was excised. Nine of twelve patients were decannulated after a mean of 12.3 months. Two of the three patients who failed decannulation had previously failed laryngotracheal reconstruction. In this series, most patients had a T-tube placed in order to stent the airway during the healing process (114).

Tracheal Resection

When the neck is extended approximately one-third of the trachea is extrathoracic, making it amenable to surgical resection without a thoracotomy. For mid-tracheal lesions, partial sternotomy can increase exposure to the mid-trachea and improve mobilization, although this is not always necessary. For distal tracheal lesions that approach the carina, sternotomy is essential.

Resection and primary anastomosis of the trachea in adults can include up to 50% of the length of the trachea or 6 cm when releasing procedures are employed. Longer segments should be managed with stents or other reconstructive methods, which will be discussed later. Laccourreye et al. (115) suggested that 3.5 cm represents the safe limit of tracheal resection without releasing maneuvers. Surgical principles for tracheal resection revolve around tension-free closure and minimization of blood supply disruption, which explains the limitations that relate to length of resection and extent of paratracheal dissection.

Most tracheal lesions are amenable to end–end anastomosis. The procedure is performed through a horizontal anterior neck incision. If a tracheotomy is present preoperatively and to be removed, the stoma site should be included in the incision line. The strap muscles are divided in the midline. If present, the thyroid gland is transected in the midline and swept off the anterior trachea. Typically the recurrent laryngeal nerves are not identified; however, the tissue in the tracheoesophageal groove is treated with care, in particular near the insertion point of the recurrent laryngeal nerve at the cricothyroid joint. The area of stenosis is entered anteriorly and only trachea with involved stenosis is removed. The precision of the entry point may be enhanced with endoscopic "marking" as described by Lichtenberger et al. (116). Conservation of healthy uninvolved trachea is of paramount importance. After resection of diseased trachea, anastomosis is performed with either absorbable suture such as Vicryl, or permanent suture such as Prolene. Careful closure of the anastomosis is important to prevent seeding of tracheal secretions into the neck which could cause infection, or air which could lead to subcutaneous emphysema (Fig. 62.11), pneumomediastinum, or pneumothorax. Finally, many surgeons place a stitch from chin to sternum or use a cervical collar to encourage neck flexion and avoid tension on the anastomosis. In the authors' institution, this is referred to as the "Grillo stitch" for the late Hermes Grillo. Other than anastomotic complication and dehiscence, common complications include wound infection, pneumonia, vocal fold paralysis or paresis, tracheomalacia, and hemorrhage (117).



Figure 62.11 Sagittal view x-ray of subcutaneous emphysema following anastomotic leak post cricotracheal resection.

In a large review from Grillo's series at the Massachusetts General Hospital, 901 tracheal resection patients were reviewed, and among those, 589 with postintubation stenosis, 208 with tumor, 83 with idiopathic stenosis, and 21 with tracheoesophageal fistula. They analyzed prognostic factors, which predict anastomotic complications that included granulation requiring debridement, symptomatic stenosis, and separation. Results showed that diabetes (OR = 3.32), long segment resections of greater than 4 cm (OR = 2.01), age less than 17 (OR = 2.26), laryngotracheal resections (OR = 1.8), and the presence of a tracheotomy preoperatively (OR = 1.79) are all important risk factors

for anastomotic failure. Idiopathic stenosis patients had an anastomotic complication rate of 2.4%, an overall complication rate of 6.6%, and a "good" outcome in 98.8% of cases. Complication rates for postintubation-related stenosis were considerably higher with anastomotic complications in 11% and the necessity for postprocedure airway appliance in 4.8% of patients (118). Within the otolaryngology literature, Lano et al. (119) reported on the Vanderbilt open airway surgery experience, also noting the increased failure rate in diabetic patients, acute inflammation, and those with multiple level stenoses (119).

Releasing Procedures

Most tracheal lesions are amenable to primary resection and reanastomosis. Most authors cite that 50% of the adult trachea can be resected and reanastomosed primarily which can be up to 6 cm in some individuals (120). Tension-free closure, as noted above, is important to anastomotic success. In situations where there is undue tension at the anastomotic site, releasing procedures can be used to gain extra length during tracheal mobilization. Resection of greater than 50% of the trachea for extended lesions is challenging. Long segments need to be managed with stent placement; however, advances in bioengineering are bringing tracheal transplantation options ever closer.

Laryngeal releasing procedures are employed for extended resections that involve the proximal trachea, and can allow for closure of defects up to 5+ cm (121). Frequently discussed, they are a rarity for busy stenosis practices and in most cases, good results can be attained without (122). In a series of 521 operations, Grillo et al. (123) only utilized releasing procedures in 6.4% of primary cases and 29% of revision cases. Dedo and Fishman (124) originally described the thyrohyoid, or infrahyoid release, which involves transecting the thyrohyoid muscle and membrane and mobilizing the superior cornu of the thyroid cartilage to allow the larynx to drop inferiorly. This technique has largely fallen out of favor due to significant postoperative swallowing issues.

More commonly used is the suprahyoid technique described by Montgomery (125). In this technique, the muscular attachments on the superior surface of the hyoid are released. The stylohyoid ligament and hyoid cartilage are then divided medial to the digastric tendon attachments separating the body of the cartilage from the greater cornu bilaterally. The suprahyoid musculature is divided between the anterior bellies of the digastric muscles allowing the body of the hyoid, larynx, and proximal tracheal to drop inferiorly. This technique is associated with fewer postoperative swallowing deficiencies because it preserves laryngeal elevation during swallow.

There are a number of intrathoracic releasing techniques that are rarely required by otolaryngologists during the care of proximal or mid-tracheal stenosis. These all require a combined cervical and mediastinal approach and can add significant complexity to the surgical procedure. Grillo describes a cadaveric study of 40 specimens where a number of thoracic releases were performed and their effects measured. By combining mobilization of the right hilum with pulmonary ligament division, dissection of the pulmonary vessels, and division of the intercartilaginous tracheal ligament, defects greater than 6 cm can be primarily anastomosed. Mobilization of the hilum can produce 3.0 cm mobility, division of the left mainstem bronchus can produce 2.7 cm, and freeing the pulmonary artery from the pericardium can produce an average of 0.9 cm in length (126).

TRACHEAL STENTS

Stent placement can be an effective means in select patients to maintain a patent airway in patients with subglottic or tracheal obstruction from malacic segments and extraluminal encroachment. While associated with high rates of complications, stents are particularly useful for palliation in patients with poor long-term prognosis, patients who have failed prior dilations and open surgical repair, those with long segment stenosis, or airways where there is a lack of framework support. They are also highly effective in treating airway narrowing for extraluminal compression from tumors. Stents come in two basic forms: silicone or metal (127). The principal argument against stent use in benign stenoses is the tissue damage incurred in previously noninvolved airway segments.

Metallic stents, while easy to place, become integrated into the tracheal wall and mucosa. This tendency serves as both a benefit and hindrance. Incorporation into the wall prevents migration and mucosalization allows for mucociliary clearance over the stent. Alternatively, metallic stents are notoriously difficult to remove and tend to form granulation tissue (128). They are typically placed via flexible bronchoscopy or under fluoroscopic guidance, easily conform to varying airway dimensions, and have a more favorable internal–external diameter ratio (129). In a review of the literature pertaining to metallic stents which included 497 patients, 34% of patients were noted to have complications (130). The most common complication was granulation formation, which represented 27% of the complications. Other complications included restenosis, migration, stent fracture, erosion, bleeding, infection, and death in 13/497 patients.

Silicone stents have been used effectively for distal tracheal and bronchial airway stenosis as well as refractory high tracheal cases. Silicone is relatively inert, produces minimal granulation tissue, and is capable of providing structure to make it sustain patency in the face of scar or external compression. Silicone stents are easier to place, move, and remove as compared to metal stents, and can be tailored to fit any airway length. Downsides to silicone stenting include the need for general anesthesia for placement and their tendency to migrate (131). To some extent, migration of silastic stents has been reduced by the presence of external studs on the outside of the stent, as in the case of Dumon stents (Bryan Corp, Woburn, MA) (132).

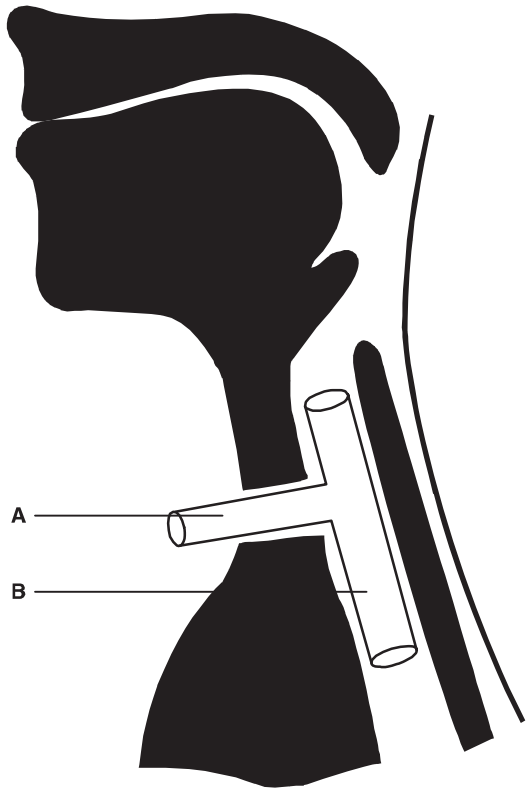


Figure 62.12 Schematic view of T-tube. "*A*" marks the horizontal, and "*B*" the inferior tracheal limb. (Used with permission from the *British Journal of Anaesthesia.* Touma O, Venugopal N, Allen G, et al. Emergency airway management in a patient with a Montgomery t-tube *in situ*. *Br J Anaesth* 2011;107:107–108.)

For tracheal and high subglottic stenosis, particularly in cases with multiple level involvement, silicon T-tubes can provide an additional option. Designed and popularized by Montgomery in the 1960s, T-tubes have a superior and inferior limb, which serve as a tracheal and subglottic stent, as well as horizontal limb that serves as a tracheotomy tube (Fig. 62.12). These can be highly effective for refractory stenosis case, but require meticulous care by the patient to keep them clean and free of crusting. They are subject to obstruction because of the unhumidified air inhaled through the horizontal segment when uncapped and the lack of inner cannula. If a tube becomes obstructed, they are removed emergently by the patient. Also, unlike regular tracheotomy tubes, these require a trip to the operating room with general anesthesia for tube changes.

Autografts

The popularity of the "augmentative" approach to airway surgery is on the decline. There are many inherent advantages, including avoiding lateral dissection which is always necessary in resection cases. Nonetheless, this approach for open stenosis management is still necessary in some cases.

Historically, a number of materials have been used to reconstruct defects of the trachea including allografts, autografts, prosthetic grafts, and now, bioengineered tracheal grafts. In clinical situations where primary anastomosis and releasing procedures are not options, autografting provides a viable alternate option. Autograft options have included fascia lata, tracheal wall, pericardium, periosteum, bony fragments, and auricular cartilage to name a few. For small defects, these can be used as the sole repair. For large defects, the materials can be used in conjunction with an additional material for support such as wire or Marlex mesh, or silicone or polyethylene stents, all of which can prevent airway collapse (133). Each autogenous technique conceptually holds promise but most have relatively high failure rates due to poor graft take and restenosis or narrowing due to scar or granulation tissue formation, in addition to various other donor site morbidities. Alternate autogenous graft options include local, regional, and free flaps. Radial forearm free flap reconstruction has been used with moderate success by a number of authors (134,135).

TRACHEAL TRANSPLANTATION/TISSUE ENGINEERING

Considerable work is currently being conducted to identify techniques for tracheal transplantation or replacement. As mentioned previously, there are limitations to the amount of trachea that can be resected and reanastomosed. While tracheal stenting is a valuable contribution to dealing with long segment stenosis, use is fraught with complication. It is for this reason, considerable effort is currently being put into identifying means of long segment tracheal reconstruction with allografting, and more recently bioengineered tissues. A transplantable or reconstructive prosthesis should be easily accepted by the host with minimal inflammatory reaction, provide airtight anastomosis and adequate rigidity to maintain the shape of the three-dimensional construct of the airway, and ideally permit ingrowth of the respiratory epithelium in the endoluminal lining (136).

Allograft

Allograft tracheal transplantations have been in large part relatively unsuccessful. Early transplantation mainly failed due to donor tissue rejection (137,138). Even with immunosuppression, nonvascularized allograft transplantation continued to fail due to poor vascular supply leading to extensive fibrosis of transplanted trachea (139).

Direct tracheal vascular anastomosis is not possible due to the nature of the network of small vessels that supply the trachea. In canine models, donor trachea has been vascularized by wrapping the donor tissue in omentum. Cyclophosphamide has been shown to adequately suppress tissue rejection (140). Interestingly, cryopreservation, storage of donor tissue at −196°C for 1 to 6 months, has been suggested in animal models to reduce acute tissue rejection as compared to naïve trachea (141,142).

Allograft transplantation in human subjects has been limited. A few scattered cases and techniques have been described. In 1979, Rose et al. (143) transplanted trachea that had been revascularized in sternocleidomastoid

muscle. Surgery was successful but no long-term follow-up was provided. Levashov et al. (144), in 1993, attempted a single staged allograft transplant wrapped in omentum. This failed at 4 months. Klepetko et al. suggest a staged procedure for omental free tissue transfer. In the first stage, the allograft is implanted into the abdominal cavity and wrapped in omentum. The second stage entails microvascular transfer into the neck with tracheal and microvascular anastomosis. In one patient, they performed the first stage successfully but ultimately did not need the allograft due to success of primary anastomosis (145).

Bioengineered Tissue

Bioengineered tissue is rapidly becoming a reality in tracheal transplantation. Ideal candidate tissue should be functional in that it can clear mucosal secretions, semi-rigid so that it can maintain the three-dimensional structure of the airway yet remain compliant during breathing, not require immunosuppression, and allow for angiogenesis to improve tissue survival (146). Current models of bioengineered tissue rely upon a scaffolding that becomes populated by the patient's own cells. Many suitable products have been tested for use. Experimental scaffolds have included synthetic material and decellularized natural matrices that support the growth of cellular material derived from recipient chondrocytes and epithelial cells (147).

Omori et al. have used a Marlex scaffold and polypropylene spiral that is encompassed by a collagen sponge scaffold derived from porcine dermal type 1 and 3 collagen. This has been well tolerated in a canine model (148) and in 2002 was used for the first time in a human subject with invasive thyroid carcinoma. At 2-year follow-up, the implant was well mucosalized and the patient experienced no complications (149).

Recent work has shown that use of the detergent enzymatic method (DEM) (150) allows for human trachea to become nearly completely acellular. By applying 25 DEM cycles, Baiguera et al. (151) generated a human acellular scaffolding that is completely devoid of cellular elements save for a few chondrocytes, while preserving the angiogenic factor basic fibroblast growth factor without destroying the histoarchitecture of the extracellular matrix or compromising the basement membrane. In 2004, using the above concept, a 30-year-old female with post-TB tracheal and bronchial stenosis, who had failed prior open subglottic stenosis and bronchial stenting, underwent a left main bronchus resection, which was replaced with bioengineered human trachea (152). The trachea was removed from a donor and underwent processing with the decellularization process described above. Using autologous bone marrow and bronchial mucosa, the acellular tissue scaffolding was populated with the patient's own cells using a complex bioreactor and finally implanted. The limitation of this procedure was the long technical processing required to construct the prosthesis.

In 2010, the same group performed a similar procedure in a 12-year-old boy (153). A 7 cm segment was transplanted, the longest section ever transplanted. Instead of a long prosthesis incubation period, this case used a decellularized trachea which *in vitro* was seeded with stem cells from bone marrow and respiratory cells. The group utilized a number of factors including erythropoietin, granulocyte-stimulating factor, and beta-transforming growth factor to encourage stem cell growth and differentiation. A temporary absorbable stent was used to provide additional airway support during the first 2 months.

An alternate method was described by Delaere et al. (154). Tracheal allograft was buried under the forearm for the revascularization of the donor tissue. The membranous tracheal wall mucosal lining of the donor trachea was removed and replaced with a buccal mucosal graft from the recipient. The graft was transferred to the trachea with its neo blood supply, the radial artery. Endoluminal graft biopsy revealed donor respiratory mucosa as well as recipient buccal squamous mucosa, and viable chondrocytes. Immunosuppression was discontinued after the confirmation of recipient cells within the airway and shortly thereafter, there were no additional donor cells noted on subsequent biopsy.

The field of regenerative medicine holds exciting promise for tracheal and subglottic reconstruction. For patients with long segment stenosis, these techniques will be life altering as they become more readily available.

HIGHLIGHTS

- Postintubation injury is the most common cause of airway stenosis.
- For many patients, endoscopic management is the only treatment necessary. This may include dilation, laser incision of stenosis, injection of steroid, and application of mitomycin-C.
- For open tracheal resection, diabetes, stenotic segments of greater than 4 cm in length, age less than 17, laryngotracheal resections, and the presence of a tracheotomy preoperatively all increase the rates of anastomotic failure.
- For tracheal resection segments longer than 5 cm, stents, flaps, and bioengineered tissue are all management options.
- The lack of dynamic motion of the scarred or damaged larynx makes many endoscopic airway surgery decisions almost arithmetical; increasing airway leads to loss of vocal and/or swallowing function, for example.

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63 Complex Upper Airway Problems

Jay B. Tuchman *Deepak K. Mehta*

The proper approach to any problem involves a well-constructed systematic plan, combined with diligent preparation and careful attention to detail, to successfully achieve the desired outcome. The principles of this methodology should certainly be adhered to when confronted with the complexities of airway management, and particularly when presented with the scenario of the difficult airway. The practitioner's margin of error dwindles in patients with deteriorating clinical status and those at extremes of age or with a predisposition toward oxygen desaturation. An organized and focused preoperative airway evaluation, resulting in the advanced recognition of an impending difficult airway, can help avoid a catastrophic situation. Assessment should include a determination regarding possible difficulties with ventilation, intubation, patient cooperation, and/or tracheostomy (1). Failure to intubate a trachea will not result in a patient's death, but inadequate preparation, allowing the consequences of "can't intubate" to proceed along the slippery slope toward "can't ventilate" may very well do so. Routine preparation and planning includes the availability of multiple sizes of basic equipment, optimal positioning for successful ventilation and intubation, and supplemental oxygenation (especially prior preoxygenation) throughout the airway management. The benefits of the proliferation of airway devices over the past few years should surely not be underestimated, but it is critical to realize that the choice of a particular advanced airway device does not constitute an adequate plan, and is undoubtedly not a panacea for avoiding the frightening "can't intubate, can't ventilate" clinical scenario. The development of the difficult airway algorithm of the American Society of Anesthesiology (ASA) is an embodiment of this multidimensional approach to management of the difficult airway (2). Basic management decisions include (a) awake intubation versus attempts after induction of general anesthesia, (b) noninvasive versus invasive initial approaches to intubation, and (c) preservation or ablation of spontaneous ventilation (1).

The algorithm includes a section for the awake approach to intubation, as well as an approach to situations involving failed intubation attempts after the induction of general anesthesia (Fig. 63.1). At all times, communication between services, involving a discussion of the multifaceted nature of the plan, as well as highlighting the particular involvement of each member of the operating room staff is of paramount importance in thwarting the development of this precarious scenario.

There are a multitude of pathologic characteristics associated with difficult airway management, including congenital features such as micrognathia, mandibular hypoplasia, macroglossia, cervical instability, limited mouth opening, midface hypoplasia, and facial distortion, as well as acquired conditions associated with infection, obesity, tumors, trauma, burns, and arthritis (3). The technique chosen must be tailored to the distinct disease presentation associated with the difficult airway. However, even within each situation, there may be multiple reasonable approaches, and it behooves the practitioner to be flexible and capable of changing course with alacrity, should the primary attempts prove unsuccessful. Utilizing the ASA difficult airway algorithm as a guide, we attempt to elucidate in this chapter the benefits of specific approaches, techniques and devices for particular airway scenarios, while simultaneously emphasizing the importance of a comprehensive plan for the management of each patient.

A decision to follow the pathway of awake airway management prior to anesthetic induction includes both the possibility of securing the airway via surgical access, or via noninvasive approaches such as flexible fiberoptic intubation, utilizing sedation, and topicalization of the airway (4).

In a patient with upper airway obstruction and acute respiratory distress, an urgent tracheostomy utilizing minimal sedation and maintaining spontaneous ventilation, with

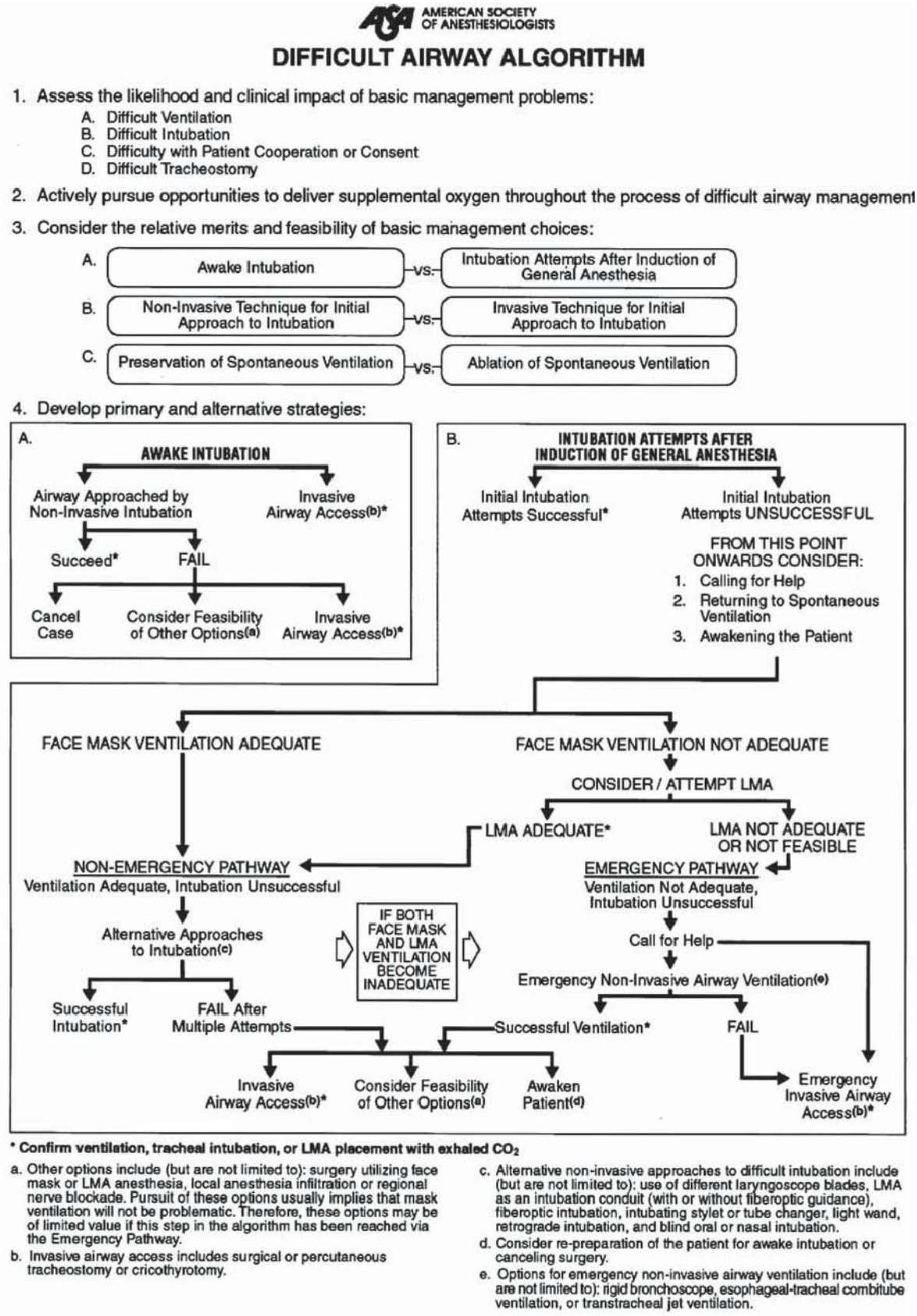


Figure 63.1 ASA difficult airway algorithm. Reproduced from American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology* 2003;98(5):1269–1277, with permission.

infiltration of local anesthetic, might be appropriate. Other situations mandating an awake tracheostomy include patients unable to tolerate general anesthesia, or patients with supraglottic abscesses or masses, which may lead to aspiration of purulent material or airway distortion complicating endotracheal intubation. There are scenarios, however, where surgical access via tracheostomy may not be feasible, such as patients undergoing neck *s*urgery, those with *h*ematomas or abscesses of the neck, *o*bese patients, and those with prior *r*adiation or *t*umors (mnemonic SHORT) (5). It is always instructive to recognize that in the rare situation where airway manipulation may be so disastrous and lead to complete decompensation, the option of femoral–femoral cannulation under local anesthesia as preparation for possible cardiopulmonary bypass should be considered (6).

The noninvasive approach of awake or sedated flexible fiberoptic intubation may be facilitated by the administration of small titrated doses of benzodiazepines, narcotics, ketamine, an antisialogogue such as glycopyrrolate, and a new agent, dexmedetomidine, resulting in a patient with reduced anxiety, decreased secretions, yet without respiratory depression. The antisialogogue also improves the effectiveness of topical anesthetics, by removing the barriers to mucosal contact. When combined with local anesthetic administered via injected nerve block techniques such as the Glossopharyngeal Nerve (GPN), Superior Laryngeal Nerve (SLN), and Recurrent Laryngeal Nerve (RLN) blocks, this may help achieve anesthesia of the nasopharynx, oropharynx, and hypopharynx in an awake, sedated patient. This allows for uncompromised airway exchange and oxygenation via spontaneous ventilation, maintenance of normal muscle tone with increased size and patency of the oropharynx, and improved upper and lower esophageal sphincter tone with intact protective airway reflexes, reducing the risk of severe gastroesophageal reflux and aspiration (3). The concern for pulmonary aspiration is a strong argument for the awake approach to intubation in patients with a difficult airway and full stomach, or those with obesity (7). However, limitations to the awake approach to intubation include young children, those with an allergy to local anesthetics, or others with an inability to cooperate due to mental retardation or dementia. Caution must also be exercised in situations where the possible negative consequences of awake attempts may be manifest, such as cardiac ischemia, increased intracranial or intraocular pressure, or neurologic damage from cervical spine instability (3).

A specific scenario of preemptive airway control unique to the fetal/neonatal population is the *Ex Utero* Intrapartum Treatment (EXIT) procedure (Fig. 63.2). Infants with a very low probability of survival, as suggested by prenatal ultrasound, due to tracheal obstruction or other airway abnormalities such as cystic hygroma, cervical teratoma, congenital goiter, or congenital high airway obstruction syndrome, are managed by maintaining uteroplacental circulation with only partial delivery. This allows time, prior to clamping of the umbilical cord, for procedures such as

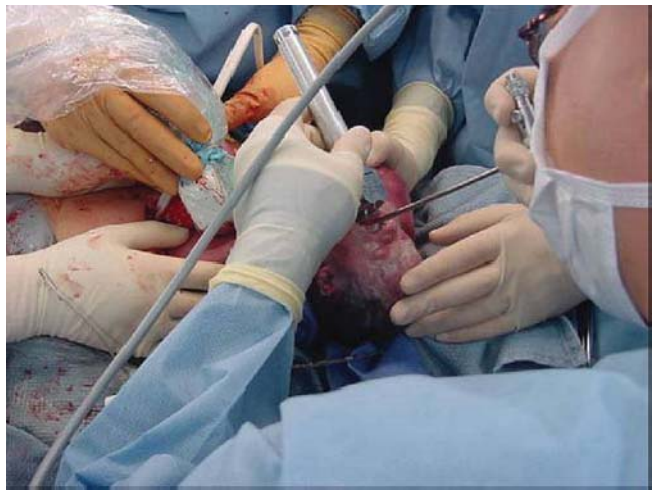


Figure 63.2 Bronchoscopy performed during EXIT procedure to secure fetal airway prior to delivery.

direct laryngoscopy, bronchoscopy, intubation, and tracheostomy to secure the airway and maintain continuous oxygenation, improving the chances of neonatal survival (8).

When the decision has been made to attempt intubation after the induction of general anesthesia, and despite an appropriate plan, the initial approach has been unsuccessful, it is prudent to repeatedly consider calling for help, returning to spontaneous ventilation if not present, and possibly even awakening the patient. The advantages of assisted spontaneous ventilation include the maintenance of oropharyngeal muscle tone, avoiding total airway obstruction, and serving as a guide to locate the glottis. If face mask ventilation is still adequate despite unsuccessful intubation, alternative approaches to intubation should be considered (1).

If further attempts are made with a standard laryngoscope, *o*ptimum *e*xternal *l*aryngeal *m*anipulation or *b*ackward, *u*pward, *r*ightward *p*ressure on the thyroid cartilage may improve the grade of laryngoscopic view. Placing a flexible stylet inside the endotracheal tube (ETT) in a hockey-stick shape may facilitate ETT placement, even when only the epiglottis or arytenoid cartilages are seen. Particularly in children with micrognathia or macroglossia, where routine rigid laryngoscopy has been previously unsuccessful, the retromolar approach to direct laryngoscopy may be useful. The head is turned slightly to the left, and a straight Miller 1 blade (even in older children) is introduced while the right corner of the mouth is retracted (Fig. 63.3). Sweeping the tongue to the left, the laryngoscope is advanced between the tongue and lateral pharyngeal wall, overlying the molars, until the epiglottis is visualized (Fig. 63.4). The movement of the head and lateral placement of the blade allows for bypassing the tongue, a reduced need for soft tissue displacement, and improved line of site visualization (9).

Flexible fiberoptic bronchoscopy remains the gold standard for management of the difficult airway. Advantages of flexible fiberoptic bronchoscopy include those related to the



Figure 63.3 Placement of laryngoscope blade for retromolar technique. Courtesy of Larry Borland, MD.

device and to the technique itself. The flexible bronchoscope allows flexibility and adaptability to varying airway anatomy with minimal manipulation, is applicable to both oral and nasal approaches in all age groups, and gives the practitioner the ability to provide both oxygen and topical anesthesia during intubation (10). The specific technique as described below decreases the trauma and cardiovascular response to airway instrumentation, has a consistently high success rate, and allows for confirmation of position. Improved digital technology obtains clearer images, even in the neonatal population, with the smallest scope sized 2.2 mm, and able to fit through a 2.5 ETT (9). Light sources and video systems have been incorporated into the newer bronchoscopes, allowing for increased portability, as well as the ability to display a larger image of the airway. The improved technology still comes at a high cost, with frequent maintenance necessary due to the fragility of the flexible scopes. There is a significant learning curve with the fiberoptic scope and maintenance of one's skills requires continuous utilization (11).

Optimal positioning for fiberoptic bronchoscopy requires the patient's head to be slightly extended at the atlanto-occipital joint, while a jaw thrust, and at times tongue traction, is performed by an assistant, opening the posterior pharynx for an ideal view of the laryngeal opening. The flexible bronchoscope must be kept rigid, placing the tip of the scope in the midline. Specially designed oral airways may help facilitate midline placement during oral fiberoptic intubation, whereas nasal fiberoptic bronchoscopy will intrinsically allow for easier midline placement (10). The approach of choice for the pediatric patient is generally the nasal fiberoptic; however, due to the distinct possibility of adenoid shearing or epistaxis, premedication with topical vasoconstrictors is ordinarily undertaken. Nasal fiberoptic intubation can be greatly assisted by the modified nasal trumpet (Fig. 63.5), allowing spontaneous ventilation and the administration of volatile anesthetic, while fiberoptic intubation ensues via the other nares (Fig. 63.6). The modified nasal trumpet technique has

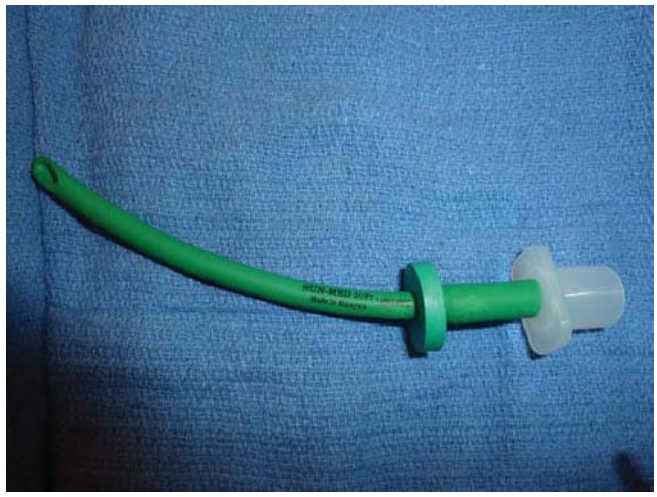


Figure 63.5 Modified nasal trumpet to help facilitate spontaneous ventilation while maintaining anesthetic depth for flexible fiberoptic laryngoscopy.



Figure 63.4 Improved laryngoscopic view obtained with retromolar technique. Courtesy of Larry Borland, MD.



Figure 63.6 Flexible fiberoptic laryngoscopy facilitated by modified nasal trumpet.

great utility in the pediatric population, or those with an inability to cooperate and tolerate an awake approach to intubation (9). Despite successful placement of the fiberoptic scope into the trachea, the practitioner may experience resistance to the ETT upon attempted advancement into the trachea. A helpful hint to avoid catching the ETT on the arytenoid cartilages is to place the ETT bevel *d*own on the fiberoptic scope for *o*ral intubations and bevel *u*p for *n*asal intubations *(mnemonic UNDO)* (12). The major drawback of the fiberoptic scope is that excessive secretions or bleeding may render the scope completely unusable, particularly with the neonatal scope, which lacks a channel for suctioning or administering local anesthetic (10). This weakness argues strongly in favor of mandating the clinician to master a number of other techniques, as part of the comprehensive approach to airway management we have described above.

Aside from the standards of direct laryngoscopy and flexible fiberoptic laryngoscopy, this chapter focuses on six other main categories of devices that may be utilized, avoiding the need to resort to a surgical airway such as a cricothyroidotomy or tracheostomy. These include indirect laryngoscopes, rigid fiberoptic stylets, intubating or lighted stylets, video laryngoscopy, laryngeal mask airway (LMA)–guided intubation, and rigid fiberoptic bronchoscopy.

The first indirect rigid fiberoptic-enhanced laryngoscope (Fig. 63.7), the Bullard (Gyrus ACMI, Norwalk, OH), was originally designed for use in the difficult pediatric airway and is available in both adult and pediatric sizes. Although still quite expensive, this instrument, as well as other similar models such as the WuScope (Pentax, Orangeburg, NY) and Upsherscope (Mercury Medical, Clearwater, FL) cost less than the flexible scope, and are less prone to damage (13). The Bullard is the most versatile of these devices, and may be utilized for both oral and nasal intubations in syndromic patients with mandibular hypoplasia, as well as those with limited neck extension, prominent upper incisors, or mouth opening as little as 6 mm. The utility of these devices, however, may be limited in patients with absent midline structures, due to their dependence on normal supraglottic anatomy and lack of panoramic view. Oxygen insufflation, instillation of local anesthetics, and improved suctioning of secretions versus the flexible scope may be achieved through the working channel, but suctioning through the suction channels in these devices still remains suboptimal. The device should be placed in the mouth at the midline, and then positioned like a laryngoscope blade to pick up the epiglottis (Fig. 63.8). The fiberoptic bundle located on the posterior aspect of the blade provides a 55-degree field of view at the level of the larynx, improving visualization around the base of the tongue, without the need for physical alignment of the oral, pharyngeal, and laryngeal axes. The ETT is loaded on the rigid stylet positioned to the right of the viewing lens and specifically designed to match the indirect laryngoscope, advancing the ETT into the trachea from right to left under direct visualization. Loading the ETT backwards on the original wire stylet with the bevel directed right, or aiming the stylet at the middle-third of the left vocal fold may help avoid the right arytenoid when attempting to pass the ETT off the stylet. Practice remains very important, as the method of visualization is vastly different than standard laryngoscopy, with a significant learning curve necessary to achieve consistent success (13).

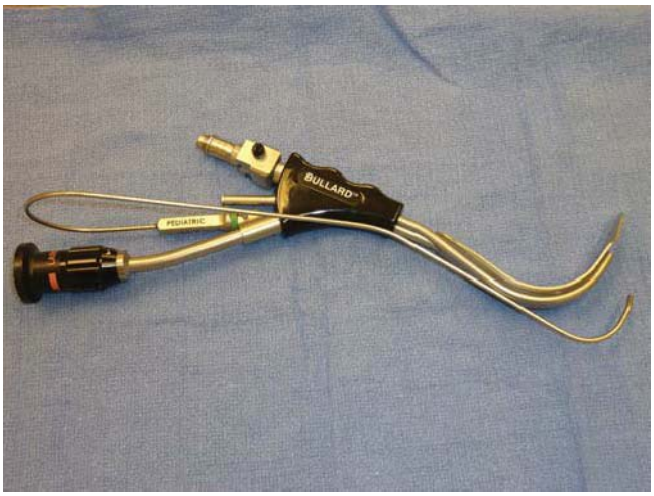


Figure 63.7 Bullard laryngoscope.



Figure 63.8 Intubation performed by anesthesiologist with the Bullard laryngoscope.



Figure 63.9 Airtraq optical laryngoscope.

The Airtraq (Prodol Meditec, Vizcaya, Spain) is a newer disposable rigid optical laryngoscope that may also be utilized without aligning oral, pharyngeal, and laryngeal axis, with a guide channel included to enable direction of the ETT toward the vocal cords. The image is transmitted to a proximal viewfinder through a combination of lenses and a prism, rather than fiber optics (Fig. 63.9). The device includes a built-in heater, which prevents fogging of the distal lens, and a low-temperature LED light source which may last up to 90 minutes, but both require at least 30 seconds of preparation. The Airtraq may be beneficial in patients with cervical spine disease, but requires a larger mouth opening of up to 16 mm and may be difficult to insert in patients with a short jaw or large chest (14,15).

The Shikani optical stylet (SOS; Clarus medical, Minneapolis, MN) (Fig. 63.10) was initially designed by an ENT surgeon, and is a rigid, yet malleable metal stylet with a fiberoptic light source, which delivers an image to an eyepiece or video camera. This device has a preformed hockey-stick shape and may be used in both adult and pediatric patients for oral intubation, with or without direct laryngoscopy. Neck extension is not required for this technique and offers the advantage of displacing soft tissue and enabling oxygen delivery during intubation attempts (Fig. 63.11). One must exercise caution, however, when utilizing this oxygen-delivery system in infants and neonates, due to concerns of pneumothorax (16,17). Unlike the Shikani stylet which utilizes a midline approach, the Bonfils Intubation Fiberscope (Storz, Tuttlingen, Germany) is an optical stylet without a malleable stylet, utilizing a retromolar approach, as the fixed 40-degree curvature is inadequate when utilizing a midline approach (18). As with other fiberoptic techniques, these devices require a significant learning curve, may be quite fragile, and attempts to secure the airway may be complicated by fogging, bleeding, and secretions. A benefit of the optical stylet over flexible fiberoptic laryngoscopy is the ability to visualize the tip of the ETT passed into the trachea and improved maneuverability of the stylet's tip (17).

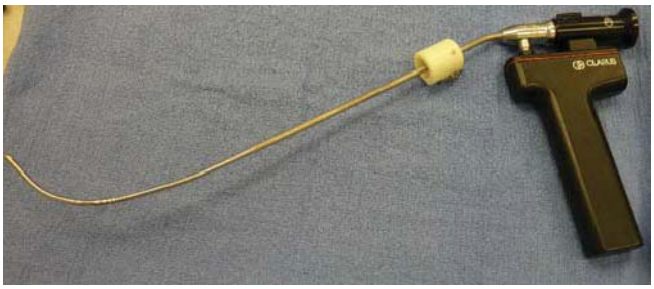


Figure 63.10 Shikani optical stylet.



Figure 63.11 Intubation performed by anesthesiologist with the Shikani optical stylet.

An alternative approach under general anesthesia involves an intubating stylet used as an introducer or guide for placing the endotracheal tube. The Eschmann Tracheal Tube Introducer (Portex Limited, Hythe, UK) or "gum elastic bougie" is a 60 cm long 15 Fr catheter with a "j" tip at the distal end and was originally described by MacIntosh in 1949. Generally, when standard direct laryngoscopy has only achieved visualization of the epiglottis, the bougie is hooked under the epiglottis and advanced into the trachea until a clicking sensation is felt over the tracheal rings. If the bougie is placed correctly, it will lodge in a distal airway at the 30 to 35 cm mark. The ETT is then slid over the

bougie into the trachea, and may sometimes be facilitated by a jaw thrust or by rotating the bevel of the endotracheal tube posteriorly to avoid catching structures of the laryngeal aperture. If the bougie has been incorrectly placed in the esophagus, the entire bougie will advance without any resistance. Confirmation of correct placement is confirmed by routine methods of capnography and auscultation of breath sounds. A similar device, the Cook Airway Exchange Catheter (Fig. 63.12) (Cook Inc., Bloomington, IN), was originally designed as a tube exchanger for use in the difficult airway, but may have the additional advantage of ventilation in an emergency situation, due to its hollow lumen and proximal port adapter (19).

A lighted stylet (light wand), equipped with a high-intensity light at the tip, may also be utilized to secure the difficult airway using the principle of transillumination (Fig. 63.13). Due to the technique's ability to achieve

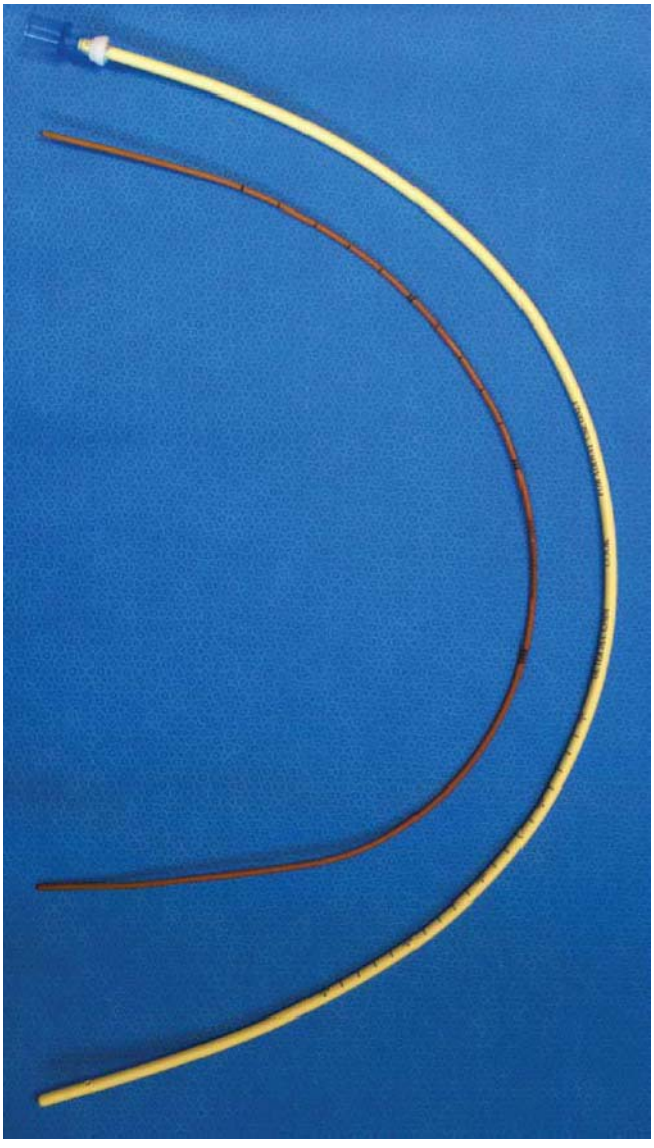


Figure 63.12 Intubating stylets: Gum Elastic Bougie and Cook Airway Exchange Catheter.



Figure 63.13 Light wand.

intubation without neck movement, the light wand may be particularly helpful in patients with cervical spine fractures. Similarly, the device may be utilized in patients without intrinsic laryngeal or oropharyngeal pathology, where there may still be difficulty obtaining a laryngoscopic view, such as micrognathia or temporomandibular joint (TMJ) abnormalities. Successful placement may be achieved by dimming the lights and curving a well lubricated lighted stylet 45 to 90 degrees, while carefully maintaining the tip of the stylet within the tip of the ETT to avoid airway trauma. The stylet is passed along the curvature of the tongue until the middle of the neck is transilluminated by a clearly circumscribed circular light, signifying appropriate positioning for gently sliding the ETT off the stylet into the trachea. If the ETT is caught on the epiglottis, the stylet may be withdrawn and placed more posteriorly, allowing placement of the ETT underneath the epiglottis, or the bevel of the ETT may be rotated. Drawbacks to this technique include the blindness of the approach and its consequent risk of bleeding, as well as the large diameter of the stylet, restricting the approach to larger children and larger ETTs. The light wand may also be less successful in obese patients and should not be utilized to secure the airway in the presence of airway tumors, laryngeal injuries, or retropharyngeal abscesses (19).

Video-assisted laryngoscopy is a versatile new technology, with earlier designs incorporating an ultrathin fiberoptic bundle into an angulated blade (AVIL) or coupling a light source, video processor and monitor with a MacIntosh laryngoscope (Storz DCI) (13). More recently, the Glidescope (GVL, Verathon, Bothell, Washington), with a miniature video chip embedded into a modified MacIntosh laryngoscope and a blade angled 60 degrees upward, has been extensively studied. The extraordinary ability to achieve improved laryngeal exposure with less force upon laryngoscopy and minimal cervical manipulation (Fig. 63.14), while simultaneously placing these images in real-time on display monitors, greatly increases the success of intubation even in the difficult airway, while facilitating both teaching and learning (20,21) (Fig. 63.15). At times, an awake Glidescope laryngoscopy after topicalization with nebulized 4% lidocaine may avoid the need for an awake intubation (22). The advantages of a similar skill set to routine direct laryngoscopy, reduced fragility of the fiberoptic element, no need for an external light source have made the Glidescope a ubiquitous presence in both the perioperative and prehospital settings (13). The most notable drawback to the Glidescope is that despite the improved laryngoscopic view, significant difficulty may still be encountered in placing the ETT through the vocal cords. All of these devices require at least some mouth opening to pass the device, and may be complicated by fogging, bleeding, and secretions. Midline placement of the blade and utilization of a preshaped ETT conforming to the convex curvature of the blade or the rigid stylet which accompanies the device will improve the rate of converting



Figure 63.14 Improved laryngoscopic view obtained utilizing Glidescope.

a good laryngoscopic view into a routine intubation using the technology of video laryngoscopy (23,24). At times, it is necessary to retract the stylet or manipulate the ETT 180 degrees to avoid the anterior tracheal wall (25). It is important to watch both insertion of the blade and later the ETT into the mouth, to avoid injury to the oropharyngeal



Figure 63.15 Intubation performed by anesthesiologist utilizing Glidescope.

structures, thereby guarding against the tendency to focus too extensively on the monitor (26). The Glidescope may also be utilized for scenarios where continuous glottic viewing may be beneficial such as confirmation of ETT exchange or visualization of laryngeal function, as well as for viewing passage of nasogastric tubes, transesophageal echocardiography probes, or upper gastrointestinal equipment (13).

For the pediatric population, a multitude of new video laryngoscopes that do not require neck extension have been designed, including those with camera integration into the laryngoscope blade, such as the Glidescope Cobalt (Verathon, Bothell, Washington) and Storz video laryngoscope (Karl Storz, Tuttlingen, Germany), as well as those utilizing prisms and mirrors, such as the Airtraq optical laryngoscope described above (Prodol Meditec, Vizcaya, Spain) and Truview EVO2 (Truphatek International, Netanya, Israel). Each of these new devices has their own particular advantage. The Glidescope Cobalt has multiple sizes of blades for different ages of children, as well as a warming device at the tip of the blade to reduce fogging. The Storz Video Laryngoscope can be used for direct laryngoscopy and converted to video laryngoscopy; a particularly useful tool in the suspected, but unconfirmed difficult pediatric airway. The particular advantage of the Airtraq is its portability and one time disposable use, making it well suited for nonoperating room use. The Truview EVO2 provides a wide angle magnified view, and provides an infant blade with a port for oxygen insufflation (27,28).

Despite the effectiveness of video laryngoscopy in managing the difficult intubation, its utility is surpassed by that of the LMA. The LMA is a minimally invasive airway device inserted blindly into the hypopharynx, sitting over the laryngeal opening, with its tip overlying the esophagus. The supraglottic device consists of an inflatable mask fitted against the periglottic tissues, to form a seal above the glottis, achieving ventilation of the lungs via a tube exiting the mouth (29). The concept of the LMA as a supraglottic ventilatory device was introduced into mainstream clinical practice in 1988 in the United Kingdom, approved by the Food and Drug Administration in 1991 in the United States, and has now become ubiquitous in the practice of anesthesia, emphasizing its ability to support ventilation without the need for endotracheal intubation. The LMA has proven to be beneficial in the management of difficulty with both intubation and ventilation and was added to the most recent edition of the ASA's difficult airway algorithm in 2003 (2). The LMA is routinely used in remote locations to administer anesthesia, as well as to facilitate bronchoscopy and tracheobronchial stent placement, awake craniotomy and stereotactic procedures and transesophageal echocardiography (30). Perhaps the most useful attributes of the LMA, are its utility in patients who cannot be ventilated by conventional mask ventilation, as well as serving as a conduit for endotracheal intubation either blindly, with an intubating stylet (31) or fiberoptic technology (32), or even for high-frequency jet ventilation (33).

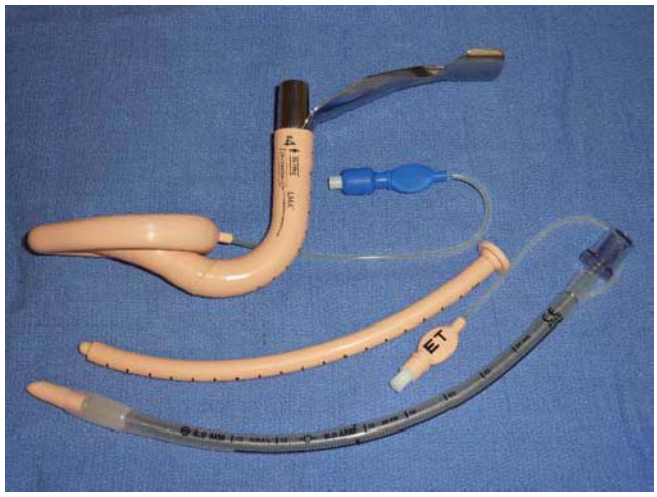


Figure 63.16 Fastrach intubating LMA with endotracheal tube.

The classic LMA does not protect the airway from regurgitation or aspiration, cannot be utilized in situations of subglottic obstruction, and cannot be used with airway pressures greater than 20 to 25 cm H_2O (34). Other supraglottic airway designs have incorporated gastric tubes or room for placement of separate gastric tubes through their device to reduce the possibility of aspiration (35). The Fastrach LMA is designed as an intubating LMA (Fig. 63.16), through which an ETT may be passed blindly into the trachea, and after which the LMA may either be left in place or removed using a specially designed pusher. This device was developed due to the shortcomings of the sizing of the classic LMA and need for specialized maneuvers to successfully pass the ETT through the LMA when used to facilitate intubation (36).

Although the Fastrach cannot be used for the pediatric population below 30 kg, a classic LMA may still be used as a conduit for insertion of the ETT (37). The LMA may serve as an adjunct for ventilation, while proceeding with attempts to secure the airway via intubation. Proper placement places the classic LMA with its distal opening overlying the glottis facilitating blind intubation; however, the most successful method for LMA-guided intubation in children utilizes the flexible fiberoptic scope as a stylet (Fig. 63.17) to advance the ETT through the LMA. The inability to pass the pilot balloon of a cuffed ETT may limit the feasibility of this technique in the younger age groups. However, the practitioner may cut the pilot balloon to facilitate placement of the cuffed ETT and then reconstruct the pilot balloon by inserting an IV catheter into the cut end of the tubing, removing the needle and attaching a one way Luer lock valve port adapter to the end of the IV catheter (Fig. 63.18). Another approach utilizes the specialized Air-Q LMA, with a wider and shorter tube than the standard LMA, accommodating the pilot balloon and minimizing the risk of accidentally pulling the ETT when removing the LMA (Fig. 63.19). A stabilizer bar is provided



Figure 63.17 Flexible scope used as a stylet to facilitate LMA-guided fiberoptic intubation.



Figure 63.19 Comparison of the wider and shorter shaft of the new Air-Q LMA with the classic LMA.

by the manufacturer to wedge inside the ETT, allowing successful removal of the LMA without catastrophic removal of the ETT (27).

Finally, ventilation utilizing an anterior commissure scope or rigid bronchoscope should be considered before proceeding with a surgical airway, such as a cricothyroidotomy or tracheostomy. These may also be helpful in ventilating the patient while a surgical airway is created. Alternate utilities of the rigid bronchoscope include the facilitation of endotracheal intubation by passing the rigid Hollinger telescope (Fig. 63.20) through the lumen of an appropriate sized endotracheal tube and under direct visualization passing the endoscope through the larynx for placement of the endotracheal tube. A gum elastic bougie or a Cook Airway Exchange Catheter may also be passed through the lumen of the bronchoscope, followed by removal of the bronchoscope and securing of the airway (38). Clearly, in difficult situations, preparation for a surgical airway should be considered, and at times initiated with possible life-saving results.

The major indication for cricothyroidotomy is the inability to establish an airway through orotracheal or nasotracheal intubation, which may be due to difficult patient anatomy, excessive bleeding in the mouth or nose, massive facial trauma, or airway obstruction resulting from angioedema, trauma, burns, or a foreign body obstructing the airway. The rate of failed emergency department intubations and subsequent surgical airway management is lower than 0.6%. In the emergency department, cricothyroidotomy has been used for 1.0% to 2.8% of all intubation attempts in patients with trauma. Whenever possible, cricothyroidotomy should be performed by physicians fully trained and skilled in carrying out the procedure, such as emergency physicians, surgeons, and intensivists. Surgical

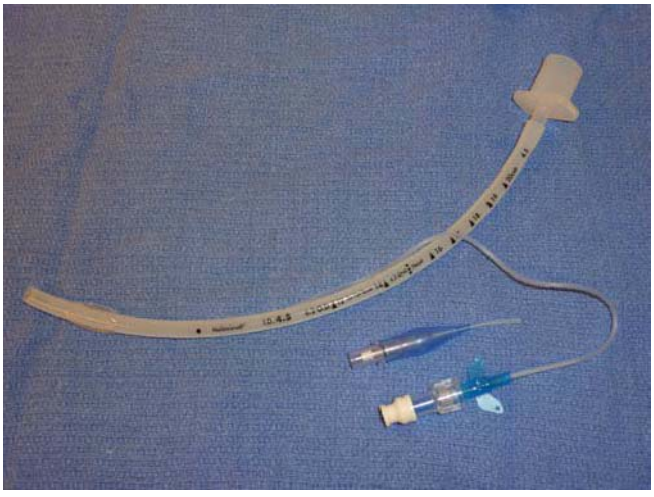


Figure 63.18 Reconstruction of the pilot balloon after LMA-guided fiberoptic intubation with a cuffed ETT.

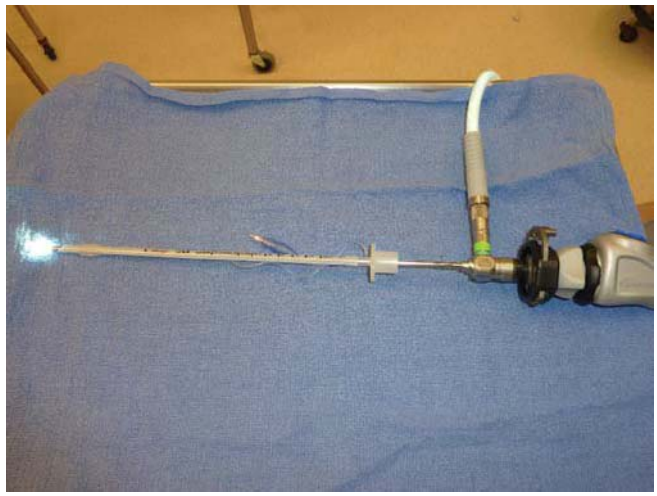


Figure 63.20 Hollinger telescope.

cricothyroidotomy involves inserting a tracheostomy tube into the trachea through an incision in the cricothyroid membrane. In needle cricothyroidotomy, a catheter is placed over a needle that penetrates the membrane, allowing ventilation by a pressurized stream of oxygen. Because the catheter has a smaller diameter, it is less effective in providing adequate ventilation and should be used only as a temporizing measure while preparation is made for surgical cricothyroidotomy or tracheostomy. Needle cricothyroidotomy is the preferred method of establishing an emergency airway in children younger than 10 to 12 years, since the larynx is more easily damaged by surgical cricothyroidotomy in this age group, with a higher incidence of postoperative airway complications.

To perform cricothyroidotomy, stabilize the larynx with your thumb and middle finger, and use your index finger to palpate the thyroid cartilage. Move your index finger down until you palpate the cricoid cartilage. The space between the thyroid and cricoid cartilages is the cricothyroid membrane. Use the scalpel to make a 2.5-cm vertical incision through the skin and subcutaneous tissue. Use the curved hemostat to make a blunt dissection in the subcutaneous tissue. Next, use the scalpel to make a horizontal incision through the cricothyroid membrane. Extend the incision laterally, turn the blade, and extend it in the opposite direction. Once the trachea has been entered, make sure the blade stays within the incision, so that communication with the trachea is never lost. Insert a tracheal hook, and pull upward on the distal portion of the incision, elevating the larynx. Once the tracheal hook is in place, you may remove the blade. Insert a Trousseau dilator and open the membrane vertically, then insert the tracheostomy tube. The anesthesia circuit is then connected to confirm the position of the tube within the airway (39).

In conclusion, the key to success when presented with difficult airway is preparation and a systematic approach for unexpected failure. In an unanticipated difficult tracheal intubation after routine induction of an adult or pediatric patient, each practitioner should become comfortable with a number of difficult airway tools to secure the airway, without the need to resort to surgical management. The key to success is utilization of these devices in routine intubations to achieve a high degree of comfort, allowing a degree of confidence to be present when greeted with the unexpected.

In our experience, utilizing video laryngoscopy in the manner described in this chapter should provide an improved laryngoscopic view to facilitate intubation. If difficulty is still encountered in placing the ETT despite the improved view, an intubating stylet or flexible fiberoptic scope may be employed to achieve tracheal intubation (40). Should these methods still prove unsuccessful, or in the desperate situation of failed intubation, increasing hypoxemia and difficult ventilation, the LMA Fastrach should be placed for adults, with the ETT passed into the trachea (41). In the pediatric population, the Air-Q LMA may be placed to facilitate ventilation, with a flexible fiberoptic scope or intubation catheter passed through the LMA to serve as a guide for the endotracheal tube to secure the airway. Clearly, a continuous dialogue and communication between the anesthesiologist and ENT surgeon, while simultaneously following an orderly and structured plan is critical for safety and success. Utilizing the ASA's Difficult Airway algorithm can help both the surgeon and anesthesiologist in avoiding the disastrous situation from developing, as well as grappling with unforeseen and challenging circumstances with a calm demeanor and appropriate focus.

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64 Advanced Airway Management—Intubation and Tracheotomy

Karen M. Kost

INTUBATION

History

The history of intubation is much more recent than that of tracheotomy. Up until the 19th century, tracheotomy, although considered to be dangerous, was also the most reliable method of achieving tracheal intubation.

The human glottis was first viewed in 1854 by Manuel Garcia, a Spanish vocal pedagogue, with a tool he developed using two mirrors and the sun as an external light source (1,2).

In 1858, a Parisian pediatrician, Eugene Bouchut, reported on a small straight metal tube he had developed that could be advanced into the larynx. He used this new nonsurgical orotracheal intubation device to bypass laryngeal obstruction resulting from diphtheria in seven cases. He went on to develop a set of tubes that could be used as an alternative to tracheotomy for cases of diphtheria, despite severe criticism from his colleague Armand Trousseau (3).

In 1878, Wilhelm Hack of Freiburg published two papers describing the use of nonsurgical orotracheal intubation (a) in the removal of vocal fold polyps and (b) to secure the airway in a patient with acute glottic edema (4). Visualization of the glottis had been indirect, through the use of mirrors, until 1895 when Alfred Kirstein performed the first direct laryngoscopy, using a modified esophagoscope he called an "autoscope" (5).

In 1913, Chevalier Jackson developed a new laryngoscope. It included a sliding removable portion for introduction of an endotracheal (ET) tube or bronchoscope as well as a light source at its distal tip (6). In the same year, Henry Janeway, an American anesthetist, designed a laryngoscope with several modifications specifically for tracheal intubation. His goal was to deliver volatile anesthetics through direct intratracheal insufflation. The intubating laryngoscope he developed had batteries within the handle to power the distal light source, a notched blade for keeping the tracheal tube midline during intubation and a slight curve at the distal tip of the blade. His work is largely credited with the subsequent incorporation of direct laryngoscopy and tracheal intubation into the specialty of anesthesia (7).

Subsequent noteworthy contributions included the work of Sir Ivan Whiteside Magill, who introduced the technique of awake blind nasotracheal intubation. The Magill forceps he designed for this purpose continue to be widely used in many hospitals across North America (8,9). In 1943, Sir Robert MacIntosh developed the Macintosh curved laryngoscope, which has withstood the test of time as the most popular laryngoscope blade for orotracheal intubation (10). MacIntosh also developed the precursor to the current ET tube introducer (often referred to as a "stylet"), used for difficult intubations.

Indications

Intubation is the placement of a flexible tube (most often made of polyvinyl chloride) into the trachea to maintain an open airway or to serve as a conduit through which certain drugs can be administered. Patients are usually intubated for controlled mechanical ventilation since an ET tube will provide a good seal for controlled ventilation with consistent inspired volumes and pressures compared with noninvasive methods.

Intubation is frequently performed in critically injured, ill, or anesthetized patients to facilitate ventilation of the lungs. Nonoperative indications (Table 64.1) include, but are not limited to the following: (a) head injury with loss of gag or cough reflex; (b) airway obstruction from laryngeal edema, epiglottitis, oropharyngeal, or laryngeal neoplasms; (c) neck trauma or multisystem trauma; (d) pulmonary toilet; and (e) respiratory failure, as may occur with pneumonia, emphysema, chronic obstructive pulmonary disease, and even asthma. Operative indications for ET intubation

TABLE 64.1 NONOPERATIVE INDICATIONS FOR INTUBATION

- Head injury with loss of gag or cough reflex
- Airway obstruction from laryngeal edema, epiglottitis, oropharyngeal, or laryngeal neoplasms
- Neck trauma or multisystem trauma
- Pulmonary toilet
- Respiratory failure from pneumonia, emphysema, chronic obstructive pulmonary disease, or asthma

(Table 64.2) include (a) protection of the airway from aspiration; (b) surgical procedures of the head and neck; (c) all situations involving the use neuromuscular paralysis; and (d) procedures that may involve intracranial hypertension.

Airway Assessment

In order to avoid unpleasant surprises and potential complications, patients should be carefully evaluated prior to proceeding with intubation. A history should be taken to assess past surgical procedures, comorbidities, and current medications. The airway history (Table 64.3) should be detailed and should include inquiries into the following conditions that may affect the intubation technique: (a) prior intubation, difficult or complicated intubation; (b) prior airway surgery, airway trauma, and head and neck neoplasms; (c) prior radiotherapy to the neck; (d) presence of dentures or loose or capped teeth; (e) trismus, temporomandibular joint problems, or difficulty opening the mouth; (f) cervical spine disease or instability; and (g) diagnosis of sleep apnea.

The physical exam (Table 64.4) will help in further identifying any problems and begins with vital signs, including heart rate, respiratory rate, blood pressure, and oxygen saturation. Stridor, use of accessory muscles, and/or cyanosis should be noted. Following a general physical exam and evaluation of body habitus, emphasis should be placed on evaluation of the head and neck. Assessing the oropharynx is helpful in predicting ease of intubation. The Mallampati system has been designed for this purpose and divides patients into four classes based on visualization of the oropharynx. This evaluation should be conducted with the mouth widely open, the tongue protruded, and the neck extended.

TABLE 64.2 OPERATIVE INDICATIONS FOR INTUBATION

- Protection of the airway from aspiration
- Surgical procedures of the head and neck
- All situations involving neuromuscular paralysis
- Procedures that may involve intracranial hypertension

TABLE 64.3 AIRWAY HISTORY PRIOR TO INTUBATION

- Prior difficult or complicated intubation
- Prior airway surgery, airway trauma, head and neck neoplasms
- Prior radiotherapy to the neck
- Presence of dentures or loose or capped teeth
- Trismus, temporomandibular joint problems, or difficulty opening the mouth
- Cervical spine disease or instability
- Diagnosis of sleep apnea

Mallampati Classification

Class I: The tonsillar pillars are visible in their entirety—intubation is likely to be straightforward

Class II: The uvula is visible, but the tonsillar pillars are partially or completely obscured

Class III: Only a portion of the uvula and soft palate are visible

Class IV: The tongue obscures the tonsillar pillars, uvula, and soft palate. Only the hard palate is visible—intubation is likely to be difficult (Fig. 64.1)

Additional findings that may affect planning and technique of intubation include the following:

(a) Facial deformities.
(b) Trismus—ideally the mouth opening should be at least three fingerbreadths.
(c) Limited neck mobility.
(d) Thyromental space—the distance from the mandible to the thyroid should be three fingerbreadths (6 cm) or greater. It is reduced in conditions such as retrognathia.
(e) Tissue compliance—the tissue should be soft, pliable.
(f) Poor dentition with mobile or fractured teeth or prominent or large teeth may all render intubation difficult.

TABLE 64.4 PHYSICAL EXAM PRIOR TO INTUBATION

- General: body habitus, vital signs, presence of stridor
- Assessment oropharynx (Mallampati classification)
- Facial deformities
- Trismus—mouth opening should be ≥3 fingerbreadths
- Limited neck mobility
- Thyromental space—should be ≥3 fingerbreadths (6 cm)
- Presence of retrognathia
- Tissue compliance
- Poor dentition: mobile or fractured teeth, prominent or large teeth
- Large tongue and/or high arched palate
- Impaired cognition

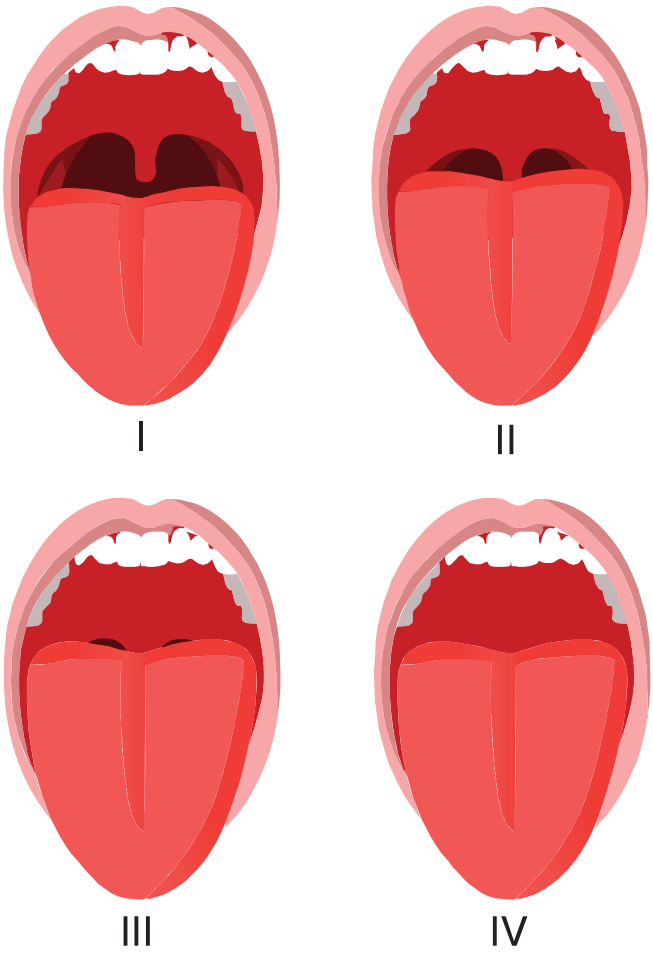


Figure 64.1 Mallampati classification.

(g) Large tongue and/or high arched palate—this may affect use of the laryngoscope or reduce visualization of the glottis. Ideally the oral cavity should be large and the tongue small.
(h) Impaired cognition.

Special Considerations

The decision to intubate or proceed to tracheotomy (Table 64.5) in any given situation must be based on a thorough review of several factors. These include the following: (a) Anticipated duration and need for mechanical ventilation. Patients with conditions such as epiglottitis, or laryngeal edema, who require short-term ventilator support are best managed with intubation. Conversely, patients with severe respiratory illnesses or head injuries who are likely to require prolonged ventilator support will benefit from early tracheotomy. (b) Skill of the anesthetist and skill of the surgeon. There are many conditions where it is appropriate to secure the airway with either ET intubation or tracheotomy. Pertinent otolaryngology examples include patients with deep neck space infections, severe facial trauma or neck trauma, and upper airway obstruction

TABLE 64.5 FACTORS IN DECISION MAKING: INTUBATION VERSUS TRACHEOTOMY

- Review of all pertinent clinical information
- Anticipated duration and need for mechanical ventilation
- Condition of the patient: for example, respiratory distress
- Skill of the anesthetist and skill of the surgeon
- Communication between anesthetist and surgeon
- Establishing a clear plan of action

from laryngeal edema or neoplasms. The decision in these cases must be predicated on the condition of the patient, the skill and experience of the anesthetist and surgeon, and review of all pertinent clinical information including the history, physical exam, imaging studies, and laboratory data. Communication between the surgeon and anesthetist is critical in establishing a clear and safe plan of action. For example, in the case of a deep neck space infection, each of the following scenarios may be correct: (i) a skilled and experienced anesthetist may feel comfortable attempting an awake fiberoptic intubation with the surgeon on "standby," scrubbed and ready to intervene with a tracheotomy; (ii) a less experienced anesthetist may defer to the skill of the surgeon in establishing the airway; and (iii) the anesthetist and surgeon may decide to proceed directly to tracheotomy because it is neither safe nor possible to attempt intubation.

Endotracheal Tube Selection

The ET tube size should be determined based on the patient's gender and clinical needs. In general, smaller tubes with an internal diameter (I.D.) between 6.5 and 7.5 are preferred in adult females while slightly larger tubes with an I.D. of 7.0 to 8.0 are used in males. In patients with airway compression or narrowing, smaller tubes may be chosen. Obese patients generally require slightly larger tubes to compensate for the increased weight on the chest and higher ventilation pressures. It is prudent to have several sizes available. There are several different types of ET tubes, including commonly used polyvinyl chloride tubes, armor tubes, and laser-resistant tubes. Specific tube shapes have been developed for nasotracheal and orotracheal intubation, and particular surgical situations such as tonsillectomy (Fig. 64.2).

Orotracheal Intubation

The most widely used route for intubation is orotracheal, in which an ET tube is passed through the mouth and vocal folds into the trachea. It is the simplest technique and that with which anesthetists and critical care physicians have the greatest experience and familiarity. It is appropriate for many operative otolaryngology cases including sinonasal and otologic procedures. It may also be used



Figure 64.2 *Left to right*: orotracheal tube, nasotracheal tube, tonsillectomy tube, armor tube.

for parotidectomy, excision of neck masses, and neck dissections provided the tube is secured away from the surgical side and access to the oral cavity is not required. Orotracheal intubation may be accomplished blindly or with the help of fiberoptic scopes. In the majority of cases, however, a rigid curved MacIntosh laryngoscope is used to facilitate the intubation.

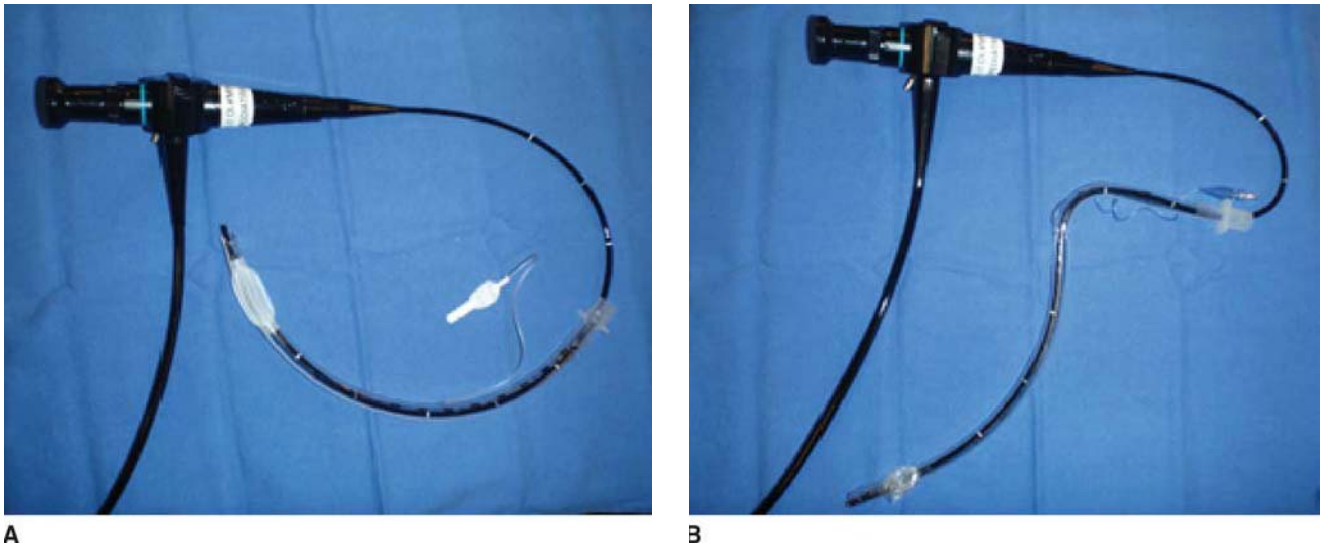
Prior to initiating the intubation, the patient should be positioned with the neck slightly flexed on the chest and the head slightly extended on the neck. The patient should be preoxygenated by delivering O_2 through a well-fitted mask. The pharynx and oral cavity should be thoroughly suctioned. The right-handed physician stands at the head of the bed, and holds the MacIntosh laryngoscope in the left hand. The right hand gently opens the mouth, being careful not to impale the lips on the teeth, and the left hand introduces the laryngoscope into the right side of the mouth, displacing the tongue over to the left as the tip is advanced into the vallecula. The larynx is lifted anteriorly to expose the glottis. The ET tube, held in the right hand, is advanced into and through the glottis. Pressure on the cricoid cartilage may be used to facilitate intubation in an anteriorly positioned larynx and has the added advantage of decreasing the risk of aspiration by closing the opening to the esophagus. Following intubation, air entry into both lungs is verified and the tube is secured in position with tapes.

In difficult cases where the first few intubation attempts fail, a different approach should be considered. This may include using intubation aids such as the GlideScope, or switching to a different technique altogether, such as intubation over a flexible fiberoptic bronchoscope.

In patients with limited mouth opening, or a narrow airway from whatever reason, awake intubation over a flexible fiberoptic bronchoscope (Fig. 64.3) provides direct visualization of the glottis and adds a measure of safety. This technique is one of the cornerstones of difficult airway management. Patient comfort is greatly improved with good topical anesthesia of the oral cavity and pharynx and the addition of a superior laryngeal nerve block. Use of an oral airway prevents biting on the ET tube and bronchoscope. Flexible fiberoptic intubation is very useful in cases of laryngeal edema, deep neck space infections, laryngeal papillomatosis, and other neoplasms.

Nasotracheal Intubation

Nasotracheal intubation is another means by which the airway can be protected. It is very useful and provides unhindered access for major head and neck oncologic procedures involving the oral cavity and oropharynx. It may also be used when orotracheal intubation is not possible or otherwise contraindicated. Nasotracheal intubation is



A B

Figure 64.3 **A:** Fiberoptic orotracheal intubation. **B:** Fiberoptic nasotracheal intubation.

best used for short-term airway protection because of the high incidence of sinusitis, serous otitis media, acute otitis media, and the risk of alar necrosis associated with the more prolonged use of these tubes. It is contraindicated in patients with midface fractures involving the cribriform plate or fovea ethmoidalis because of the risk of entering the brain.

Nasotracheal intubation may be performed blindly, or with the use of rigid or flexible laryngoscopes. Retrograde techniques are also described but are beyond the scope of this chapter.

In the awake patient, nasotracheal intubation is better tolerated than orotracheal intubation. Adequate preparation of the patient is a wise investment in time and will ensure a smooth procedure. A quick look at the nose with a nasal speculum will help identify septal deviations or other anatomic abnormalities that may interfere with the intubation. Good topical anesthesia and vasoconstriction can be achieved by packing the nose with cotton wool impregnated with lidocaine and a decongestant. Alternatively, topical sprays may be used. Topical anesthesia of the pharynx can be obtained by using lidocaine which is either gargled or nebulized. A superior laryngeal nerve block can also be a helpful adjunct. With good topical anesthesia and vasoconstriction, the nasal cavity can be dilated with progressively larger nasal "trumpets." Ideally the tube should be warmed prior to use to make it more pliable. The warmed, lubricated nasotracheal tube is inserted into the nasal cavity and advanced to the pharynx. At this point, an intubating laryngoscope in the left hand is placed in the right side of the oral cavity and advanced to the vallecula. The tip of the nasotracheal tube, visible on the posterior pharyngeal wall, is grasped with a Magill forceps held in the right hand, and advanced through the glottis. Good air entry to both lungs is verified, and the tube is secured.

When a difficult intubation is anticipated, fiberoptic nasotracheal intubation (Fig. 64.3) is a good choice. It is an extremely important and successful technique in patients with difficult airways. In particular, it should be considered in patients with limited neck mobility, limited mouth opening, and a short thyromental space. Intubating patients having received prior radiotherapy or surgery to the head and neck can be extraordinarily difficult. In these cases, fiberoptic nasotracheal intubation is likely to be successful, and is especially attractive because it can be performed on the awake, spontaneously breathing patient. The nose and upper airway are prepared with topical anesthesia as previously described. The nasotracheal tube is threaded over the fiberoptic bronchoscope. A size 7 ET tube is the smallest size that will accommodate an adult bronchoscope. A pediatric bronchoscope must be used with size 6 or 6.5 ET tubes. The bronchoscope is introduced into the nose and advanced through the glottis. The nasotracheal tube then follows over the bronchoscope down through the glottis and into the trachea.

Blind nasotracheal intubation is a rarely used "rescue technique" when advancing the tube with the help of a laryngoscope or when fiberoptic intubation or orotracheal intubation is not possible. Patients must be breathing spontaneously. Topical anesthesia is used as much as the situation permits. The tube is introduced through the nose, and advanced into the hypopharynx, with the operator listening for breath sounds as the tube approaches the glottis. The tube is advanced through the glottis just as the next inspiration is begun. Air entry is verified, and the tube is secured. Tips to facilitate passage through the glottis include external pressure on the neck and use of a stylet through the ET tube after it has passed through the nasopharynx. It must be emphasized that this technique is difficult, requires skill and experience, and is associated with higher complication rates than other techniques.

Intubation Aids in the Difficult Airway

In difficult cases where the first few intubation attempts fail, a different approach should be considered. This may include using intubation aids (Table 64.6) such as the GlideScope, or switching to a different technique altogether, such as intubation over a flexible fiberoptic bronchoscope. Repeatedly attempting to intubate orotracheally after a few failed attempts may lead to airway edema, trauma, and bleeding, rendering both visualization and ventilation by any means difficult. What started as a routine intubation becomes a potentially life-threatening emergency.

The most frequently used intubating instrument is the MacIntosh laryngoscope (Fig. 64.4) with the curved blade. This laryngoscope, in its original design, is intended to be held in the left hand. A mirror image of the MacIntosh blade is available for left-handed operators to hold in the right hand leaving the dominant hand for intubation. It is introduced into the left side of the mouth and may also be used in patients with right-sided facial abnormalities or injuries. The English MacIntosh laryngoscope has become the preferred instrument in many centers, because of the continuous curve along the entire length of the blade, and the distal extension of the vertical step and flange. Considered together, these modifications provide a better view of the glottis in many cases. A very large number of subtly modified curved blades, all with intended specific uses, have also been developed (11).

TABLE 64.6 INTUBATION AIDS IN THE DIFFICULT AIRWAY

- Intubation over a fiberoptic bronchoscope
- Use of a stylet or a lighted stylet
- Use of a GlideScope
- Straight laryngoscope blades
- Fiberoptic viewing laryngoscopes

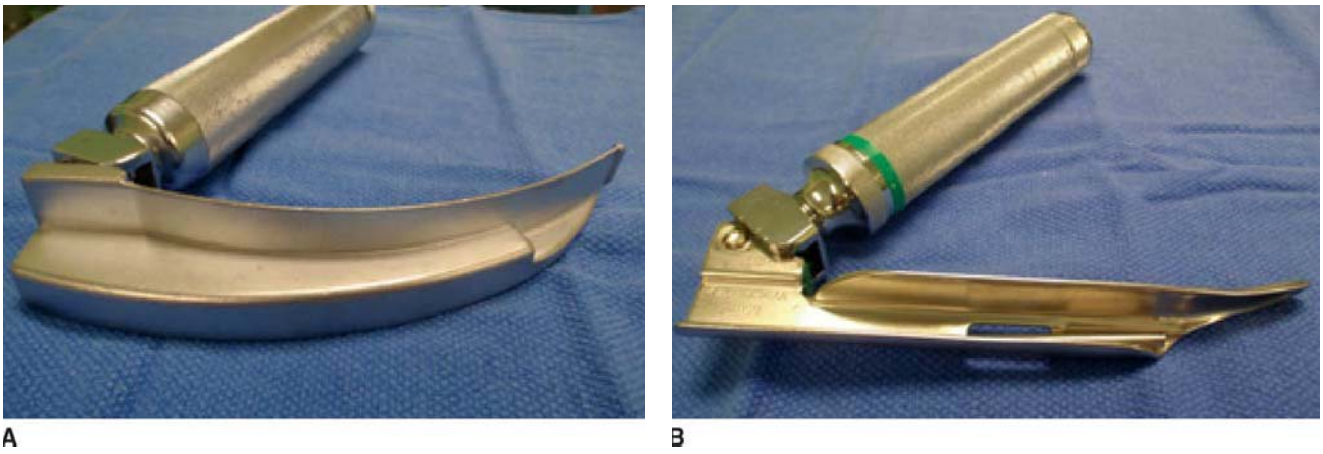


Figure 64.4 **A:** Curved MacIntosh blade. **B:** Straight Miller blade.

An impressive variety of straight blades also exists, of which one of the earliest and still most commonly used is the Miller laryngoscope blade (Fig. 64.4). It is straight, with a gradual curve 5 cm from its narrow tip, and a smaller vertical step compared to the MacIntosh blade. Straight blades are intended to "entrap" and lift the epiglottis, in contrast to the curved blades. Straight blades are especially useful in patients with limited mouth opening as is often the case in previously operated or radiated necks. In these situations, the slimmer blade fits more easily between the teeth, and the distal curved tip allows visualization of the laryngeal inlet. Because the space for maneuvering the ET tube is limited with this type of blade, use of a stylet is recommended (11).

A number of stylets are available to facilitate intubation. They are long, thin, malleable devices that are inserted into ET tubes and bent or adjusted to a desired shape and curvature. They may be entirely within or extend beyond the ET tube. Some even have a small light at the distal end. The curve of the ET tube afforded by the stylet is helpful when the larynx rests in an anterior position.

The occasional failure of direct laryngoscopy to provide an adequate view for tracheal intubation in the difficult airway led to the development of alternative devices such as the lighted stylet, and a number of indirect fiberoptic viewing laryngoscopes, such as the fiberscope, Bullard scope, Upsher scope, and the WuScope. A detailed discussion of each of these devices is beyond the scope of this chapter. Though these devices can be effective alternatives to direct laryngoscopy, they each have certain limitations, and none of them is effective under all circumstances. One important limitation commonly associated with these devices is fogging of the lens.

The introduction of digital technology has led to the development of several video laryngoscopes designed to facilitate tracheal intubation. The GlideScope emerged in 1991 as the first of several similar devices. The GlideScope incorporates a high-resolution digital camera, which is connected by a video cable to a high-resolution light crystal display monitor (Fig. 64.5). The high degree of success in intubating difficult airways with the GlideScope is the result of five special features. (a) The sharp 60-degree angulation of the blade reduces the need for displacing the tongue anteriorly, thereby improving the view of the glottis. (b) Instead of being at the tip of the blade, the CMOS APS digital camera is located at the point of angulation of the blade, providing a better view of the field in



Figure 64.5 GlideScope with recessed position of digital camera and light crystal display monitor.

front of the camera. (c) The recessed position of the video camera shields it from blood and secretions that might otherwise obstruct the view. (d) The video camera has a relatively wide viewing angle of 50 degrees. (e) The incorporated heated lens helps prevent troublesome fogging of the lens. The blade of the GlideScope is introduced as for a MacIntosh blade, and advanced through the oropharynx with the operator viewing the procedure on the monitor. When the optimal view is achieved, the ET tube is introduced and guided into the larynx, with the help of the image from the monitor. The use of a stylet precurved at approximately 60 degrees facilitates access to the glottic opening.

The GlideScope has been shown to improve laryngeal views compared with direct laryngoscopy with high success rates of intubation in normal airways, following failed direct laryngoscopy, and in predicted difficult airways (12). In the latter situation, the success of the GlideScope is approximately 92% on the first attempt, and increases from 96% to 100% after more than one attempt. In contrast, increased laryngoscopy attempts are associated with increased morbidity. The most important predictors for failure with the GlideScope include a thyromental distance of less than 6 cm and abnormal neck anatomy such as a neck mass or history of prior irradiation. Important predictors of failure for direct laryngoscopy include the combination of a high Mallampati score and reduced thyromental distance, as well as abnormal neck anatomy (12). This highlights the importance of careful preoperative patient assessment, and discussion between the anesthesiologist and surgeon to come up with a thoughtful plan that includes alternative techniques such as flexible fiberoptic intubation.

In summary, there exists a large and ever-expanding array of intubating aids and devices for management of the difficult airway. Although each has its place and utility, it should be emphasized that fiberoptic orotracheal or nasotracheal intubation remains a cornerstone in the management of the patient with a difficult airway.

The Hunsaker Tube and Jet Ventilation in Microlaryngeal Surgery

Microlaryngeal surgery involves sharing the airway. A balance must be achieved between airway control and ventilation and the need for adequate laryngeal visualization and exposure.

In 1967, Sanders introduced jet ventilation for use during rigid bronchoscopy (13). In the 1970s, the concept was adapted for use in microlaryngeal surgery as a means of providing adequate ventilation and maximizing exposure. The technique involves positioning and suspending a laryngoscope to expose the glottis. An injector cannula, tightened to the laryngoscope, allows for the high-pressure delivery of air from above the vocal folds. Exhalation is passive, and requires an unobstructed airway. The technique offers excellent exposure of the larynx at the expense of airway control.

TABLE 64.7 ADVANTAGES OF HUNSAKER TUBE IN MICROLARYNGEAL SURGERY

- Can be used with stylet
- Excellent exposure
- Laser safe
- Versatile

The technology has been further modified for supraglottic, subglottic, and transtracheal jet ventilation.

Several tubes have been developed for subglottic ventilation, but their use was limited by problems such as misalignment, inadequate ventilation, inability to monitor airway pressures, and the risk of airway fires with laser use.

In 1994, Hunsaker introduced a special laser-safe subglottic tube designed specifically for microlaryngeal surgery (14). Airway pressures and end-tidal CO_2 could be monitored through the tube that was attached to a dedicated jet ventilator.

The Hunsaker Mon-Jet tube offers excellent laryngeal visualization and anesthetic safety. It is very versatile and can be used in patients with comorbidities, obesity, and difficult airways (Table 64.7). It provides excellent laryngeal exposure for a wide range of endolaryngeal procedures using laser, cold steel, or the microdebrider (15,16). When used with the laser, it is important to keep oxygen concentrations as close to room air as possible in order to prevent airway fires. In addition, the subglottic position minimizes vocal fold movement during surgery.

The tube itself is 35.5 cm long with an inner diameter of 2.7 mm and an outer diameter of 4.3 mm. Because it is made with a nonflammable fluoroplastic material, it can be safely used with lasers. A metal stylet adds some rigidity to the tube, thereby facilitating intubation. The green basket at the end of the tube helps center the tube within the trachea, and prevents the jet port from coming into direct contact with the mucosa (Fig. 64.6). There is a 1-mm port for monitoring airway pressures and end-tidal CO_2 that opens 3.2 cm above the jet port.

The intubation technique is the same as for orotracheal intubation with a MacIntosh laryngoscope. Once in proper

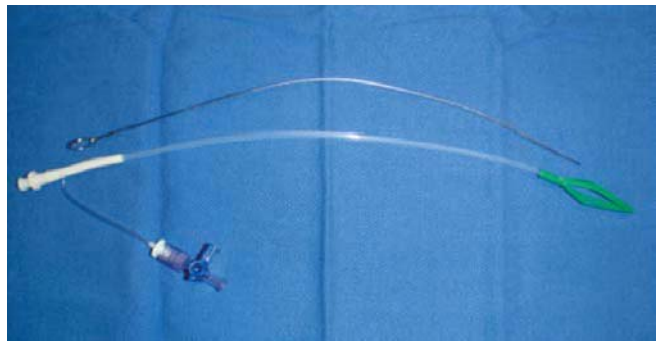


Figure 64.6 Hunsaker tube. Note *green* basket and metal stylet.

TABLE 64.8 COMPLICATIONS FROM JET VENTILATION WITH THE HUNSAKER TUBE

- Hypoxia and/or hypercarbia
- Bleeding into the trachea from the surgery
- Barotrauma

position, the jet port and monitoring port of the tube are attached to the jet ventilator. An automated jet ventilator is preferred because of the automatic "shut-off" if airway pressures exceed preset limits. The tube should be secured at the corner of the mouth and supported in order to avoid kinking. When the laryngoscope is not in position or the patient's mouth is closed, an oral airway should be used to allow passive exhalation.

Complications from this technique (Table 64.8) are seen in less than 2% of cases and consist mostly of hypoxia and/or hypercarbia and rare bleeding down the trachea from the surgical procedure. In all these cases, the Hunsaker may be exchanged for a laser-safe ET tube. Appropriately securing the tube is important to avoid kinking. Barotrauma can be largely prevented with an automated jet ventilator (16).

The Laryngeal Mask Airway

The laryngeal mask airway (LMA) was developed in the 1980s by Dr. Archie Brain as a supraglottic airway device that could be used as an alternative to (a) the more invasive ET intubation, or (b) face-mask ventilation, which is difficult to control. The LMA consists of an inflatable mask attached to a tube that exits through the mouth and can be connected to a ventilator (Fig. 64.7). The mask contours the periglottic tissues while occupying the hypopharyngeal space. Once inflated, it forms a seal above the glottis in contrast to an ET tube, which forms a seal within the trachea. It requires some training, but is relatively easy to insert, can be used blindly without accessory instruments, and is associated with infrequent complications. An important limitation is that it does not protect against abdominal contents and aspiration. Many modifications of the original device have emerged to adapt to particular clinical situations and expand the indications for use. The LMA, or one of its modifications, can be used in the following situations: (a) as a routine airway or ventilation device, (b) in emergency cases with a "cannot intubate, cannot ventilate" scenario, and (c) with the modified LMA Fastrach, as a conduit for ET intubation (17).



Figure 64.7 Classic LMA.

The original device, the "LMA Classic," is useful for short, elective, nonotolaryngology cases requiring general anesthesia in the supine position. Because a fiberoptic endoscope can easily be passed through the LMA, it is useful in otolaryngology for diagnostic evaluation of the larynx and during percutaneous tracheotomy. The LMA Classic has also been shown to be very useful in the emergency or nonemergency management of patients with difficult airways. Examples include patients with the following conditions: (a) cervical spine immobility or instability; (b) morbid obesity; (c) micrognathia; (d) congenital syndromes such as Treacher-Collins, Pierre-Robin, and Down syndrome; and (e) unexpected failed intubation with difficult face-mask ventilation (Table 64.9). Indeed, the LMA has been incorporated into the "Practice Guidelines for the Management of the Difficult Airway" by the American Society of Anesthesia (ASA) Task Force on Management of the Difficult Airway (17).

A modified version, the intubating LMA Fastrach, was introduced in 1997 and is intended to facilitate blind or fiberoptically guided ET intubation in difficult airways such as C-spine injuries, where head position must remain neutral (18). It consists of a hollow 13-mm stainless steel tube connected distally to the laryngeal mask. Proximally, a handle helps with insertion and placement. Once it is positioned, a special ET tube can be advanced through the

TABLE 64.9 ADVANTAGES OF THE LARYNGEAL MASK AIRWAY

- Less invasive than ETT
- Can be used blindly without accessories
- Can be used with fiberoptic scope
- Useful in difficult airway. For example, C-spine instability, obesity, micrognathia
- Useful in emergencies. For example, failed intubation
- Few complications

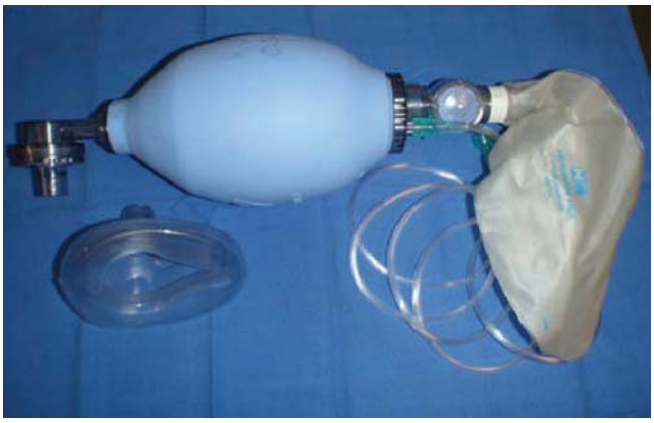


Figure 64.8 Mask and resuscitation bag.

lumen into the trachea either blindly or over a fiberoptic bronchoscope. The intubating LMA Fastrach is a well-recognized "rescue device" for difficult airways. The C-Trach represents an additional modification with a camera integrated into the LMA, allowing the operator to visualize the ET tube being introduced through the glottis (18).

Noninvasive Ventilation

This approach relies on the use of a well-fitted mask covering the nose and mouth, along with a self-inflating resuscitation bag (Fig. 64.8). Maintaining a proper seal between the mask and the patient's face is necessary for adequate ventilation. This may not be possible in patients with facial trauma or severe facial deformities. In obese patients or those with difficult anatomy, the use of nasopharyngeal and oropharyngeal airways may be helpful. Although useful as a temporizing solution prior to definitive airway protection, the bag and mask technique provides no protection from aspiration, and maintaining an adequate seal quickly becomes tiring for the operator.

Complications of Intubation

Many if not most complications are preventable with careful planning, selection of the appropriate intubation technique, and attention to technical detail. Not surprisingly, complications are much more frequent following difficult or traumatic intubations (Table 64.10).

Nasal trauma may occur during nasotracheal intubation with possible injury to the mucosa, septum, turbinates, and adenoids. Nasotracheal tubes kept *in situ* postoperatively increase the risk of nasal alar injury, sinusitis, and otitis media. Long-term sequelae include nasal synechia as well as scarring and distortion of the nasal tip and/or ala. Although some epistaxis is common with nasotracheal intubation, it is usually self-limited. Nasal trauma can be minimized by maximally decongesting the nose, using nasal trumpets for dilatation, and warming and lubricating the nasotracheal tube.

TABLE 64.10 COMPLICATIONS OF INTUBATION

- Lip injury
- Dental injury
- Nasal trauma (nasotracheal intubation)
- Mucosal injury
- Macroglossia
- Laryngeal/tracheal trauma
- Bronchial intubation
- Esophageal intubation
- Esophageal/pharyngeal/pyriform sinus perforation
- Intracranial intubation
- Pulmonary edema
- Barotrauma (with jet ventilation)
- Airway obstruction
- Nerve injuries
- Cervical spine injuries
- Corneal abrasions

Lip trauma usually occurs on the right upper lip as a result of inattentive laryngoscopy during intubation. It is usually self-limited and requires only comfort measures.

Dental injuries occur in approximately 1 in 4,500 cases and usually involve the maxillary central incisors. These injuries are most common in young children, in patients with preexisting periodontal disease, and in cases where intubation is difficult. Chipped or cracked teeth should be located and removed to prevent tooth aspiration.

Macroglossia, or massive tongue swelling, has been reported, and is thought to result from venous and lymphatic obstruction of the tongue. It is associated with prolonged procedures and compression of the tongue by the ET tube. Less commonly, it may be seen with angiotensin-converting enzymes. In extreme cases the airway may need to be secured with a long nasal trumpet or nasotracheal tube.

Mucosal injury to all areas of the oral cavity and pharynx is possible and may occur from the laryngoscope, oral airway, ET tube or any other device that is used. Up to 40% of patients complain of sore throat following intubation, with even larger numbers in cases of traumatic intubation. Fortunately, most symptoms resolve in 24 to 48 hours.

Laryngeal trauma from intubation may occur in up to 6% of cases and is most likely following traumatic intubation. Injuries may include vocal fold lacerations or hematoma, arytenoid dislocation or subluxation, vocal fold paralysis, and granuloma formation. Use of large tubes, particularly in females, results in tissue ulceration of the posterior larynx and increases the risk of posterior glottic stenosis. The risk is even greater in agitated patients with nasogastric tubes and gastroesophageal reflux.

Tracheal trauma may be related to several factors. An overinflated cuff that exceeds capillary perfusion pressures

results in local tissue hypoxia, necrosis, and eventual healing with malacia or stenosis. Use of large ET tubes, especially in females, may similarly result in stenosis. Intubating stylets, tube exchangers, and malpositioned tubes may also result in tracheal injury. In young children, edema in the subglottic area following extubation increases airway resistance and may result in croup-like symptoms.

Bronchial intubation, especially of the right mainstem bronchus, is relatively common and may manifest as absence of breath sounds on the left side and asymmetric chest expansion. It is even more common in children and may be undetected until hypoxia, atelectasis, or even pulmonary edema further complicate the situation.

Inadvertent esophageal intubation is not uncommon, and, provided it is recognized, can be quickly rectified without adverse effects such as hypoxia. Preoxygenation prior to intubation provides a "safety cushion" of 6 to 9 minutes before hypoxemia occurs. Presence of an end-tidal CO_2 is crucial in confirming placement of the ET tube.

Perforation of the esophagus, pharynx, and pyriform sinus are all possible, particularly with difficult intubations. These are serious complications that may progress to neck abscesses, subcutaneous emphysema, pneumothorax, mediastinitis, sepsis, and death. Early recognition and treatment are important because the mortality associated with mediastinitis is at least 50%.

Intracranial intubation is a rare but disastrous complication that usually results from attempted nasotracheal intubation in the presence of skull base fractures or facial trauma.

Pulmonary edema may occur following sudden relief of chronic airway obstruction. It may manifest in the operating room (OR), or later in the recovery room following extubation. Hypoxia, difficulty ventilating the patient, and pink foamy fluid in the ET tube should arouse suspicion as to the cause. The diagnosis is confirmed with a chest radiograph. Treatment usually consists of mechanical ventilation with positive end-expiratory pressure (PEEP) and diuretics.

Barotrauma is usually associated with jet ventilation techniques such as those used in microlaryngeal surgery. High-flow insufflation through catheters distal to the glottis may result in air tracking into peribronchial tissues. Unrecognized, the situation may progress to pneumomediastinum or tension pneumothorax. As discussed previously, use of Hunsaker tubes with automated jet ventilators is helpful in minimizing the risk of these injuries.

Airway obstruction may occur from occlusion of the tube from blood or secretions. Other potential causes include kinking of the tube or, more rarely, cuff herniation over the tip of the tube. Tubes may also become dislodged or disconnected, particularly when they are hidden under surgical drapes. Early recognition is key in rectifying the problem and preventing adverse effects.

Nerve injuries usually result from pressure and may involve the lingual nerve, hypoglossal nerve, recurrent laryngeal nerve, and internal branch of the superior laryngeal nerve. Fortunately, the vast majority are temporary and self-limited. Rare cases of transient hyposmia have been reported following nasotracheal intubation.

Cervical spine injury usually results from excessive neck manipulation and force in attempting to intubate patients with preexisting disease such as ankylosing spondylitis and rheumatoid arthritis. In patients with C-spine fractures, inadequate immobilization prior to intubation may aggravate or worsen the injury. Fiberoptic intubation is often a safer choice in these individuals.

Corneal abrasions are relatively common injuries associated with general anesthesia. They may result from a mask or other object rubbing against the eye or from the eyes being left partially open during anesthesia. Ophthalmology should be consulted for abrasions. Treatment usually consists of antibiotic ointment with an eyepatch. These injuries may be prevented by taping the lids closed and applying eyepads, particularly during head and neck surgery.

TRACHEOTOMY

Introduction (History)

The word "tracheotomy" is derived from the Greek words "tracheia arteria," meaning "rough artery," and "tome," meaning "to cut." The word "tracheostomy" comes from the Greek ending "stoma," which means "to finish with an opening or mouth." Although strictly speaking, "tracheostomy" should be used when a permanent opening is intended, nowadays the two terms are used rather loosely and interchangeably (19).

Tracheotomy has a long and colorful history. The first reference to the procedure can be found in the sacred book of Hindu medicine, the Rig Veda, dated to approximately 2000 BC. Alexander the Great is reported to have performed a tracheotomy in the fourth century BC when he "punctured the trachea of a soldier with the point of his sword when he saw a man choking from a bone lodged in his throat" (20). Antonio Musa Brasavola is credited with the first successful procedure, when he documented saving the life of a patient close to death from an "abscess of the windpipe" in 1546. The first work devoted solely to tracheotomy consisted of a 108-page book written and published in 1620 by Nicholas Habicot of Paris. In it, he described four successful tracheotomies, one of which involved a 14-year-old boy who intentionally swallowed a bag of gold coins to prevent their theft. The bag became lodged in his esophagus, producing upper airway obstruction. Habicot relieved the obstruction by performing a tracheotomy, and subsequently manipulated the bolus of coins, facilitating its esophageal descent. The boy recovered, and several days later the coins were recovered from the rectum. Despite these success stories, tracheotomy remained a marginal procedure viewed with suspicion and fear for several centuries because of very high morbidity

and mortality rates. Echoing these thoughts, Fabricius ab Aquapendente wrote: "The terrified surgeons of our times have not dared to exercise this surgery and I also have never performed it. Even the mention of this operation terrifies the surgeons; hence it is called the scandal of surgery." In 1799, when Dr. Elisha Dick recommended that a tracheotomy be performed for a patient in airway distress, two colleagues vocally opposed him, and on December 14, 1799, George Washington died of an acute upper airway obstruction.

It was not until the 19th century that prevailing attitudes toward tracheotomy began to change rather dramatically. Although the procedure had been previously described in children, first in 1766 by Caron to remove a bean lodged in the airway, and later in 1782 by Andrée, it was the description of a life-saving tracheotomy in a child in 1825 that seems to have singularly had the greatest impact. In that year, Bretonneau saved the life of a 5-year-old girl called Elisabeth de Puysergur who was suffering from diphtheria by performing a tracheotomy (19). Shortly thereafter, in 1833, Armand Trousseau recounted, "I have now performed the operation in more than 200 cases and I have the satisfaction of knowing that one-fourth of these operations were successful" (21).

Gradually, the repertoire of indications for tracheotomy cautiously expanded to include not only upper airway obstruction from croup and diphtheria, but also that resulting from trauma, tuberculosis, or syphilis. During the early 20th century, tracheotomy found a brief new indication in the administration of general anesthesia, and was touted as the only means of securing an airway. As the use of ET intubation was popularized, however, this particular use waned. During this time, subjects such as technique, complications, tube morphology, tracheostomy placement, and anesthesia were hotly debated in the medical literature, and there were almost as many views as there were surgeons.

It was to be the work of Chevalier Jackson, in 1909 (22) that would finally dispel the aura of fear and mystery that for so long had been associated with tracheotomy. Only then was the procedure firmly established as a useful tool in the surgeon's armamentarium. Jackson standardized the technique and indications for the operation, and demonstrated that with attention to a few key technical details, the morbidity and mortality from the procedure could be dramatically reduced to acceptable levels. He emphasized the importance of a long incision, avoidance of the cricoid cartilage, routine division of the thyroid isthmus, slow and careful surgery, use of a proper cannula, and meticulous postoperative care. Of the latter, Jackson wrote that "after-care in tracheotomy cases is one of good plumbing, that is, keeping the pipes, both natural and artificial, clear of obstruction. Air must be piped not merely into the trachea, but also into the lungs, and it must be the constant duty of someone to know by seeing, feeling, and hearing that it gets there." Jackson's thoughtful advice was in large part responsible for reducing the mortality of tracheotomy to less than 2% and reducing the incidence of laryngeal stenosis, particularly in children.

Indications for Tracheotomy

In most instances, ET intubation is used for short-term airway protection and/or ventilation. Over half of modern-day tracheostomies are performed on critically ill patients requiring prolonged mechanical ventilation. Other indications include pulmonary toilet, sleep apnea, chronic lung disease, primary alveolar hypoventilation syndrome (Ondine curse), and conditions requiring home mechanical ventilation (23,24). The need to establish a surgical airway may become more emergent in upper airway obstruction from trauma, neoplasms, deep neck space infections, surgery, and foreign bodies (Table 64.11).

The primary objective of a tracheotomy is to secure an artificial airway. Over the years, the indications for tracheostomy have continued to change in parallel to the evolution of medicine. Current major indications for tracheotomy include (a) relief of upper airway obstruction (both acute and chronic), (b) providing a means for assisted mechanical ventilation, and (c) enabling more efficient tracheobronchial toilet (Table 64.11). The decision to carry out a tracheotomy must be carefully considered, weighing the relative advantages and risks of tracheotomy versus alternative methods of providing an artificial airway. Factors influencing the decision include the facilities of the institution, the skills of the personnel, the particular features of the patient's airway and respiratory physiology, and the specific disorder or disease process and its likely course (25).

Whenever possible, patients with upper airway obstruction should be managed initially by ET intubation in order to stabilize the airway and the patient's general condition. Extubation is often possible as the condition improves. Examples may include the management of acute epiglottitis in children or adults, and angioneurotic edema of the larynx.

Patients with upper airway obstruction, from laryngotracheal trauma or neoplasms of the upper aerodigestive tract, may be stabilized with ET intubation initially but are likely to require conversion to a tracheotomy. In children, tracheotomy may be necessary to protect the airway in

TABLE 64.11 INDICATIONS FOR TRACHEOTOMY

- Prolonged mechanical ventilation
- Pulmonary toilet
- Upper airway obstruction, acute or chronic

conditions such as laryngeal papillomatosis and subglottic hemangioma.

Tracheotomy is often necessary in patients with chronic upper airway obstruction. Examples include patients with nasal and craniofacial anomalies, such as Crouzon's disease, large nasal encephaloceles, Treacher-Collins syndrome, subglottic stenosis, and laryngeal and subglottic webs. Premature infants with respiratory insufficiency who require artificial ventilation for long periods are at risk for developing iatrogenic laryngeal or subglottic stenosis from chronic airway management.

Patients with central nervous system disorders, stroke, drug ingestion, or respiratory failure, who are anticipated to require prolonged ventilatory assistance, should undergo early conversion from ET intubation to tracheotomy to reduce the risk of laryngeal stenosis and other laryngeal complications from prolonged ET intubation.

Tracheotomy may facilitate management of patients who require ongoing pulmonary toilet. These include individuals with chronic obstructive pulmonary disease, adult respiratory distress syndrome, and crush injuries to the chest.

Surgical Airway Techniques

Cricothyrotomy

Cricothyrotomy is particularly useful when intubation is not possible, and tracheotomy cannot be performed because there are no landmarks, the trachea is below the manubrium (e.g., kyphoscoliosis), or there is a large mass such as a goiter obscuring the trachea. Contraindications to cricothyrotomy include laryngeal trauma and transection of the airway. It should not be performed in neonates or children because of the high risk of cricoid injury and subglottic stenosis. In practice, cricothyrotomy is used primarily by emergency room physicians and others with limited airway experience because it is relatively simple and rapid, with little tissue between skin and the airway. It is only very rarely used by otolaryngologists. The primary objective is to establish an airway. Once this has been accomplished, conversion to a tracheotomy between the second and third tracheal rings should be undertaken within 48 hours or as soon as the patient is stable in order to avoid subglottic stenosis.

Equipment necessary includes a 15-blade scalpel, hemostats, a tracheal or cricoid hook, tracheal dilator, and a small cannulating device such as a no. 4 or no. 6 tracheotomy tube (Fig. 64.9). If for any reason a tracheotomy tube is unavailable, a shortened ET tube or anything that can be connected to a bag-valve mask is appropriate. Preassembled kits for cricothyrotomy are also commercially available (Fig. 64.10).

Providing the C-spine has been cleared, the patient is positioned with a shoulder roll and the head is extended on the neck. A skin preparation solution is used only if time permits. Local anesthesia is used if the patient is awake



Figure 64.9 Equipment necessary for performing a cricothyrotomy. From *left to right*: 15 blade scalpel, hemostats, a tracheal or cricoid hook, tracheal dilator, and a small cannulating device such as a no. 4 or no. 6 tracheotomy tube.

or responsive; otherwise, it may waste valuable time. Next, the larynx is grasped and stabilized between the thumb and second and third fingers of the nondominant hand. A 15 blade scalpel is used to make a 3- to 4-cm vertical skin incision that extends slightly beyond the length of the cricothyroid membrane. The incision is deepened to expose the cricothyroid membrane. If necessary, a hook placed under the thyroid cartilage with upward traction may be used to improve exposure. Once identified, the membrane is incised horizontally closer to the superior border of the cricoid in order to avoid the cricothyroid vessels and vocal folds (Fig. 64.11). A tracheal dilator is then used to enlarge the aperture and permit insertion of the tracheal cannulation device (Fig. 64.12). If a tracheal dilator is not

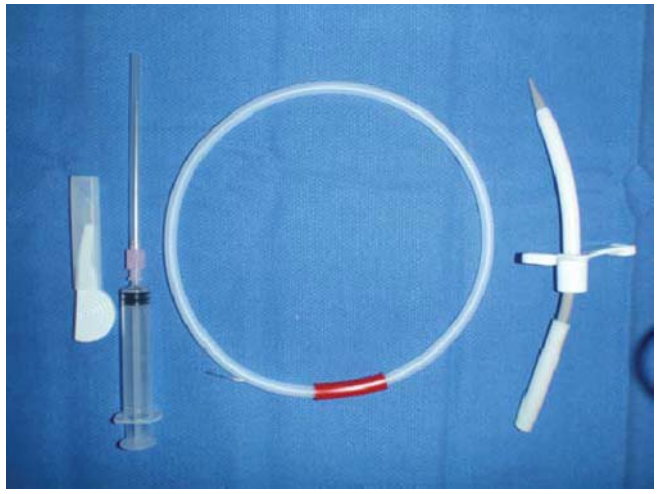


Figure 64.10 Example of preassembled commercially available kit (Cook) for cricothyrotomy: *left to right*: scalpel, syringe with 18-gauge introducer needle, J-wire, airway catheter preloaded with dilator.

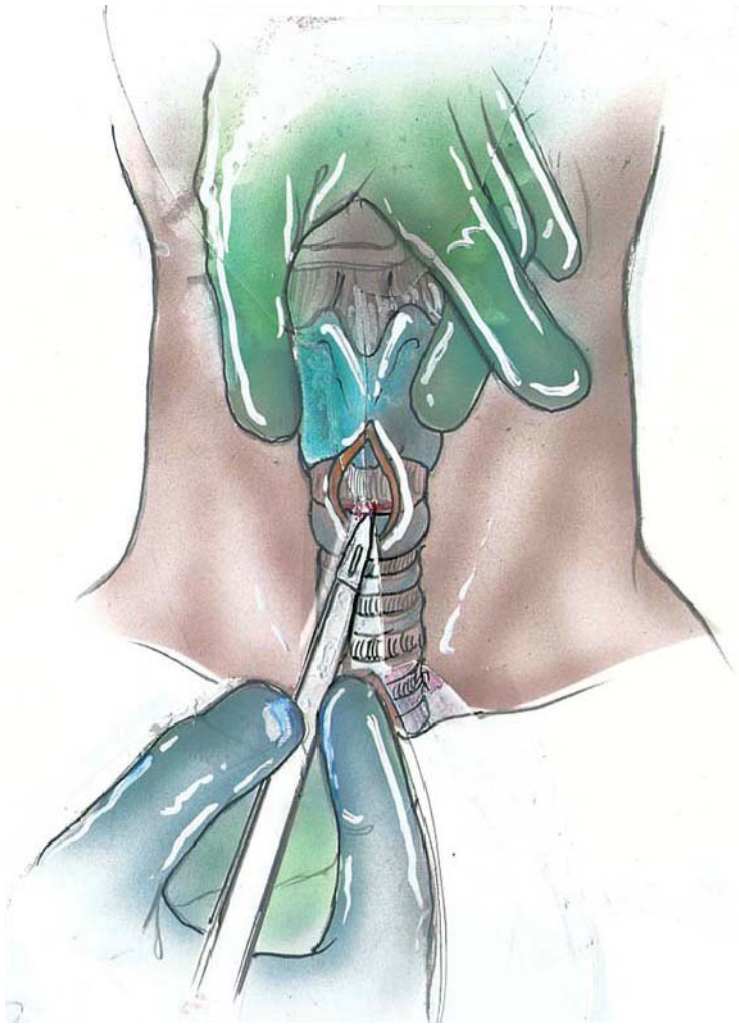


Figure 64.11 Cricothyrotomy: A 3- to 4-cm vertical incision is made from the lower border of the thyroid cartilage to just below the cricoid cartilage. The cricothyroid membrane is then incised horizontally.

available, a Kelly clamp, hemostat, or mosquito may be used for the same purpose. Once inserted, the tracheal cannula is attached to a ventilating device, and the chest auscultated for breath sounds. The tube is secured with sutures and/or tapes as available (26).

Complication rates range from 9% to 40% and vary as a function of patient anatomy and degree of technical comfort with the procedure. The most frequent complications include bleeding and tube misplacement. Bleeding is usually easily managed by direct pressure, use of a local hemostatic packing material such as Gelfoam or Surgicel, or by simply clamping and tying/suturing the offending vessel. Tube displacement/misplacement is a potentially fatal complication. Airway sounds must be verified at the time of tube insertion. Later, displacement of the tube into the pretracheal soft tissues may go unnoticed until the patient is hypoxic, suddenly requires high ventilation pressures, or develops massive subcutaneous emphysema. This is particularly likely in obese patients. Other complications include injury to the recurrent laryngeal nerve(s), vocal folds, the posterior tracheal wall, and the thyroid or cricoid cartilages. Pneumothorax and pneumomediastinum are usually the result of barotrauma from ventilation. Late complications such as dysphagia, dysphonia, infection, and subglottic stenosis occur in up to 50% of patients not converted to tracheotomy in a timely fashion (26).

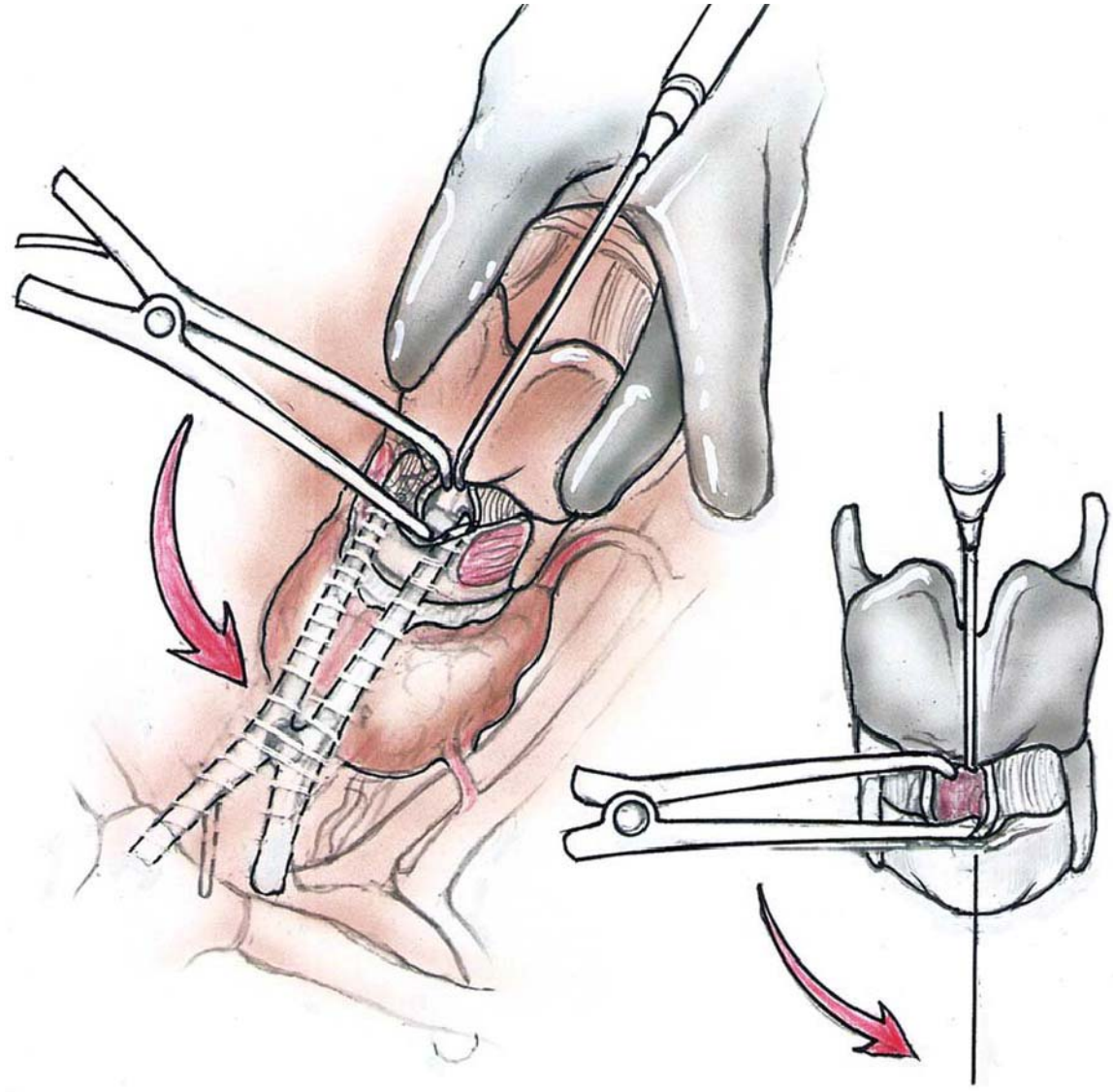
Emergency Tracheotomy

Emergency bedside open tracheotomy is required in the most dire circumstances as a life-saving measure, when other options such as intubation or tracheotomy in the OR are not available or suitable. Situations involving severe facial or laryngeal trauma may make intubation an unsuitable, even dangerous choice. Indications for emergency bedside tracheotomy are rare, and include impending or actual cardiac or cardiorespiratory arrest from airway obstruction. Because death from anoxia occurs in approximately 5 minutes, an emergency tracheotomy must be performed very quickly, yet safely, in a less than ideal setting.

The surgeon should therefore be focused on establishing the airway. Other tasks such as establishing intravenous access, administering medications, and placing a mask with oxygen should be delegated.

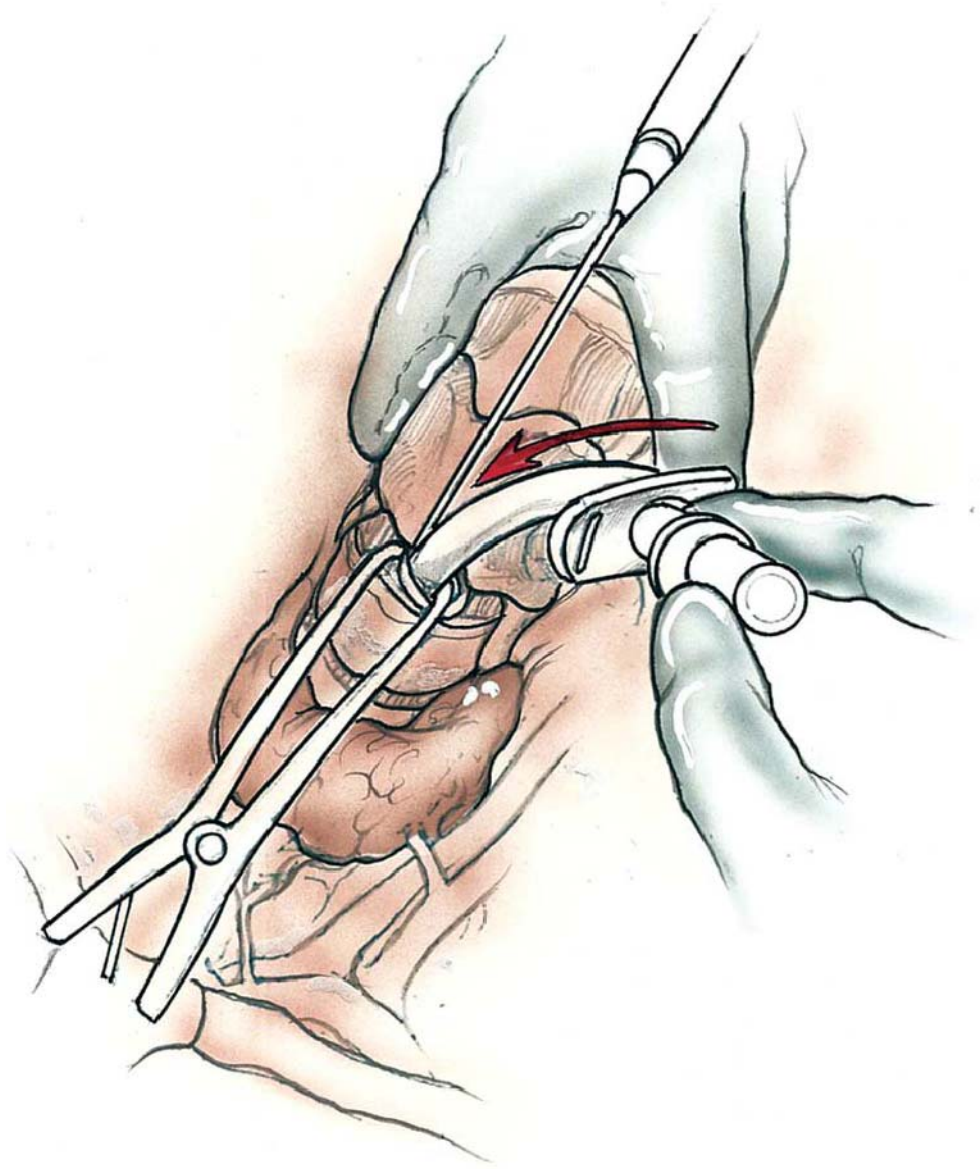
Every emergency room should have a preassembled, easily available tray with the instruments required for a tracheotomy (Table 64.12). The tray should be placed next to the surgeon and the essential instruments laid out in a near-to-far sequence: a 15 blade scalpel, swabs on clamps, retractors (if available), a self-retaining retractor, mosquitos, cricoid hook(s), an 11 blade scalpel for opening the trachea (optional), a Trousseau or tracheal dilator, and two sizes of cuffed tracheostomy tubes (the estimated "ideal" size, and one smaller size) (Fig. 64.13). In the event that no such tray is available, the bare essentials include a blade, mosquito, and tube for the airway (tracheostomy tube, ET tube, etc.). If possible, another physician should assist; otherwise the nearest nurse or resident is recruited to help (27). No time should be wasted on a formal prep and drape or on setting up electrocautery if it is not immediately available.

Unless it is contraindicated, the patient is positioned with a makeshift shoulder roll and the head extended on the neck. The right-handed operator should be on the patient's right, and the assistant on the patient's left. If 180 degrees of the tracheal circumference is palpable, it is grasped and lifted; otherwise it is stabilized between the thumb and the index and third finger of the nonoperating hand. A midline vertical incision through the skin and platysma is made from just below the cricoid to



A

Figure 64.12 **A:** Cricothyrotomy: A tracheal hook is used to retract the thyroid cartilage superiorly, while a Trousseau dilator is inserted perpendicular to the trachea and then rotated inferiorly to enlarge the opening.



B

Figure 64.12 *(Continued)* **B:** A small tracheostomy tube is inserted.

TABLE 64.12 TECHNICAL TIPS FOR EMERGENCY TRACHEOTOMY

- Remain calm and focused on the task at hand
- Do not waste time on prep, cautery, or other tasks
- Minimum equipment includes a scalpel, mosquito, and airway cannula
- Stay midline
- Displace the thyroid isthmus superiorly or inferiorly, or incise it
- In difficult cases, find the airway with an 18-gauge needle on a 10-mL syringe and incise vertically above and below
- Use the tube size that will most easily fit
- Attend to hemostasis after the airway is safely established

the sternal notch. The assistant then grasps the trachea between the thumb and ring finger, leaving the index and middle finger to spread the incision (Fig. 64.14). The assistant's free hand is used to sponge or tamponade bleeding. The operator then incises through the midline raphe of the strap muscles and positions the self-retaining retractor between the strap muscles. The pretracheal space and the thyroid are now exposed. If possible, the thyroid is displaced superiorly or inferiorly to expose the trachea. Otherwise, the isthmus is divided between a mosquito placed on the contralateral side and a second mosquito placed on the ipsilateral side. If possible the ends are tied. The assistant then lifts the trachea upward with one or two hooks, and an 11 blade scalpel is used to incise the



Figure 64.13 Equipment necessary for performing an emergency tracheotomy. From *left to right*: 15 blade scalpel, swabs on clamps, retractors (if available), a self-retaining retractor, mosquitos, a cricoids hook, an 11 blade scalpel for opening the trachea (optional—not shown), a Trousseau or tracheal dilator, and two sizes of cuffed tracheostomy tubes.

membrane between the second and third rings. Tracheal retention sutures are generally not used because of time constraints. A mosquito is used to spread the opening first vertically then horizontally. The mosquito is exchanged for a tracheal dilator through which the tracheostomy tube is inserted. The tube should be held at 90 degrees to the trachea, with the tip perpendicular to the opening for insertion. With the tip of the tube in the tracheal lumen, the tube is rotated to lie parallel with the trachea as it is completely inserted (Fig. 64.15). The cuff is inflated and the tube immediately attached to an adaptor for ventilation. Bleeding is then controlled with ties, clips, or sutures as necessary. Cautery should be avoided because of the high oxygen concentration in the area and consequent risk of fire (27).

In some cases, identification of the airway may be very difficult because of preexisting conditions such as scarring, previous surgery and/or radiotherapy, a midline neck mass and kyphoscoliosis, all of which may completely obscure landmarks. In these situations, percutaneous ventilation

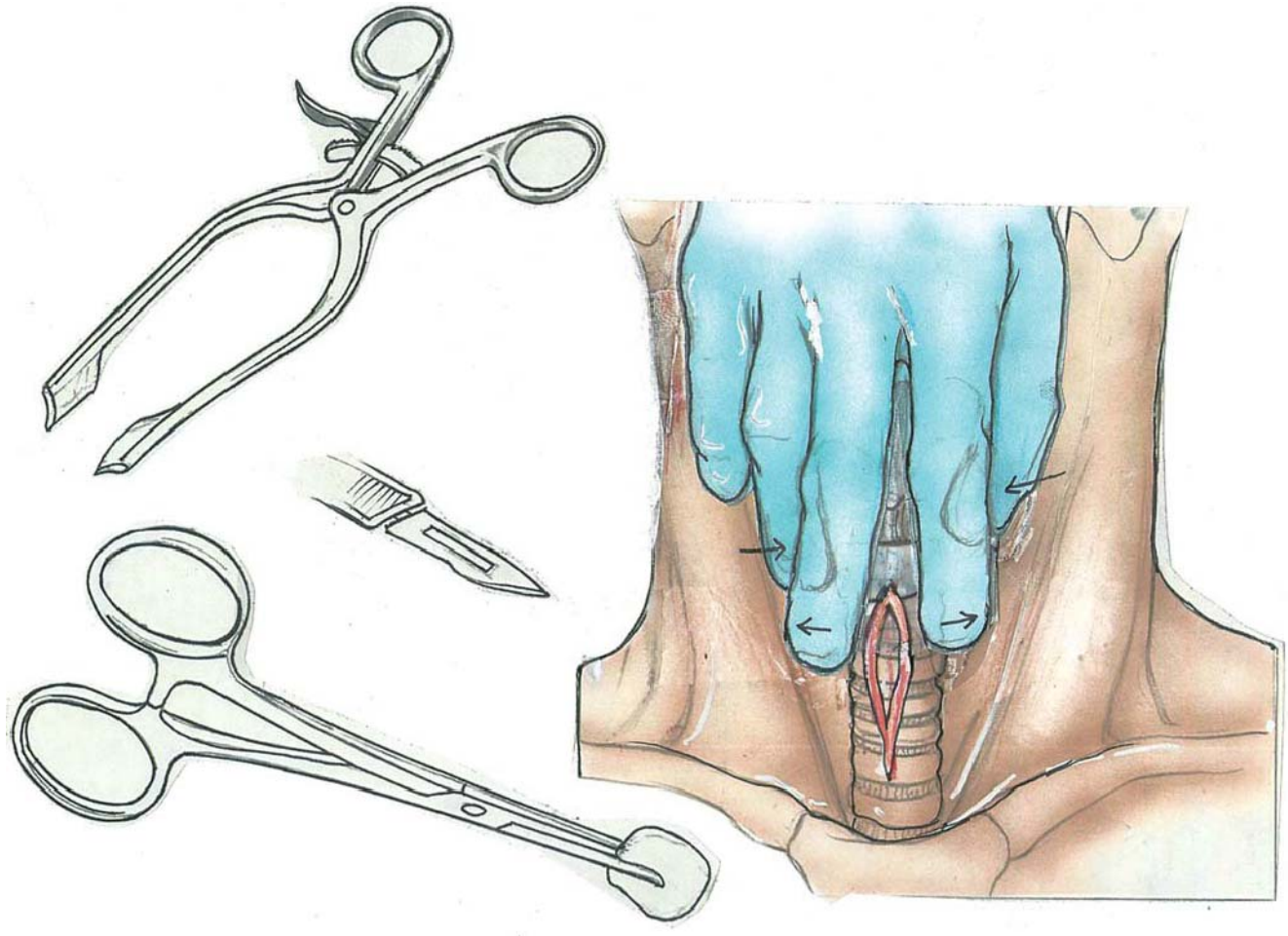


Figure 64.14 Emergency tracheotomy: position of hands during the initial dissection. The operator is on the right side and holds the scalpel with the operating hand and a self-retaining retractor with the non-operating hand. The assistant is on the left side and holds and raises the trachea with the thumb and ring fingers of the operating hand, reserving the index and middle fingers to spread the incision open; the non-operating hand is used to tamponade bleeding.

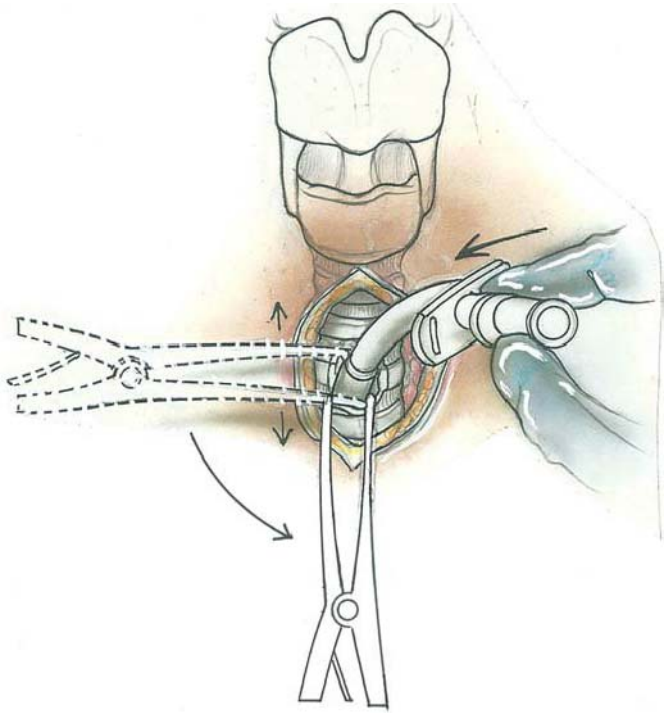


Figure 64.15 Emergency tracheotomy: The tracheostomy tube is first inserted perpendicular to the trachea; once in the trachea, it is rotated 90 degrees to the desired position.

through a transtracheal or cricothyroid puncture may buy time. If this is not possible, an 18-gauge needle attached to a syringe may be used to enter the trachea, with the position confirmed by the aspiration of air. A vertical incision made above and below the needle allows the mosquito, followed by the tracheal dilator, to sufficiently enlarge the opening for insertion of the tracheostomy tube.

The complication rate associated with emergency tracheotomies is significantly higher than that associated with "elective" tracheotomies. This being said, successfully accessing the airway is lifesaving. Adverse events may be dealt with when the patient is stable. Complications are fully discussed later in the chapter.

Open Surgical Tracheotomy

Preoperative Planning

Every effort should be made to optimize the patient's comorbidities prior to surgery. Coagulopathies should be corrected to an international normalized ratio (INR) of less than 1.5, with greater than 50,000 functioning platelets. Cessation of aspirin or other nonsteroidal anti-inflammatory drugs for 7 days preoperatively is ideal but not absolutely necessary. Clopidogrel bisulfate (Plavix) is an antiplatelet agent that should also be discontinued 7 days prior to surgery if at all possible. Use of aspirin and clopidogrel bisulfate together is very common in patients who have had cardiac stent placement, strokes, and/or myocardial infarctions. Patients on both drugs have a higher incidence of perioperative bleeding and at least one of these agents should be stopped prior to tracheotomy. Patients on warfarin should stop the drug 5 days prior to surgery or should receive infusions of fresh frozen plasma or intravenous or oral vitamin K for rapid reversal of anticoagulation. A crossmatch should be obtained if the hemoglobin is less than 100.

Traditionally, tracheotomy has been performed in the OR, which is fully equipped with adequate lighting, suction, and assistance. Admitted patients as well as those from the emergency room are best transferred to the controlled, monitored setting of the OR whenever possible. Adult, intubated patients in the intensive care unit (ICU) may undergo tracheotomy (open or percutaneous) safely either at the bedside (28–30) or in the OR (31,32) with comparable complication rates.

The anesthesia team plays an important role during the procedure monitoring the airway and vital signs and keeping the patient stable. Patients suffering from chronic respiratory insufficiency and high CO_2 levels may lose their respiratory drive or even develop pulmonary edema once the airway has been established with a tracheotomy. Support in the form of assisted ventilation and appropriate pharmacologic intervention is usually sufficient although cardiopulmonary resuscitation may be necessary in severe cases.

The choice of tracheostomy tube is important. The purpose of a tracheostomy tube is (a) to provide an airway, (b) to provide for the possibility of mechanical positive-pressure ventilation if needed, (c) to reduce the risk of aspiration by sealing the trachea, and (d) to provide a means of suctioning the tracheobronchial tree (14). Factors influencing tube selection include the shape of the tube and the neck plate. If a cuffed tube is necessary, it should be a

TABLE 64.13 PREDICTED NECK THICKNESS (CM) AS A FUNCTION OF NECK CIRCUMFERENCE (NC IN CM) AND ARM CIRCUMFERENCE (CM)

	NC Supine						
	30	35	40	45	50	55	60
Arm circumference							
20	0.5	0.8	1.1	1.4	1.7	2.1	2.4
25	0.6	0.9	1.3	1.6	1.9	2.2	2.5
30	0.8	1.1	1.4	1.7	2.0	2.4	2.7
35	0.9	1.2	1.6	1.9	2.2	2.5	2.8
40	1.1	1.4	1.7	2.0	2.3	2.7	3.0
45	1.2	1.5	1.9	2.2	2.5	2.8	3.1
50	1.4	1.7	2.0	2.3	2.6	3.0	3.3
55	1.5	1.8	2.2	2.5	2.8	3.1	3.4
60	1.7	2.0	2.3	2.6	2.9	3.3	3.6

RMSE: 0.4 cm

low-pressure, high-volume cuff to reduce the possibility of tracheal stenosis. Tubes with an inner cannula provide an added measure of safety in that the inner cannula can be quickly removed in the event of a mucus plug, leaving the open outer cannula *in situ* and the airway protected.

Preoperative planning should also account for the need for any special type of tracheostomy tube. For instance, obese patients with thick pretracheal soft tissues are likely to require extended-length tubes to decrease the risk of accidental decannulation or tube displacement. It has been shown that pretracheal soft tissue thickness (Table 64.13) can be reliably predicted within 4 mm in obese patients as a function of neck and arm circumference (33). Using Table 64.13, it can be seen that a patient with a neck circumference of 55 cm and an arm circumference of 50 cm would have a pretracheal soft tissue thickness of 3 cm. A proximally extended tracheostomy tube would be required in this patient since "standard" tubes have a much shorter proximal length. It should be noted that tracheostomy tubes with either proximal or distal extensions are available. Tubes with adjustable flanges and those made of softer, thermolabile materials for anatomically difficult necks or tracheas are also available. Choosing the correct tracheostomy tube preoperatively is helpful in decreasing postoperative complications such as accidental decannulation, skin maceration/infection, granulation tissue, and tracheitis, all of which may be related to ill-fitting tubes.

In order to avoid surprises, it is imperative to examine the patient preoperatively with particular attention to the neck. The presence of a midline neck mass or high innominate artery may necessitate modification of the level of incision or entry into the trachea, or both. Patients who have undergone prior surgery or radiotherapy to the neck may have scarred, fibrotic, indurated tissue that precludes the ability to identify any landmarks. In these cases, slow, careful, midline dissection prevents injury to adjacent structures such as the carotid artery and allows identification of the airway. Patients with severe cervical osteoarthritis, kyphoscoliosis, or other conditions, in whom the neck cannot be hyperextended, present a formidable surgical challenge. In these situations, meticulous midline dissection with maximal upward traction on the cricoid may help pull the trachea into the accessible portion of the neck.

Surgical Technique

The patient is placed on the operating table with a rolled towel or sheet under the shoulders to extend the neck unless the patient has documented or suspected cervical spine injuries. In such cases, extension of the neck is contraindicated because of the risk of spinal cord compression. Adults with airway obstruction may not be able to tolerate the supine position, and tracheotomy may need to be performed with the patient sitting up at 45 degrees. The use of local or general anesthesia must be dictated by the circumstances. Patients with a marginal airway and respiratory distress should be managed with local anesthesia alone without sedation, for fear of suppressing the respiratory drive. In more elective situations with a protected or airway, either general anesthesia or local anesthesia with intravenous sedation may be appropriate. In children, the procedure is typically carried out under general anesthesia.

The neck, face, upper chest, and shoulders are prepared with a povidone-iodine (Betadine) or other suitable solution, and appropriately draped to allow easy access to the neck. The cricoid cartilage and sternal notch are identified and the incision site is determined. Lidocaine (Xylocaine) 1% with 1:100,000 epinephrine is injected into the skin and subcutaneous tissue at the incision site; this maneuver results in vasoconstriction and decreases cutaneous bleeding.

A transverse incision is made approximately 1 cm above the suprasternal notch or 2 cm below the cricoid cartilage. Sharp dissection is carried through the subcutaneous tissue and platysma. Exposure may be achieved with self-retaining retractors or four small rake retractors.

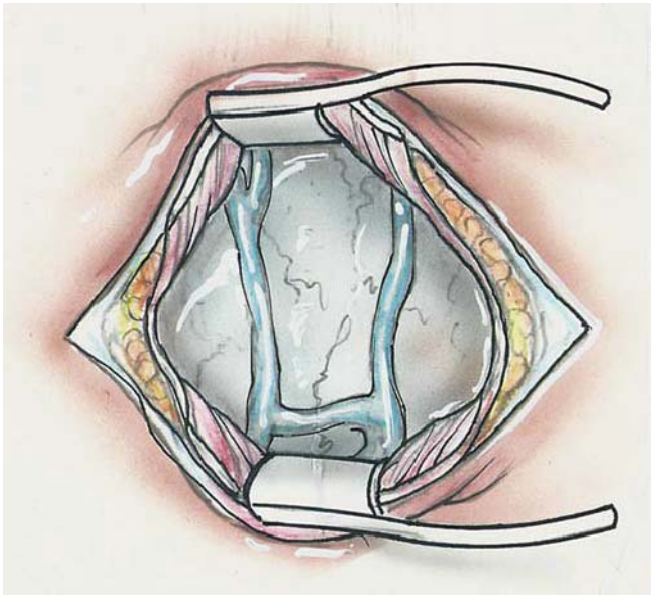


Figure 64.16 Incision extends through the platysma to expose the anterior jugular veins and the fascia overlying the strap muscles.

The anterior jugular vein(s) should be identified and retracted laterally (Fig. 64.16). It is not necessary to ligate these vessels unless they are inadvertently cut or injured, or there is a midline communicating branch. The strap muscles are divided in the midline and retracted laterally (Fig. 64.17A). The thyroid isthmus is visualized and the anterior wall of the trachea identified (Fig. 64.17B). In adults, the thyroid isthmus can often be retracted superiorly and the trachea entered (Fig. 64.17C). If the trachea cannot be exposed otherwise, the isthmus is undermined, clamped on each side with hemostats or Kelly clamps, transected, and ligated with 2-0 silk or Vicryl sutures on a cutting needle. In patients with a very thin or fatty thyroid, the isthmus may be divided with electrocautery. In patients under local anesthesia, it is important to inject additional lidocaine in the paratracheal tissues prior to opening the trachea in order to obtain effective anesthesia. Once the trachea is identified, a tracheal hook is placed under the cricoid or in the area of the second tracheal ring and secured by an assistant to immobilize the trachea in the wound. It is important to enter the trachea with a scalpel; electrocautery should be avoided because of the risk of airway fire. In infants and children, a vertical incision is made through the second and the third or the third and the fourth tracheal rings without removing any cartilage. Traction sutures are then placed just lateral to the incision (Fig. 64.18).

In adults, the anterior portion of the second, third, or fourth tracheal ring may be removed to facilitate insertion of the tracheostomy tube. In most older patients, the tracheal ring will be calcified, and heavy scissors must be used to excise a small portion of the tracheal ring after transverse cuts have been made in the area just above and below the tracheal ring. This maneuver effectively leaves a rectangular window in the trachea (Fig. 64.19). If necessary, the opening may be enlarged by removing additional cartilage with a Kerrison rongeur. Removal of the anterior aspect of the tracheal ring ensures that the cannula is placed in the trachea rather than in a false passage anterior to the trachea (24).

Traction sutures are placed to reduce the possibility of creating a false passage in the event that the tracheostomy tube becomes displaced in the immediate postoperative period before a tract has been formed. These are more easily placed in the trachea with a ligature carrier loaded with 2-0 silk (Fig. 64.20) rather than with a curved needle. While the tracheal hook retracts the trachea inferiorly, the ligature carrier is passed through the interspace just above the ring superior to the stoma and into the lumen, with care taken not to penetrate the posterior tracheal wall. A small, curved clamp is used to grasp the suture and to stabilize it while the ligature carrier is removed. A similar procedure is carried out inferiorly. Alternatively, traction sutures may also be placed in the lateral tracheal wall. The traction sutures are then tied and fixed to the skin of the chest with adhesive tape.

With the cricoid or tracheal hook still in place, the tracheostomy tube may be introduced either by pulling on the traction sutures to "exteriorize" the trachea or by inserting a Trousseau dilator into the tracheal opening. Once the tracheal opening is satisfactorily exposed, the cannula may be introduced into the stoma. This is begun with the cannula at right angles to the trachea; then, as the cannula is inserted, it is turned so that its axis is parallel to that of the trachea (Fig. 64.21A). This eliminates the difficulty encountered in trying to pass the cannula over the patient's chest. An obturator should always be utilized while the cannula is inserted. Once the cannula is properly placed in the trachea, the obturator is removed promptly and the inner cannula inserted. Once the tracheostomy tube is in place, and adequate ventilation through the tracheostomy tube is assured, the ET tube or bronchoscope utilized for stabilizing the airway may be removed.

The tracheostomy cannula is secured by suturing the neck plate to the skin and by tracheostomy tapes tied securely with a square knot with the neck flexed. Only one fingertip should be admitted between the tape and the patient's neck, and the tapes should be tied over the skin. Bulky dressings under neck tapes should be avoided as they compromise the stability of the tracheostomy tube in the early postoperative period and facilitate displacement, a potentially fatal complication. Neck tapes should be avoided completely if they lie over a regional or free flap because of the risk of compromising the blood supply. In these cases, the tube is secured only with sutures to the underlying skin (Fig. 64.21B).

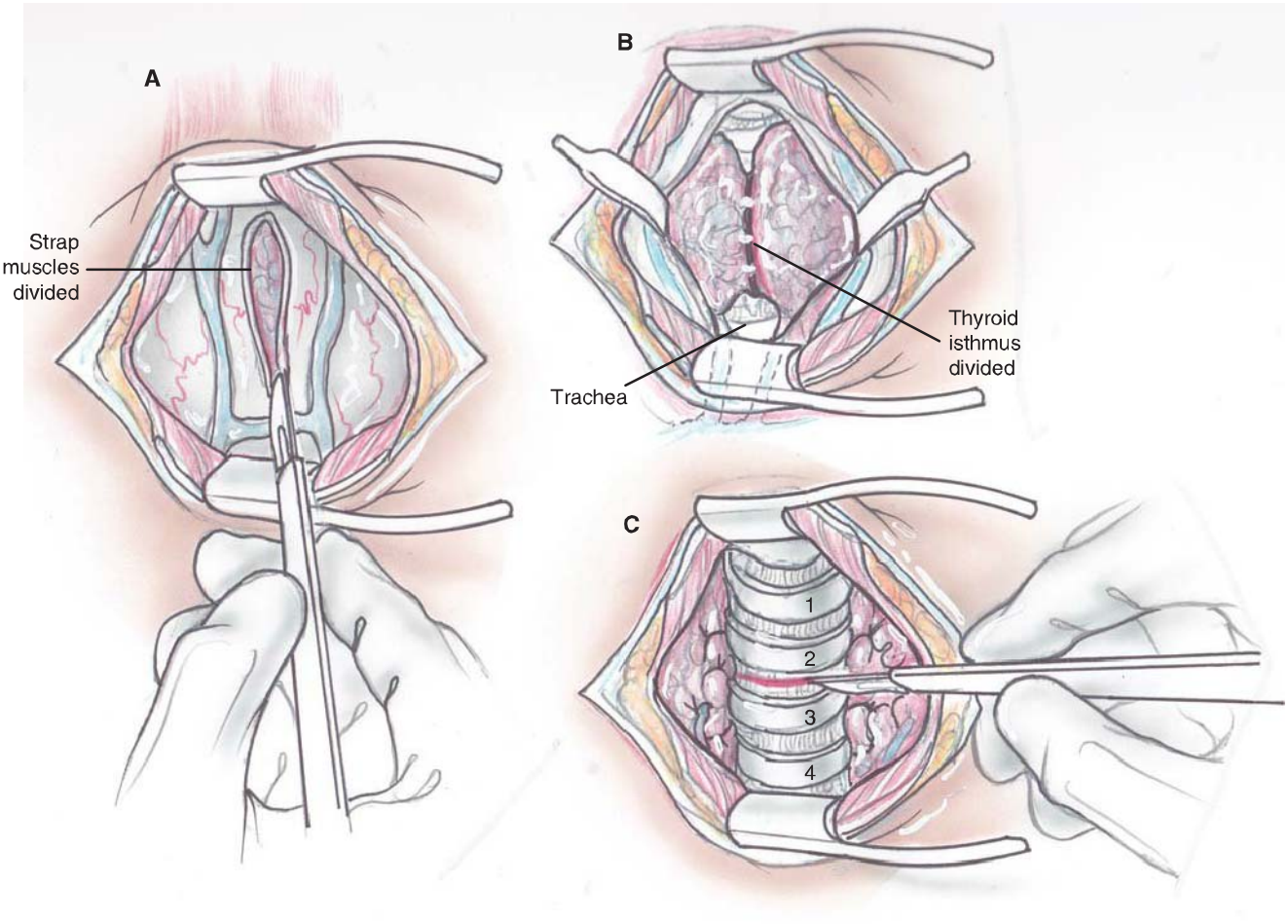


Figure 64.17 **A:** The strap muscles are divided along the midline raphe and retracted laterally. The trachea and thyroid gland are identified. **B:** The thyroid isthmus is retracted superiorly, or divided, as required. **C:** The first three or four tracheal rings are exposed. The trachea is entered between the first and second or second and third tracheal rings.

When tracheotomy is carried out under ideal circumstances, with enough time for vasoconstriction, bleeding is minimal. It is important to secure all bleeding points, with either ligatures or electrocautery, to prevent bleeding postoperatively. Caution should be exercised when using electrocautery close to the trachea because of the risk of airway fire. To reduce the possibility of this catastrophic event, the patient should be ventilated on the lowest possible oxygen concentration, and the trachea should never be entered with electrocautery.

A chest radiograph should be taken in the recovery room to rule out complications such as pneumothorax and pneumomediastinum.

Modifications of Tracheotomy

Several modifications of the "standard" tracheotomy technique have been described. The Bjork flap was originally described in 1960 as a means of facilitating tracheostomy tube reinsertion in the event of accidental decannulation in patients with difficult necks (34). This tracheal flap, which usually includes the second and third tracheal rings, is based inferiorly and is sutured to the inferior skin edge. In obese patients, the flap may not be long enough to reach the skin. In these cases, "defatting" the skin may be necessary to allow approximation of the tracheal flap to the skin. If the flap is not adequately sutured to the skin, it may be dislodged during attempted tube reinsertion and result in respiratory obstruction through a valve effect. The flap should not include more than two rings because of the subsequent risk of tracheomalacia or tracheostenosis.

The creation of a permanent stoma is more correctly referred to as a tracheostomy. It should be considered in patients in whom other options are not available or appropriate. Obstructive sleep apnea, progressive neuromuscular diseases, and severe laryngotracheal stenosis would be examples of conditions where tracheostomy is

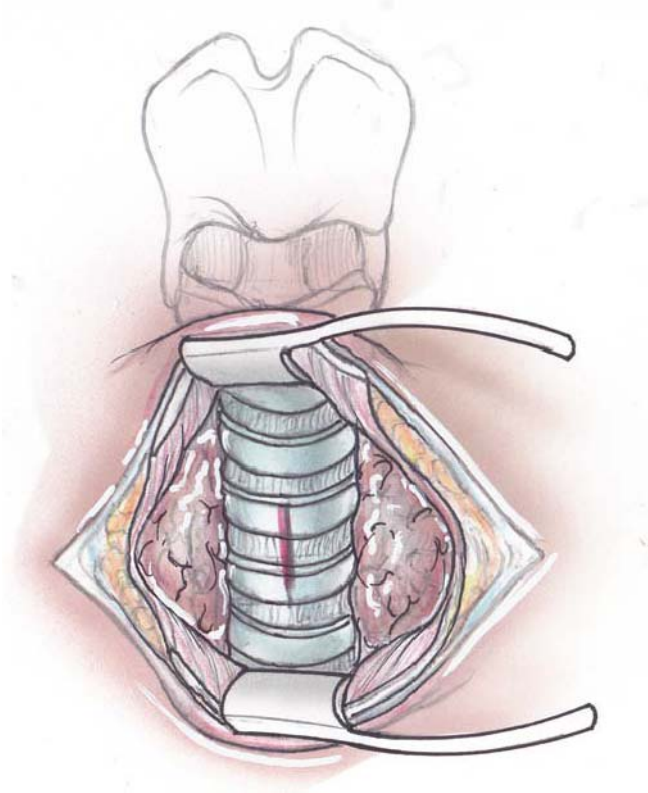


Figure 64.18 In infants and children, a vertical incision is made through the second and third or the third and fourth tracheal rings. No cartilage is removed. Traction sutures are then placed lateral to the incision.

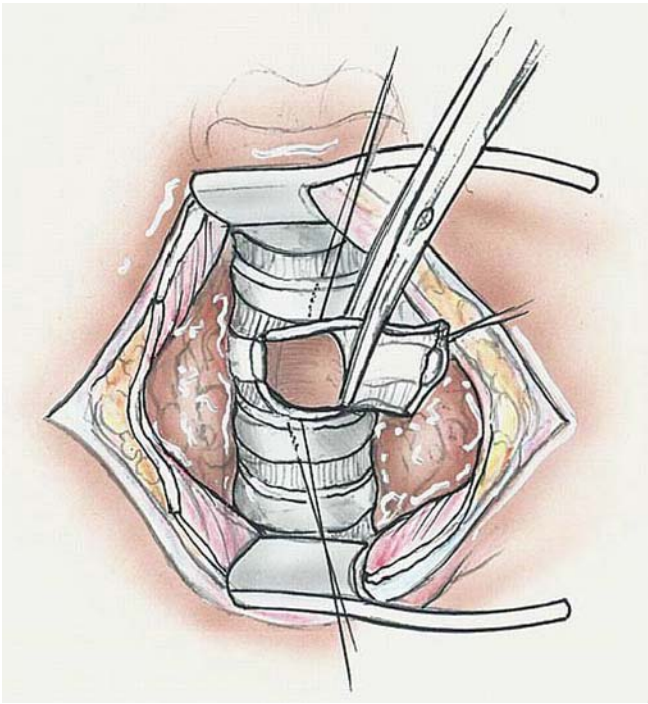


Figure 64.19 In adults, the anterior portion of the second, third, or fourth tracheal ring may be removed, leaving a rectangular window. Traction sutures may then be placed either laterally or superiorly and inferiorly.

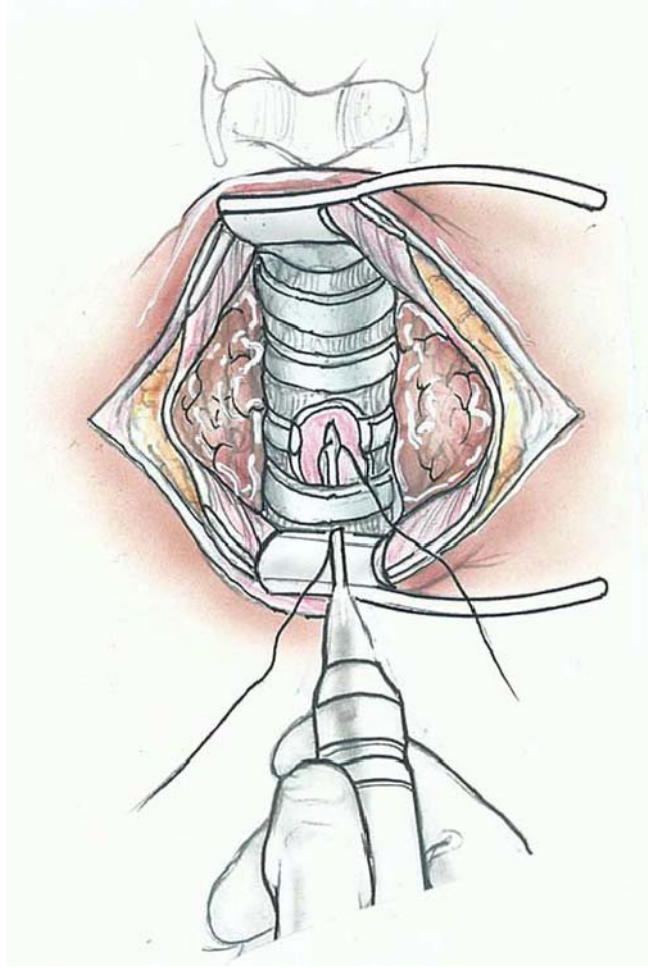
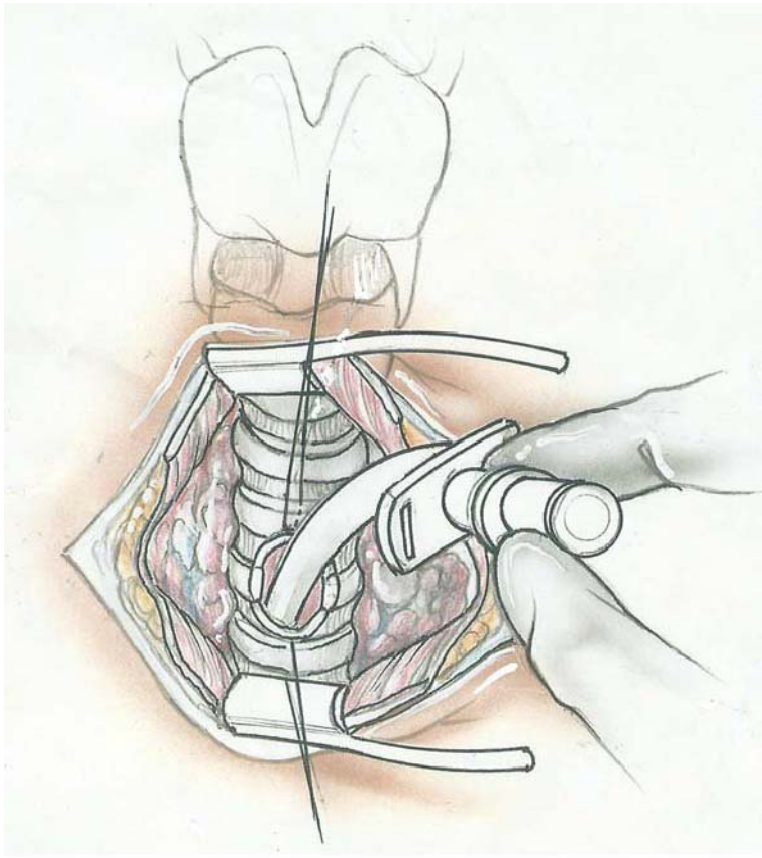
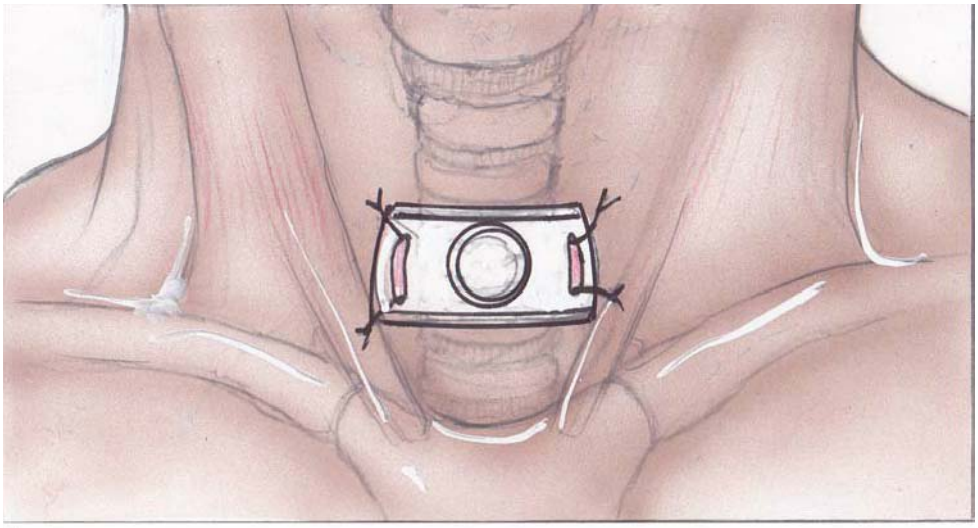


Figure 64.20 Traction sutures are placed in the trachea with a ligature carrier loaded with 2-0 silk.

likely to be needed for several years or perhaps even for life. The technique for surgically creating a permanent tracheostomy, along with additional modifications to allow for speaking, has been described by Eliachar (35). The procedure is surgically more complex than tracheotomy and involves suturing the mucosa of the trachea to skin circumferentially. An omega skin incision is made and carried down through the platysma, and subplatysmal flaps are elevated (Fig. 64.22). The strap muscles are separated along the median raphe, exposing the thyroid isthmus, which is divided and oversewn. The lobes are dissected off the anterior tracheal wall and anchored laterally to the ligament of the sternocleidomastoid muscle. With the anterior tracheal wall exposed, a superiorly based flap incorporating the second and third or third and fourth tracheal rings is created. This flap is securely sutured to an appropriately defatted superior skin edge (Fig. 64.23). The inferior skin flap must be elevated below the clavicles and then defatted to allow for a tension-free approximation to the inferior and lateral portions of the tracheal opening (Fig. 64.24). A cuffed tracheostomy tube is generally left



A



B

Figure 64.21 **A:** The tracheostomy tube is inserted into the trachea. **B:** The neck plate is sutured to the skin.

in position for the first 12 to 24 hours and then removed to allow healing between skin and tracheal mucosa. The more frequently reported complications include suture line dehiscence, granulation tissue, wound breakdown, and infection. Healing of the stoma is usually complete in 22 to 30 days, but can take as long as 40 days in patients who are obese or diabetic, as well as in those having received previous radiotherapy to the neck.

Postoperative Care

Postoperative care of the tracheotomy site is made considerably easier if there is the opportunity for preoperative teaching. Knowing what to expect helps both children and adults undergoing the procedure to adjust to this new way of breathing. Evidence indicates that patients undergoing tracheotomy experience a reduced quality of life (36). Appropriate teaching, family counseling, and

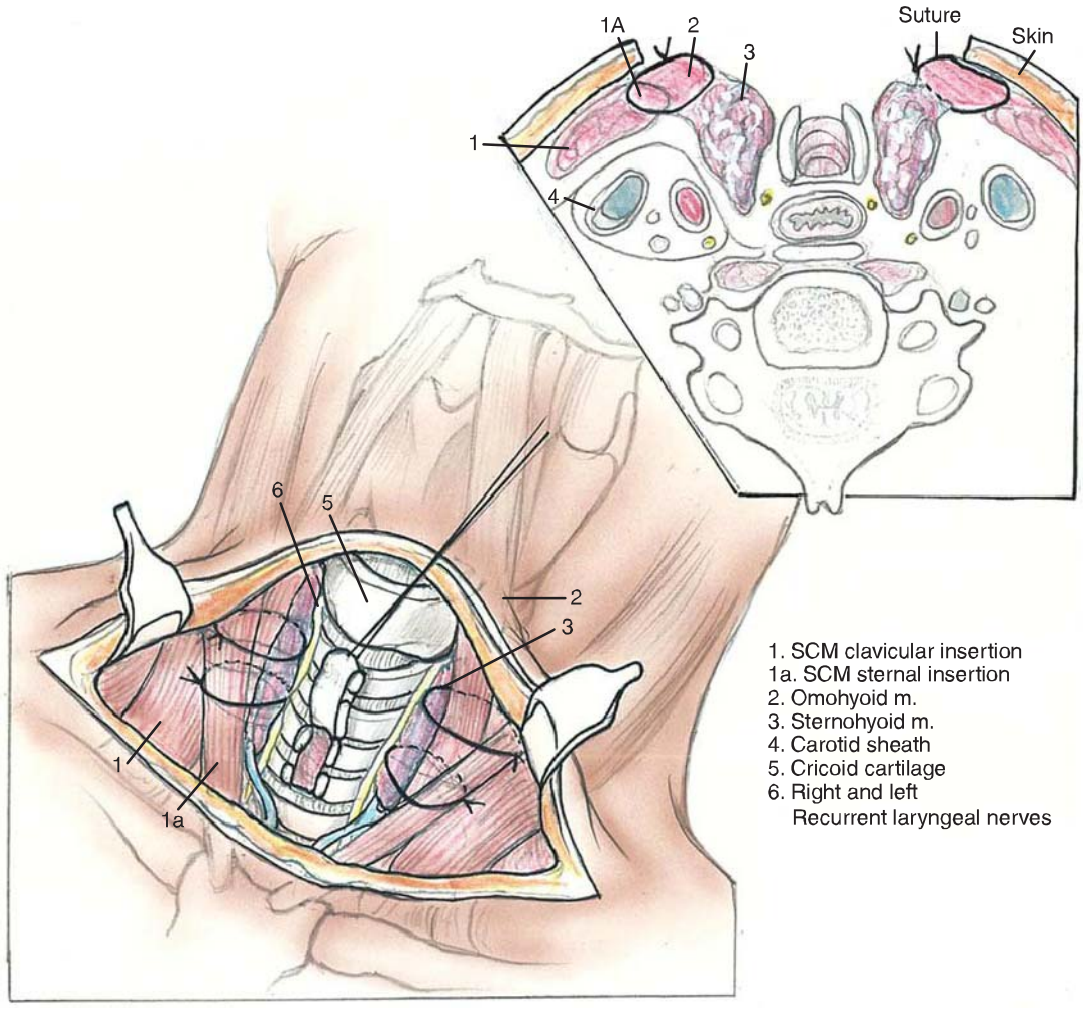


Figure 64.22 Note omega incision cresting over the cricoid cartilage. Generous subplatysmal flaps are raised superiorly and inferiorly. The anterior tracheal wall is completely exposed by suturing the thyroid lobes and strap muscles laterally to the sternal tendon of the sternocleidomastoid muscle. Customized to the patient's anatomy, a superiorly based anterior tracheal wall flap is elevated. **Inset:** Axial image of the thyroid lobes and strap muscles sutured to the tendon of the sternocleidomastoid muscle.

highly skilled nursing care are all key factors in reducing anxiety and ensuring a smooth postoperative course. Ideally, a multidisciplinary tracheotomy team involving a physician, nurse, respiratory therapist, and speech-language pathologist should be intimately involved in posttracheotomy care. Each member of the team plays a critical role in coordinating and delivering the complex care tracheotomy patients require (37). The team assists with wound care, tracheotomy tube changes, deglutition, communication, decannulation, and teaching of the patient and caregivers. The presence of a multidisciplinary tracheotomy team produces measurable results in terms of decreased postoperative morbidity: the frequency of tube obstruction decreases, the use of speaking valves increases, and patients are decannulated more rapidly (38) (Table 64.14).

In the initial postoperative period, patients are placed in a semi-Fowler position to maximize the ease of coughing and deep breathing, to facilitate suctioning, and to minimize discomfort. Vital signs require frequent monitoring because changes in blood pressure, respiratory rate, or pulse rate may indicate a new or ongoing respiratory problem, or that the tube may be plugged or have come out of the trachea. Agitation, anxiety, and restlessness may all indicate hypoxia and should not be dismissed or treated with anxiolytics.

Tracheal suctioning is performed to maintain pulmonary toilet and patency of the tracheostomy tube. Initially, this should be done as aseptically as possible and may be necessary three to four times daily. Either a portable or a wall-suction unit may provide the negative pressure needed for suctioning. Patients on mechanical ventilation are at risk for hypoxia and cardiac arrhythmias during suctioning because oxygen-rich air is suctioned and catheters may be too large. This can be prevented by ventilating the patient on 100% O_2 for at least five breaths before and after suctioning, and limiting suctioning to less than or equal to 12 seconds with a small catheter. As an alternative to this

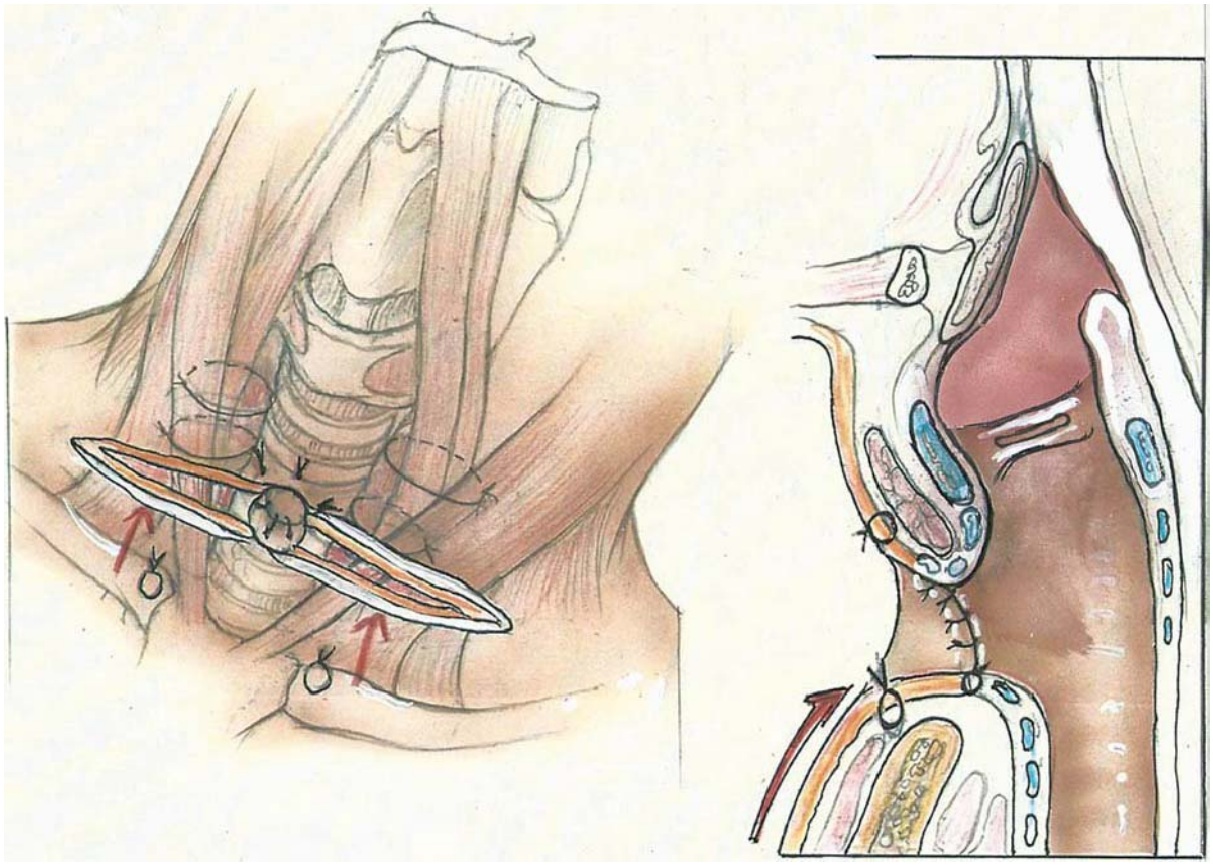


Figure 64.23 The superiorly based tracheal flap is sutured to the superior skin flap. The extensively undermined inferior flap is advanced and sutured to the lower edge of the trachea. "Suspensory" sutures may help support the flap. **Inset**: The upper and lower skin flaps are sutured to the trachea. Note the dimples from the supporting sutures on the lower flap.

open technique, a closed, multiple-use suction catheter contained within a sheath may be used (39). Similarly, in order to avoid mucus plugging of the tube, the inner cannula must be removed frequently for cleaning. Currently, inner cannulas are either disposable or reusable.

Humidification is extremely important in order to facilitate mucociliary transport of secretions and to prevent serious complications such as crusting, accumulation of secretions, and eventual obstruction of the airway. Humidification is usually carried out by a tracheal mask. The use of a T tube is avoided owing to the torque exerted on the tube, which traumatizes the tissue every time the patient moves.

Meticulous local wound care is of paramount importance. The tracheostomy site should be cleaned as necessary with normal saline or hydrogen peroxide to prevent breakdown of the skin and the progression from wound colonization to infection. Initially, this is likely to be three or four times daily. The twill tapes that hold the tracheostomy tube in place should be changed as necessary when soiled. The skin under the tracheostomy neck plate should be kept dry with a thin nonadherent dressing such as Telfa to prevent skin maceration. It takes at least 48 to 72 hours for a tract to form around the tracheotomy tube. Accordingly, the surgeon should avoid changing the tube until adhesions form between the overlying soft tissues and the trachea. Accidental decannulation in the early postoperative period can be very dangerous because the tissues collapse, sealing off the airway, and increasing the possibility of tube misplacement in a false passage when reinsertion is attempted (Fig. 64.25). Changing the tracheostomy tube requires skill and preparation, and early on it is not necessary unless the patient is to be changed from a cuffed to an uncuffed tube or if the cuff fails. Safe tube replacement in the first 48 hours requires the following (Table 64.15):

1. Optimal patient positioning
2. Assistance
3. Adequate light
4. Tracheal hook
5. Suction
6. Two tracheostomy tubes: ideal and smaller size
7. Tracheostomy tube exchanger

The use of a tracheostomy tube exchanger may be a very helpful adjunct for early tracheostomy tube changes. The exchanger is a long semiflexible tube with a central lumen through which ventilation is possible. The exchanger is inserted into the tracheostomy tube, which is then removed and replaced with the new tube. The exchanger "guides" the new tracheostomy tube into the trachea. If for any reason the new tracheostomy tube is difficult to

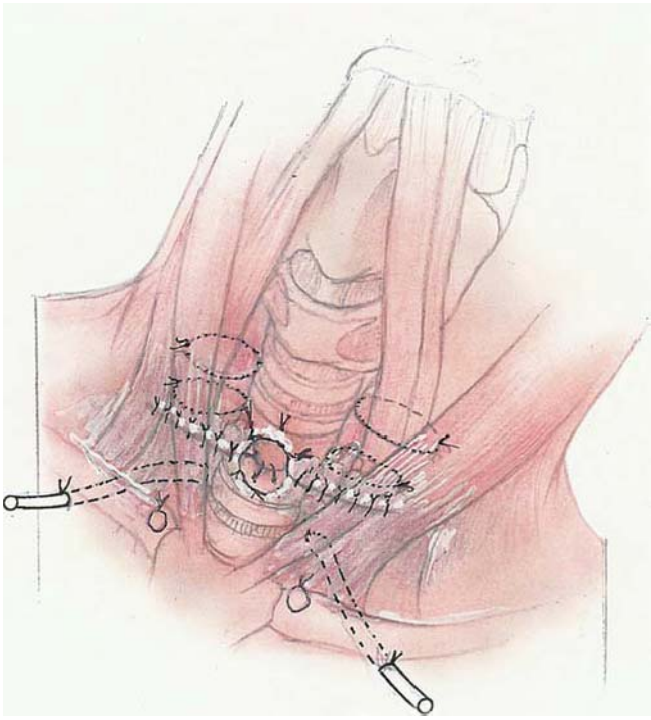


Figure 64.24 Final closure illustrating approximation of skin flaps to trachea. The laterally displaced thyroid and strap muscles are visualized through the skin. The suspension sutures supporting the lower flap can also be seen through the skin. Drains are brought out through separate stab wounds.

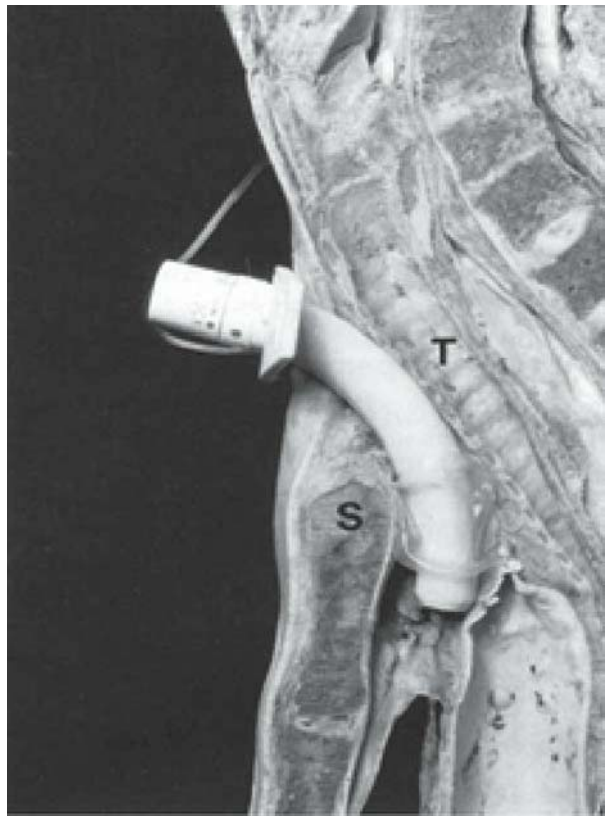


Figure 64.25 Mechanism of false passage between the sternum (*S*) and the trachea (*T*). (From Myers EN, Stool SE, Johnson JT, eds. *Tracheostomy*. New York: Churchill Livingstone, 1985:150.)

replace, ventilation may be temporarily continued through the exchanger.

Patients who do not require a cuffed tube may benefit from a Passy-Muir or speaking valve in the postoperative period. This one-way valve allows inspiration through the tracheostomy tube and closes on expiration, deflecting air through the vocal folds and permitting phonation. It has also been noted that these valves improve swallowing mechanics by restoring subglottic pressure, thereby facilitating deglutition. Contraindications for use of a speaking valve include (Table 64.16) a cuffed tracheostomy tube, upper airway obstruction, bilateral vocal fold paralysis, severe tracheal stenosis, copious inspissated secretions, and cognitive dysfunction.

Decannulation in adults can be safely accomplished by following a few simple steps. Indirect or flexible endoscopy should be used in both children and adults to ensure that the upper airway is adequate and the larynx is competent. Granulomas projecting into the stoma should be removed. The tube may then be downsized and plugged during waking hours. The period of plugging allows for adequate evaluation of airway adequacy. It also affords time for laryngeal adductor reflexes to be activated. The patient must be instructed to remove the plug in the event of dyspnea or shortness of breath. If the plug is not tolerated further, the nature of the obstruction must be investigated before further attempts at decannulation. If the patient tolerates the plug for 24 hours, the cannula can be removed and the stoma covered with a light dressing and occlusive tape,

TABLE 64.14 POSTOPERATIVE TRACHEOTOMY CARE

- Preoperative teaching
- Multidisciplinary tracheotomy care team
- Appropriate monitoring of vital signs
- Suctioning as required with preoxygenation
- Frequent cleaning/changing of the inner cannula
- Meticulous local wound care

TABLE 64.15 REQUIREMENTS FOR EARLY TRACHEOSTOMY TUBE CHANGE

1. Optimal patient positioning
2. Assistance
3. Adequate light
4. Tracheal hook
5. Suction
6. Two tracheostomy tubes: ideal and smaller size
7. Tracheostomy tube exchanger

TABLE 64.16 CONTRAINDICATIONS TO A SPEAKING VALVE

1. Cuffed tracheostomy tube
2. Upper airway obstruction
3. Bilateral vocal fold paralysis
4. Severe tracheal stenosis
5. Copious inspissated secretions
6. Cognitive dysfunction

which is changed as necessary. In the vast majority of cases, the stoma will close by secondary intention within a few days. The resultant scar from a transverse incision is cosmetically superior to that from a vertical incision.

Complications

Complications of tracheotomy may be divided into intraoperative, immediate postoperative, and late postoperative complications. The majority of complications are preventable and occur in the postoperative period. For admitted patients or airway emergencies, the surgery is best done in the controlled setting of the OR if possible. For those patients in respiratory distress, the airway should be secured whenever possible by insertion of an ET tube prior to proceeding to the OR. For adult intubated ICU patients, the procedure may also be safely performed at the bedside, provided adequate light, suction, and assistance are available.

Intraoperative Complications

Hemorrhage

Hemorrhage may be related to the patient ingesting anticoagulants, aspirin, or other nonsteroidal anti-inflammatory agents. These may contribute to excessive bleeding during the procedure and in the immediate postoperative period. Patients with coagulation disorders, such as hemophilia, leukemia, and liver disease, may also have excessive bleeding. Every effort should be made to correct these problems preoperatively unless the situation is emergent, in which case correction may be undertaken during the procedure and the surgeon must be absolutely meticulous in controlling the bleeding (Table 64.17).

Bleeding during tracheotomy may be minimized by careful attention to detail. When using local anesthesia, the procedure should not be begun until adequate vasoconstriction has been achieved. Bleeding is usually minimized by staying in the midline with the dissection, being cautious to dissect layer by layer, and maintaining adequate light and assistance with retraction of the soft tissues. This is particularly important in the pediatric age group, where the great vessels are vulnerable because of their proximity to the surgical site. Bleeding from transection of the anterior jugular vein, or the thyroid isthmus, are possible and should be dealt with appropriately by identifying, ligating, or cauterizing the offending vessel. Careful preoperative examination allows identification of a high innominate artery possible and injury preventable. In the unlikely event of injury to the innominate artery, repair requires the expertise of a vascular surgeon. Introduction of the tracheal cannula may cause a paroxysm of coughing, and bleeding may occur at that time. Retraction, suction, and lighting will facilitate identification and ligation of the involved vessel. Packing should be avoided because extravasation of air through the packing during coughing may predispose to subcutaneous emphysema.

Intraoperative Tracheoesophageal Fistula

Intraoperative tracheoesophageal fistula is unusual, but has been reported when the tracheal wall has been injured inadvertently, usually during an "urgent" tracheotomy with overpenetration of the trachea itself. If this is recognized at the time, it may be necessary to open the neck once the airway has been established and individually close the wounds in the trachea and the esophagus.

Pneumothorax

Pneumothorax is most likely to occur in a patient suffering from air hunger. It may also be due to direct puncturing of the pleura by the surgeon. This latter situation is most common in children, in whom the apex of the lung protrudes into the lower neck and is more vulnerable to injury. Pneumothorax may also occur when the tracheostomy tube is inserted between the anterior wall of the trachea and the soft tissues of the anterior mediastinum, creating a "false passage". This condition is much less likely to occur if the cannula is inserted with adequate exposure, retraction, and the use of traction sutures.

Pneumomediastinum

Pneumomediastinum occurs more commonly in children and is usually noted on routine postoperative chest radiographs. Predisposing factors include excessive dissection of the paratracheal soft tissues, breathing against an obstructed airway, and excessive coughing that forces air from the open tracheostomy into the deeper planes of the neck. Patients with pneumomediastinum are generally asymptomatic, and no therapy is required.

Postobstructive Pulmonary Edema

Cardiopulmonary arrest may occur in patients who have had chronic air hunger and elevated CO_2 levels. Sudden

TABLE 64.17 INTRAOPERATIVE COMPLICATIONS

- Hemorrhage
- Pneumothorax
- Pneumomediastinum
- Fire
- Intraoperative tracheoesophageal fistula
- Postobstructive pulmonary edema

relief of chronic upper airway obstruction may also result in congestive heart failure and pulmonary edema. This occurs from extravasation of fluid into alveoli from the sudden reduction of obstruction-induced PEEP. This possibility should be discussed with anesthesia in the event that cardiopulmonary resuscitation is necessary.

Fire

Fire during tracheostomy is a rare but catastrophic event. External burns may result from the use of electrocautery shortly after prepping the skin with alcohol-containing solutions. This is of particular concern in hirsute patients, in whom body hair interferes with the drying of the solution. Therefore, every effort should be made to ensure that the operative field is completely dry prior to electrocautery use, or the solutions should be avoided when possible.

Fire may also occur when using electrocautery in the presence of high concentrations of oxygen, whether delivered by mask (as in local procedures) or via the ET tube under general anesthesia. Oxygen concentrations should be kept at a minimum safe concentration for the patient, and cautery should never be used to enter the airway. In the unfortunate instance of an airway fire, the immediate response includes turning off the oxygen, changing the ET tube, and the use of water in the field, followed by bronchoscopy to assess the extent of injury. Medical treatment consists of antibiotics, steroids, and observation in the ICU. The best treatment consists of instituting all measures necessary to prevent such events.

Immediate Postoperative Complications

Tube Obstruction

Tube obstruction, a potentially fatal complication, may be caused by thick mucus or blood clots. This problem is largely preventable with attentive nursing care, proper humidification, and frequent suctioning. Routine use of a tracheostomy tube with an inner cannula allows regular inspection, cleansing, and suctioning. If for some reason the obstructed tube cannot be cleared, it should be removed and replaced (Table 64.18).

Displaced Tracheostomy Tube

Displacement of the tracheostomy tube may occur at any time and is potentially fatal (Fig. 64.25). This complication is most dangerous in the immediate postoperative period before a tract has formed in the soft tissues around the tracheostomy tube. Obese patients are particularly vulnerable to tube displacement because of the inadequate length of standard tracheostomy tubes. Insertion of an extended length tracheostomy tube at the time of surgery largely prevents this problem. Other patient factors that may predispose to displacement of the tube include excessive coughing and agitation. Additional factors include incorrect placement of the opening into the trachea, creating a false passage, loosening of the neck tapes as a result of resolution of subcutaneous emphysema, poorly tied tracheotomy tapes, failure to suture the neck plate to the skin, and use of bulky dressings.

Displacement of the tracheostomy tube should be suspected when a patient with a fresh tracheotomy develops respiratory distress or is suddenly able to speak. Tube displacement may be managed by one of two ways. (a) Reinserting the tracheostomy tube: pulling on the previously placed traction sutures and then returning the sutures to a position parallel to the patient's neck. This effectively retracts the skin and helps bring the stoma into the wound. A tracheal hook, if available, may further improve visualization of the tracheal opening. The tracheostomy tube is then inserted and adequate ventilation verified. (b) If reinserting the tube fails, is deemed too difficult, or if a patient is known to have difficult anatomy, it may be best to secure the airway by reintubating the patient and later identifying and opening the tracheostomy tract.

TABLE 64.18 EARLY POSTOPERATIVE COMPLICATIONS

- Tube obstruction
- Displaced tracheostomy tube
- Postoperative hemorrhage
- Wound infection
- Subcutaneous emphysema

Postoperative Hemorrhage

Postoperative bleeding may occur when the vasoconstriction from the epinephrine wears off or if vessels that were injured during surgery were not ligated and/or cauterized. Treatment requires identification and ligation of vessels. For "oozing," use of a hemostatic packing such as Surgicel may be helpful. Coagulopathies should be identified and corrected. If there is significant bleeding, and visualization at the bedside is difficult, the patient should be returned to the OR, the wound explored, and hemostasis secured.

Wound Infection

The tracheal wound is colonized within 24 to 48 hours by many species of organisms, including *Pseudomonas* and *Escherichia coli*, as well as Gram-positive cocci (40,41). It is not possible to prevent colonization. Tracheostomy tubes are also colonized by bacteria such as *Staphylococcus epidermidis*, which are imbedded in biofilm. The longer the tube is in place, the heavier the load of biofilm. This biofilm functions as a "coat of armor" of sorts, effectively protecting bacteria from local and/or systemic antibiotics. A true infection of the tracheal stoma is uncommon. Antibiotics simply select for colonization by a resistant organism and should not be used. Regular tracheostomy tube changes every 2 weeks for admitted patients may decrease the incidence of granulation tissue and biofilm formation (40).

The fundamental principles of tracheotomy wound care consist of meticulous hygiene with suctioning, cleansing,

dressing and tie changes, and tube changes when necessary to remove crusts and necrotic debris, thereby reducing bacterial load. Traction sutures should be removed when the tract has formed (3 to 4 days). True infection with surrounding cellulitis is unusual and should be treated with organism-specific antibiotics as well as aggressive local wound care with debridement.

Tracheobronchitis may be due to underlying disease or aspiration, or both. Treatment is with suctioning, vigorous pulmonary exercise (blow bottles, cupping and clapping, ambulation), and judicious administration of antibiotics.

Rarely, necrotizing stomal infections may occur, with substantial loss of soft tissue down to and including the tracheal wall. Further progression of the process may result in carotid artery exposure, with its attendant risks. Management includes aggressive wound debridement and cleaning with antiseptic dressings as well as culture-guided antibiotics. Rarely, local flaps may be necessary to provide soft tissue coverage to vital structures.

Subcutaneous Emphysema

Air may be forced into the subcutaneous tissues during or shortly after tracheotomy. Factors predisposing to this complication include excessive coughing, use of an uncuffed tracheostomy tube, tight suturing of the wound around the tracheostomy tube, and packing of the wound. Emphysema is usually mild and may be diagnosed by palpating crepitus in the tissues of the neck, chest, or face. Subcutaneous emphysema is generally prevented by using a cuffed tracheostomy tube and not packing the wound. If the condition is severe, the wound should be opened and any packing removed. Otherwise, no treatment is necessary because the air is slowly absorbed from the tissues.

Late Postoperative Complications

Granulation Tissue

Granulation tissue is considered to be a late complication or sequela of tracheostomy, variably reported as occurring in 3% to 80% of cases (40). It is commonly seen in children, especially those in whom a fenestrated tube has been used. The clinical importance of granulation tissue lies in its ability to bleed, complicate tracheostomy tube changes, delay attempts at decannulation, and completely obstruct the tracheostomy tube with potentially catastrophic results. Factors thought to favor formation of granulation tissue include bacterial infection, gastroesophageal reflux, suture material, and powder from surgical gloves. Although a number of topical treatments such as steroid creams, antibiotic ointments and silver nitrate have been suggested, larger amounts of granulation tissue, particularly when obstructive, may require surgical excision, with or without the use of laser (Table 64.19).

The prolonged presence of the same tracheostomy tube, which is a foreign body, elicits an inflammatory tissue response favoring the growth of granulation tissue, increased secretions, and bacterial colonization with biofilm production (16). Regular tube changes on a schedule of every 2 to 3 weeks have been shown to dramatically reduce the incidence of this problem (40).

TABLE 64.19 LATE POSTOPERATIVE COMPLICATIONS

- Granulation tissue
- Tracheoesophageal fistula
- Tracheoinnominate artery rupture
- Tracheal stenosis and tracheomalacia
- Tracheocutaneous fistula
- Depressed scar

Tracheoesophageal Fistula

Late tracheoesophageal fistula is rare and may result from an overinflated or improperly fitted cuff. A malpositioned tracheostomy tube pushed to the posterior wall of the trachea against an indwelling nasogastric tube may also result in the formation of a fistula. Penetration of the posterior tracheal wall during surgery along with local infection may cause a tracheoesophageal fistula. Treatment consists of open repair with individual closure of the tracheal and esophageal defects, and interposition of soft tissue, such as muscle in the defect. Although the passage of food through the tracheostomy may be an indication of a tracheoesophageal fistula, it is more often a manifestation of aspiration. This can be confirmed on modified barium swallow.

Tracheoinnominate Artery Rupture

Rupture of the innominate artery usually occurs within the first 3 weeks after tracheotomy and may be fatal. This complication may occur in patients of any age and may be related to several factors: (a) placing the tracheostoma too low, below the third tracheal ring where the inferior concave surface of the cannula may erode the artery; (b) an aberrant or abnormally high innominate artery; (c) use of an excessively long or curved tube, with erosion of the tip through the trachea and into the vessel wall; (d) prolonged pressure on the tracheal wall by an inflated cuff; and (e) tracheal infection (42,43).

Rupture of the innominate artery is usually heralded by a "sentinel bleed," which may stop and be followed a few days later by a catastrophic hemorrhage. The patient coughs up bright red blood from the tracheostomy tube. If this sign is recognized, the cuff of the tracheostomy tube should immediately be overinflated and suprasternal pressure applied in an attempt to control the hemorrhage. If the inflated tracheostomy cuff does not prevent blood from entering the lungs, it can be changed for an ET tube that can be advanced to the desired level and the cuff inflated to control bleeding and prevent aspiration of blood. These maneuvers generally control the bleeding at least temporarily. The patient should be crossmatched and transported to the OR immediately, keeping continuous pressure

between the anterior trachea and sternum. Sternotomy and ligation of the innominate artery is a lifesaving maneuver.

Tracheal Stenosis and Tracheomalacia

Tracheal stenosis and tracheomalacia are late complications. Steps toward decreasing the occurrence of these sequelae include (a) proper placement of the tracheostomy tube between the first and third tracheal rings, (b) use of the smallest possible tube size, (c) minimizing cuff inflation pressures (less than 25 mm Hg), and (d) minimizing cuff inflation times.

Tracheocutaneous Fistula

Tracheocutaneous fistula is a persistent opening between the trachea and skin following decannulation. It occurs when there is inward growth of the skin to meet the trachea. It is more likely to occur in long-standing tracheotomies. Another less frequent cause is partial upper airway obstruction, in which case the fistula compensates for the compromised airway. This can be easily verified with an endoscopic exam prior to undertaking any repair of the fistula.

A persistent tracheocutaneous fistula results in the following problems: difficulty speaking or coughing without digital occlusion of the fistula, moist, macerated skin from mucus, and social embarrassment. Although the simplest repair consists of excising the skin within the fistula and allowing the wound to close by secondary intention, a depressed scar is likely to result. A better method entails removing a small ellipse of skin that includes the fistula. The skin is then dissected off the scar and widely undermined laterally. The strap muscles, which are scarred, are released from the trachea and reapproximated in the midline with absorbable sutures. This maneuver fills in the depressed area and separates the skin from the trachea. The skin is then closed and a light pressure dressing is applied to prevent air from escaping from the wound. Patients should be instructed to apply pressure to the area if they need to cough. The procedure requires general anesthesia in children but can be carried out under local anesthesia in the outpatient setting in adults.

Depressed Scar

A depressed scar is visible when the skin is adherent to the underlying trachea. Such scars are unsightly and draw attention because the skin moves with the trachea every time the patient swallows. They can be repaired under local anesthesia by excising the involved skin, widely undermining the edges of skin, freeing and reapproximating the intervening layer of scarred strap muscles, and closing the skin without tension.

Percutaneous Dilatational Tracheotomy in the Intensive Care Unit

Critically ill patients represent a special subset of the population by virtue of their multisystem disease and the complexity of the care they require. Tracheotomy is a frequently performed procedure in intubated ICU patients, and, not surprisingly, is associated with a higher risk (23). As such, special consideration is required in terms of indications, technique, and care. Moving these critically ill patients to the operating room with their monitors requires additional personnel and carries a number of different risks, including accidental extubation and vital sign changes requiring pharmacologic intervention (44,45).

Standard surgical tracheostomy (ST) at the bedside in the ICU is a reasonable option, with complication rates comparable to ST in the OR. This approach may be inconvenient, however, because of the need for special instrument trays, adequate suction, extra lighting, and electrocautery, which must be transported from the OR to the ICU. The lack of trained OR nurses and assistants as well as difficult visualization may compound the problem. Since most intubated, ventilated patients require an FiO_2 of greater than or equal to 30%, spontaneous ignition with the use of electrocautery is a real concern. Endoscopic percutaneous dilatational tracheotomy is an attractive alternative for patients in the ICU needing a tracheotomy because it is safe, simple, and can be performed at the bedside, reducing the need for OR time.

Seldinger's description in 1953 of catheter replacement of the needle in percutaneous anteriography over a guidewire served as a basis for the development of several percutaneous tracheotomy techniques. While many of these early procedures were quickly abandoned because of high complication rates, interest in this area persisted, and in 1985, when Ciaglia described a bedside percutaneous dilatational tracheotomy (18) technique, the procedure was rapidly adopted in many ICUs, principally by critical care physicians and anesthesiologists. The technique is based on progressive dilatation of an initial tracheal puncture. There were early concerns over safety because the procedure, as originally described, was blind. The addition of endoscopic guidance, first reported in 1990 in 61 patients by Marelli et al. (46), addressed the "blind aspect" of the procedure. Kost's series of 500 cases published in 2005 demonstrated that, with bronchoscopic visualization and attention to technical detail, endoscopic percutaneous dilatational tracheostomy (PDT) is a safe, cost-effective alternative to ST in the OR, with complication rates comparable to or lower than those of ST (47).

Cost analyses of PDT compared to ST in the OR almost uniformly agree that PDT is significantly less expensive (48). The results are more controversial when PDT is compared to ST at the bedside. Not all analyses include the cost of cleaning/sterilizing instruments, as well as the cost of the disposables associated with electrocautery (cautery tip, grounding pads). PDT is often said to be more costly because the kits are disposable and because of the added cost of bronchoscopy. While this may be correct for specific sets, several different kits are available, and the prices between them differ significantly.

Procedure time for PDT is reduced by up to 50% when compared to ST at the bedside. Although this should by no

means be the deciding factor in which technique to use, expediency when establishing an airway is advantageous.

PDT has been the subject of intense controversy, particularly in the Otolaryngology–Head and Neck Surgery community, for over a decade. The majority of published articles on the subject are from the specialties of critical care, anesthesia, and general surgery. Results from a recent survey of American residency training programs indicated that PDT was performed regularly in only 29% of Otolaryngology–Head and Neck Surgery programs. In the other 71%, program directors indicated their residents did not have the opportunity to learn PDT while on the Otolaryngology–Head and Neck Surgery service.

Patient Selection

It must be stressed that PDT is suitable only in adult intubated patients. This patient population accounts for almost two-thirds of all tracheostomies performed today (Tables 64.20 and 64.21).

Anatomical and medical suitability for this procedure must be determined preoperatively with a careful examination with the patient's neck extended (47,49). Contraindications to PDT (Table 64.21) include the inability to palpate the cricoid cartilage above the sternal notch, the presence of a midline neck mass or large thyroid gland, and a high innominate artery. Patients with these conditions should undergo ST in the OR. Coagulopathies are common in ICU patients and should be corrected as much as is medically safe preoperatively. Ideally, the number of functioning platelets should be greater than or equal to 50,000 and the INR should be corrected to less than or equal to 1.5. Patients requiring a PEEP of greater than or equal to 15 cm H_2O are at high risk for complications such as subcutaneous emphysema and pneumothorax and should undergo ST in the OR.

Nonintubated patients with acute airway compromise constitute an absolute contraindication to PDT. The procedure requires a secure airway for bronchoscopic visualization through an ET tube or LMA. PDT should never be attempted in children. The different airway dimensions and anatomy in the pediatric population as well as the technical difficulties of maintaining adequate ventilation with a bronchoscope within a small ET tube renders the procedure completely unsuitable in this age group (49). Patients having had a previous tracheostomy may undergo PDT safely if they have no other contraindications (47). Obese patients may also undergo PDT provided a proximally extended tracheostomy tube is used to reduce the risk of accidental decannulation.

TABLE 64.20 INDICATIONS FOR PERCUTANEOUS TRACHEOTOMY

- Adult intubated ICU patients

TABLE 64.21 CONTRAINDICATIONS FOR PERCUTANEOUS TRACHEOTOMY

- Unprotected airway
- Airway emergency
- Inability to palpate the cricoid cartilage
- Midline neck mass
- High innominate artery
- Children
- PEEP > 15 cm H_2O

Preoperative Planning

Preoperative testing is minimal and includes a recent chest radiograph as well as serum determination of hemoglobin, prothrombin time, partial thromboplastin time, INR, and platelets. Cross-matching is not necessary even in the presence of low hemoglobin levels. A fully equipped intubation cart should be available nearby in the event of accidental extubation during the procedure. Special consideration should be given to obese patients or those with a short thick neck. It must be emphasized that the presence of thick subcutaneous tissues in this group places them at particular risk for accidental decannulation. This potential problem may be circumvented by using a tracheostomy tube with a proximal extension (47).

As with all other minimally invasive techniques, there is a learning curve for endoscopic PDT. Familiarity with open surgical tracheotomy does not confer expertise to PDT, and appropriate training should be obtained prior to using the technique. Careful selection of patients with anatomically favorable necks for the first 30 to 40 patients allows the surgeon to gain experience and reduces the likelihood of complications.

Personnel

In addition to the attending staff surgeon, a resident or critical care colleague is required to perform the bronchoscopy, and a respiratory technician to assist in suctioning, adjust ventilator settings, and hold the ET tube firmly in position. A nurse is needed to administer medication, monitor vital signs, and help in obtaining necessary materials and instruments. The right-handed surgeon and necessary instruments are positioned to the patient's right, the respiratory technician and bronchoscope cart are to the patient's left, and the bronchoscopist is at the head of the bed.

Instruments

Currently, there are a number of commercially available kits that are similar in that they all create an initial tracheal puncture that is dilated to a size large enough to admit the preselected tracheostomy tube. Over the last decade, both the technique and instruments have been refined, and the process is continuing to evolve. The original kits contained a series of graduated dilators for progressive

dilatation. In the last several years, these graduated dilators have been replaced by a single sharply tapered dilator that simplifies the procedure. More recently, a new kit has been introduced in which the initial tracheal puncture is dilated with a pressure-controlled inflatable balloon. The purported advantage is that the balloon produces constant radial pressure on the trachea and does not cause depression of the anterosuperior wall. Although early data suggest the technique is safe, there are currently no studies to indicate it is superior. As such, selection of any particular kit is largely a question of preference.

The simplest and most thoroughly evaluated kit in North America is the Ciaglia Blue Rhino Percutaneous Introducer Kit (Cook Critical Care Inc., Bloomington, Indiana). The basic kit contains the following: a 15 blade scalpel, a 5-mL syringe, an introducer needle, a J-wire guide, an introducer dilator, a white guiding catheter, a sharply tapered single blue dilator with a hydrophilic coating, as well as 24-French, 26-French, and 28-French loading dilators (Fig. 64.26).

Other required instruments include a scalpel, curved hemostat, straight scissors, a needle driver, nonresorbable sutures, water-based lubricant, sterile saline to activate the hydrophilic coating of the single dilator, two 10-mL syringes, and an appropriately sized tracheostomy tube. The instruments should be placed on an instrument stand over the patient's bed and in the order in which they are to be used (Fig. 64.27). The preselected tracheostomy tube is fitted over the loading dilator: a no. 6 Shiley tracheostomy tube is fitted over the 26-French loading dilator while a no. 8 Shiley tracheostomy tube is fitted over the 28-French loading dilator. A no. 4 tracheostomy tube may be fitted over the 24-French loading dilator but is infrequently used. Shiley "Per-Fit" tracheostomy tubes are commercially available and have been specially designed and tapered to permit for easier insertion. The white guiding catheter is inserted into the single dilator such that the tip of the dilator rests on the ridge of the guiding catheter. An appropriately sized bronchoscope with a suction port must be chosen to fit within the ET tube while still allowing adequate ventilation. A pediatric bronchoscope may be required for ET tubes less than 7.5 mm. Almost any bronchoscope may be used in patients ventilated through an LMA. If available, a video monitor may be connected to the bronchoscope, allowing full visualization of the intratracheal portion of the procedure by the operating surgeon and assistant staff.

Anesthesia

Any procedure involving manipulation of the trachea is highly stimulating to the patient and requires adequate local anesthesia supplemented by intravenous sedation. Local anesthesia, consisting of 1% or 2% lidocaine with 1:100,000 epinephrine is used for generous infiltration of the incision site and pretracheal soft tissue. Topical anesthesia in the form of 2 mL of 2% to 4% lidocaine injected through the bronchoscope is useful in decreasing the cough reflex. Intravenous sedation is also required with the particular drug combination dependent on the needs of the individual patient and the institution. Frequently used

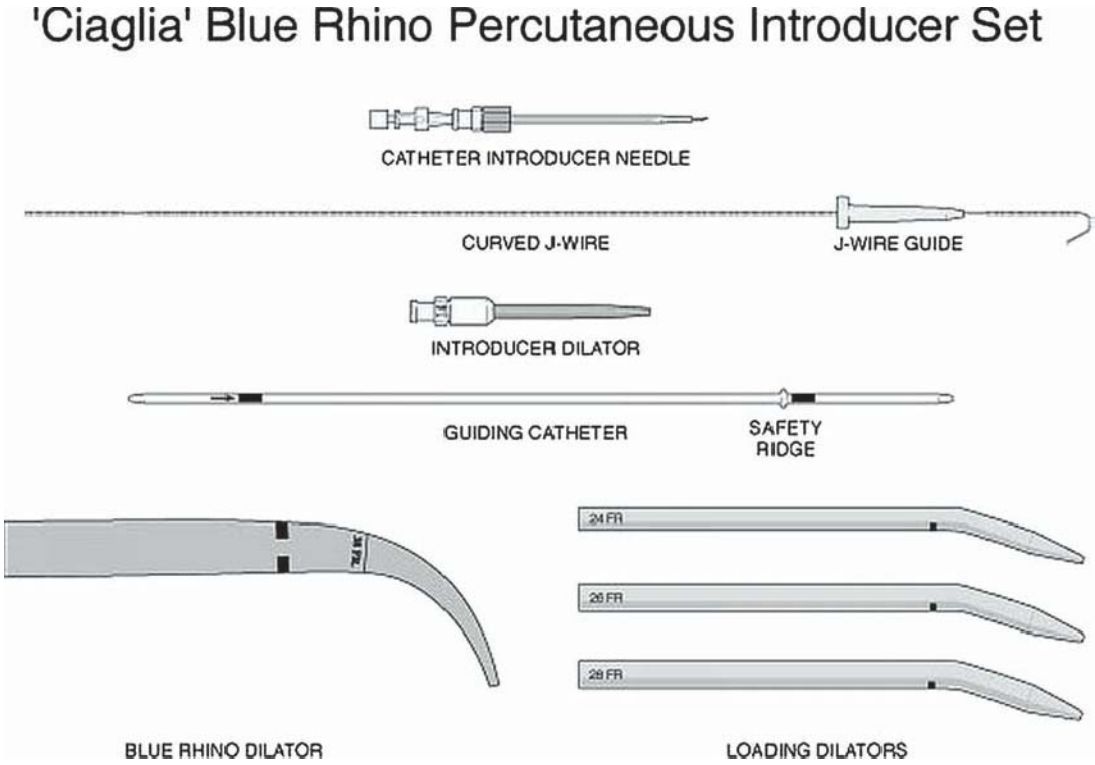


Figure 64.26 Ciaglia Blue Rhino Introducer Kit.

medications include midazolam, given a few minutes prior to commencing the procedure, followed by propofol, administered as a continuous infusion or in boluses, and sublimaze (Fentanyl). Muscle relaxants such as pancuronium bromide may be used as an adjunct in cases where agitation is a problem. The presence of an anesthetist is optional and may depend on hospital policy. Care should be exercised in administering these medications particularly in the elderly patient since large fluctuations in blood pressure and heart rate may occur even with small doses (47).

Technique

Following the administration of appropriate sedation, the patient is thoroughly suctioned and ventilator settings are adjusted to deliver 100% O_2. Vital signs including heart rate, blood pressure, and oxygen saturation are monitored continuously throughout the procedure. The instruments for the Ciaglia Blue Rhino Introducer Set are illustrated in Figure 64.26. Instruments are laid out on a Mayo stand in the anticipated order of use (Fig. 64.27). The patient is positioned as for conventional tracheostomy with the neck extended provided that there is no contraindication (e.g., cervical spine fracture). Important anatomical landmarks including the thyroid and cricoid cartilages and sternal notch are palpated. The patient's neck and upper chest are then prepped and draped in a standard fashion, and the incision site is infiltrated with 2% lidocaine with 1:100,000 epinephrine.

A 1.5- to 2-cm skin incision, just long enough to allow for the circumference of a tracheostomy tube, is made at the level of the first and second tracheal rings. This corresponds to approximately one fingerbreadth above the sternal notch or two fingerbreadths below the cricoid cartilage. The subcutaneous tissues are gently separated horizontally with a curved hemostat to allow accurate palpation of the cricoid cartilage and tracheal rings. No attempt is made to divide or otherwise manipulate the isthmus of the thyroid gland.

At this point, 1 to 2 mL of 4% lidocaine may be instilled into the ET tube in order to decrease coughing. Any tapes or ties are loosened to allow manipulation of the ET tube. From this point on, the ET tube must be held securely by the bronchoscopist or respiratory technician to prevent accidental extubation. An appropriately sized flexible bronchoscope with a suction port is lubricated at the tip and inserted through an adapter into the ET tube and advanced until the tip of the bronchoscope lies flush with the ET tube. During this step, the bronchoscope light will be seen through the incision as it is advanced into the ET tube. The ET tube (with the cuff momentarily deflated) and bronchoscope are slowly withdrawn as a unit until the incision is transilluminated and/or digital depression of the trachea is clearly visualized endoscopically. All ensuing steps are visualized through the bronchoscope. It should be noted that the ET tube cuff position will lie at, or just below, the true vocal folds and must be carefully held at all times. With the ET tube and bronchoscope properly positioned, the tracheal rings are palpated and a no. 14 or no. 16 Teflon catheter introducer needle is used to lightly depress the anterior tracheal wall between the first and second or second and third tracheal rings. The location of the needle is verified endoscopically and modified until an intercartilaginous position between 11 and 1 o'clock is achieved. At this point, the needle is inserted into the tracheal lumen taking care not to puncture the posterior tracheal wall (Fig. 64.28). The needle is removed, and



Figure 64.27 The instruments are placed on an instrument stand over the patient's bed in the order in which they are to be used. Above, from *left* to *right*: Skin preparation solution, gauze, suture scissors, forceps, needle driver and 2-0 silk for suturing the tracheostomy tube to the skin, sterile saline for activating the hydrophilic coating on the single dilator. Below, from *left* to *right*: Gauze for skin preparation, 10-mL syringe with 2% lidocaine with 1:100,000 epinephrine, 15 blade scalpel, mosquito, 5-mL syringe with sheathed introducer needle, J-wire, introducer dilator in center, single dilator pre-assembled over guiding catheter with ridge, no. 6 tracheostomy tube with pre-fitted 26-French Obturator dilator.

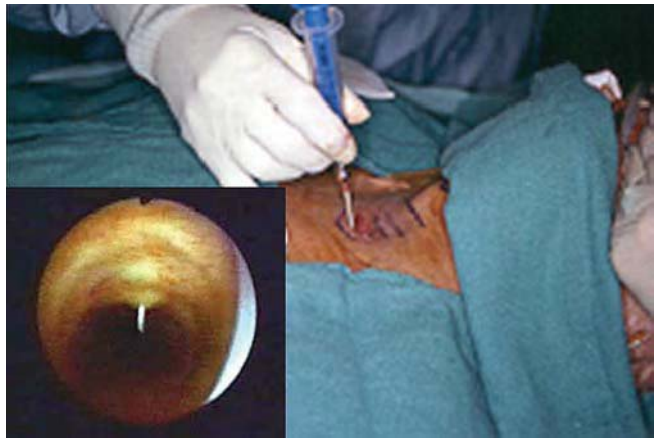


Figure 64.28 With the ET tube and bronchoscope properly positioned, the tracheal rings are palpated and a Teflon catheter introducer needle is used to depress the anterior tracheal wall between the first and second or second and third tracheal rings. The location of the needle is verified endoscopically and modified until an intercartilaginous position between 11 and 1 o'clock is achieved. At this point, the needle is inserted into the tracheal lumen taking care not to puncture the posterior tracheal wall. **Inset:** Endoscopic view of needle insertion.

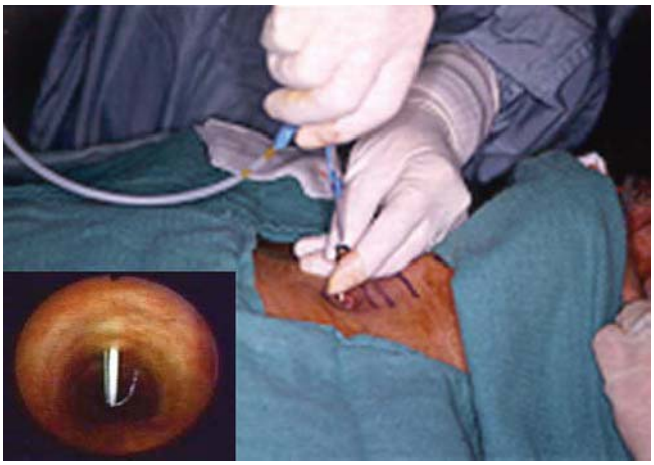


Figure 64.29 The needle is removed, and a J-tipped guidewire is threaded through the remaining catheter into the trachea. **Inset:** Endoscopic view of J-wire advanced through the catheter.

a J-tipped guidewire is threaded through the remaining catheter into the trachea (Fig. 64.29). This catheter sheath is replaced by a 14-French introducer dilator (Fig. 64.30A & B). Removal of the introducer dilator allows for passage of the



A



B

Figure 64.30 **A:** The catheter sheath is replaced by a 14-French introducer dilator. **Inset:** Endoscopic view. **B:** Introducer dilator in position. **Inset:** Endoscopic view of introducer dilator in position.



Figure 64.31 The introducer dilator is removed to allow insertion of the previously assembled guiding catheter/single which is dipped in saline to activate the hydrophilic coating. The guiding catheter/single dilator unit is held like a pen, introduced over the guidewire between the markings, and advanced in an arc conforming to the tract undergoing dilatation until the black mark of the single dilator is seen through the bronchoscope. **Inset:** Endoscopic view of single dilator/guiding catheter assembly entering the trachea.

previously assembled guiding catheter/single dilator unit, which is dipped in saline to activate the hydrophilic coating. The guiding catheter/single dilator unit is held like a pen, introduced over the guidewire between the markings, and advanced in an arc conforming to the tract undergoing dilatation until the black mark of the single dilator is seen through the bronchoscope (Fig. 64.31). Some depression of the anterior tracheal wall may occur during dilatation. Slight overdilatation and leaving the single dilator *in situ* for 10 to 15 seconds facilitate placement of the tracheostomy tube. The single dilator is removed, leaving the guidewire/guiding catheter *in situ*. The guidewire/guiding catheter unit serves as a scaffolding over which the tracheostomy tube, prefitted with the appropriately sized loading dilator, is advanced into the trachea. Two points of resistance are typically encountered during this maneuver: the interface between the loading dilator and tracheostomy tube, and upon insertion of the balloon (Fig. 64.32).

At this point, the loading dilator, guiding catheter, and guidewire are removed and replaced with the inner cannula (Fig. 64.33). The cuff is inflated, and ventilation is continued through the tracheostomy tube. The tracheostomy tube is secured with four corner sutures and tape ties (Fig. 64.34). Blood and/or secretions are suctioned from the trachea. Only when adequate ventilation is established should the ET tube be removed. The vocal cords may be inspected upon removal of the bronchoscope and ET tube.

Tracheostomy tube size is chosen based on the clinical needs and gender of the patient. Whenever possible, smaller no. 6 I.D. tubes should be used in females to reduce the likelihood of tracheal stenosis or tracheomalacia. In a patient with a short, thick neck, a proximally-extended

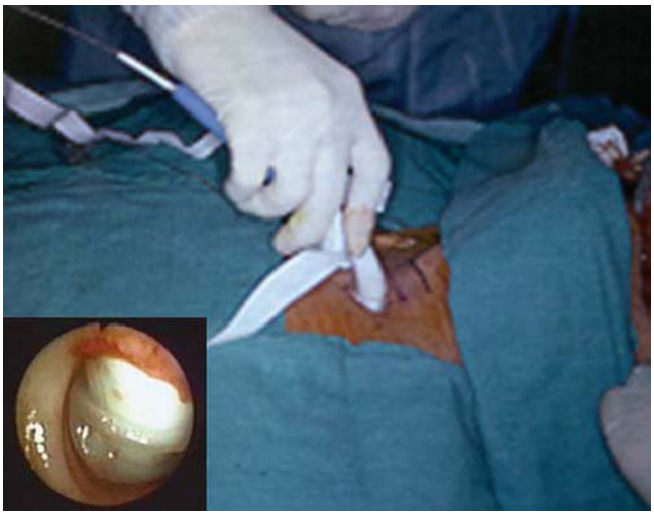


Figure 64.32 The single dilator is removed, leaving the guidewire/guiding catheter unit as a scaffold over which the tracheostomy tube, prefitted with the appropriately sized loading dilator, is advanced into the trachea. Two points of resistance are typically encountered during this maneuver: the interface between the loading dilator and tracheostomy tube, and upon insertion of the balloon. **Inset:** Endoscopic view of the tracheostomy tube and balloon entering the trachea.

tracheostomy tube should be used to prevent accidental displacement of the tube into the pretracheal soft tissue.

Depending on the degree of calcification of the tracheal cartilages, fracture of the ring immediately adjacent to the dilator may occur during dilatation. This is akin to intentionally incising one or more rings during an open ST. There is no evidence to suggest that this occurrence increases the incidence of tracheomalacia and tracheal stenosis (47).

Postoperative Considerations

Continuous vital sign monitoring should continue in the postoperative period. With the termination of the intense stimulation produced by the procedure, the effects of the sedation may become more pronounced, resulting in hypotension, tachycardia, or O_2 desaturation. All these changes may require correction with pharmacologic intervention. Suctioning may be necessary to clear secretions or blood, thus preventing a drop in O_2 saturation. A postoperative chest radiograph is required to ensure the absence of pneumothorax and pneumomediastinum.



Figure 64.33 The loading dilator, guding catheter, and guidewire are removed and replaced with the inner cannula. **Inset:** Endoscopic view of the tracheostomy tube in place.

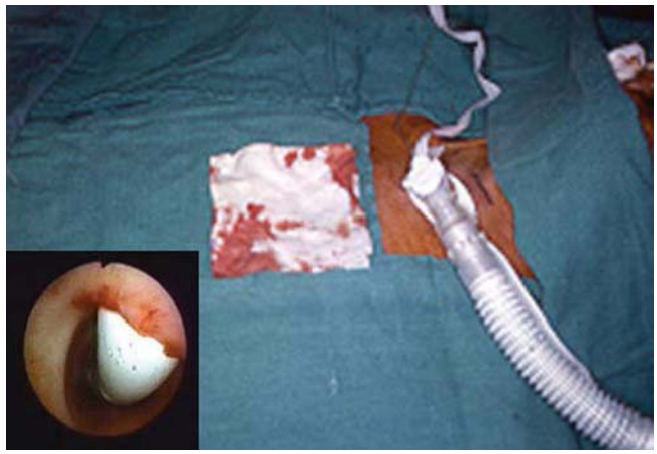


Figure 64.34 Ventilation is continued through the tracheostomy tube. The tracheostomy tube is secured with four corner sutures and tape ties. **Inset:** Endoscopic view of tracheostomy tube in place.

Many of these patients have copious secretions from the tracheostomy site from their associated pulmonary condition. A tracheostomy tube with an inner cannula facilitates care and hygiene and ensures added safety by allowing rapid removal should obstruction from secretions occur. The PDT technique is primarily dilatational with minimal tissue dissection resulting in a tighter tract and a very snug fit of the tracheostomy tube. The technique does not allow for easy placement of traction sutures at the level of the trachea. Because of these factors, the patient should be reintubated orally in the event of accidental decannulation within the first 5 to 7 days of the procedure while the tract is still relatively immature. Because of the tight tract, attempts at forcefully replacing the tracheostomy tube in an emergent situation could result in bleeding, the creation of a false passage, pneumomediastinum, hypoxia, and even death.

Complications

Potential intraoperative and postoperative complications are similar to those reported for surgical tracheotomy. Notable differences in terms of frequency are discussed below. Interpreting available data for both techniques can be difficult for several reasons: (a) Uneven reporting of complications. Examples include desaturation, subcutaneous emphysema, and infection, which frequently go unmentioned. (b) Uneven threshold for reporting of complications. In some series, even minor bleeding is reported while in others it is only mentioned if the loss is in excess of a "significant" amount (e.g., 200 mL). (c) Inhomogeneity of techniques, patient subsets, and surgeons is observed in

many studies (48,50). Fundamentally different PDT techniques are frequently considered together and compared to ST, leading to biased results (48,50). The patient subsets for PDT and ST are different and yet results from both groups are often compared. PDT patients are relatively homogeneous and consist only of adult intubated ICU patients, identified as having a higher risk of complications because of their multiple co-morbidities. Most patients undergoing ST are neither intubated, nor from the ICU. In the majority of reported PDT studies, the procedure is performed by nonsurgeons, while in virtually all ST studies the procedure is performed by surgeons. This fact can also bias results. Many or all of these inhomogeneities exist together in many reports, including meta-analyses, thus further complicating data analysis.

With the above information in mind, some general statements can be made. The overall complication rate for endoscopic PDT in the literature is approximately 9% (47). This compares favorably to that of ICU patients undergoing open surgical tracheotomy in the OR, where complication rates of 14% to 66% have been reported (47), or at the bedside where complication rates of 4% to 41% have been reported (47). Procedure-related mortality is very low for both PDT (0.5%) and ST (less than 2%). Comparative data on individual complications (e.g., bleeding, infection) for surgical and percutaneous tracheotomies vary widely, but overall PDT compares favorably to ST. Although the use of continuous endoscopic visualization has been debated in the literature, several series have shown that it is crucial to the safety of the procedure and in reducing complications (47,49).

Obese patients with a body mass index greater than or equal to 30 are at higher risk for complications. This risk is further increased in obese patients who are "more ill" as assessed by the ASA classification. The most common complication in this group is accidental decannulation owing to the thickness of the subcutaneous tissues. Use of a proximally extended cannula largely circumvents this problem. There is no data available on the risk of complications in obese patients undergoing open ST, and therefore no evidence that the risk for this subset of patients is reduced in ST (47). Early mortality in morbidly obese patients undergoing ST may be higher than in nonobese patients (51). There is no data on early mortality in obese patients undergoing PDT. There is a learning curve for endoscopic PDT, and careful selection of patients with anatomically favorable necks is advisable before proceeding to patients with thick or less favorable necks.

Desaturation

The real risk of this complication is unknown since it is infrequently reported in both the "open" and percutaneous tracheotomy literature. Brief episodes of mild oxygen desaturation may occur at the time of tracheostomy tube insertion, particularly in patients with compromised pulmonary function requiring high FiO_2 concentrations (47). The risk of such an occurrence may be minimized by thorough pre-/intraoperative suctioning of secretions and by ventilating all patients on 100% O_2 for the duration of the procedure.

Bleeding

The reported incidence of bleeding varies widely in the literature from 0% to 37% for open surgical tracheotomy compared to 1% to 19% for percutaneous tracheotomy. Overall, the incidence of bleeding complications in larger series is lower in PDT than in ST. This can be explained by the blunt nature of the technique as well as the tamponade effect of the tracheostomy tube against the tight tract that is created (47,49). Occasionally, there is bleeding from a thyroid vein at the time of initial tracheal puncture. This can be addressed by removing the needle, applying pressure for 5 minutes, and creating a new puncture. Alternatively, the procedure may be continued at the original puncture site, since the bleeding will stop with the tamponade effect of the tracheostomy tube. Minor oozing from wound edges can be controlled with simple pressure. Occasionally, a small hemostatic packing may be helpful. Although there are isolated reports of life-threatening hemorrhage for both "open" and percutaneous techniques, this rare complication usually results from an unanticipated anatomical anomaly, from violating a major vessel, or, later, from erosion into the innominate artery.

Infection

Reported infection rates vary widely from 0% to 10% for PDT compared to 0% to 31% for ST. In the largest series, the infection rate is less than 1%. The lower risk of infection in PDT can be explained by the small wound and tight tract, which reduces the surface area available for bacterial colonization compared to the more extensive soft tissue dissection in ST (47,49). Treatment principles for infection following PDT are the same as those for ST.

Accidental Extubation

The true incidence of accidental extubation for either PDT or open surgical tracheotomy is unknown because it is so infrequently mentioned in the literature. It has, however, been reported to occur with both techniques. The risk of this potentially serious complication may be reduced through the following steps: the ETT should be held and manipulated only by a physician or a respiratory therapist and such manipulation should occur only after the bronchoscope has been positioned within the ET tube and while the patient is ventilated on 100% oxygen.

Posterior Wall Injury

Occasional overzealous initial needle insertion may puncture the posterior wall, but this is clinically insignificant and is easily corrected by simply withdrawing the needle to the appropriate position. Serious posterior wall injury can be avoided by attention to technical detail (proper positioning of the guidewire, guiding catheter, and dilator)

and, most importantly, constant endoscopic visualization of the posterior wall during the procedure (47).

Technical Misadventures

Loss of the puncture site and accidental removal of the J-wire include some of the possible technical mishaps. In these instances the procedure must be continued from the previous step or started anew as dictated by the circumstances. Occasionally, dilatation may be difficult because resistance is encountered. If this is the case, the size of the incision and soft tissue "tunnel" should be verified. As a rule, the surgeon's index finger should fit comfortably in the incision and soft tissue tunnel. If not, additional spreading of the soft tissue should correct the problem. If the initial needle insertion is through a tracheal ring, dilatation will be difficult and the needle should be repositioned between rings. If the tracheostomy tube is difficult to insert, the tract should be "redilated." The use of excessive force during any step of the procedure always indicates a problem and should never be used as it is likely to lead to complications and/or damage of the instruments. Technical problems may prolong the procedure but rarely directly impact patient safety or outcome (47).

False Passage, Pneumothorax, Pneumomediastinum, and Subcutaneous Emphysema

These potentially fatal complications can be almost completely avoided by continuous bronchoscopic visualization of every step of the procedure (47). Excessive force should never be used during dilatation or tracheostomy tube insertion, and always indicates a technical problem. Subcutaneous emphysema in association with PDT is rarely reported and probably occurs in patients requiring a PEEP greater than 15 cm H_2O. For this reason, such patients should undergo ST.

Accidental Decannulation

Accidental decannulation is unusual because of the tight tract. Most at risk are obese patients or those with short thick necks in whom subcutaneous adipose tissue effectively shortens the intratracheal length of the tracheostomy tube. This potential problem may be circumvented by using proximally extended length tracheostomy tubes (47).

SUMMARY

Expertise in airway management requires a thorough understanding of airway anatomy and available management options. Intubation and tracheotomy are the most frequently used means of securing the airway. Knowing when to use one over the other must be dictated by the clinical context, as well as the skills of the anesthetist and surgeon. Communication between all involved medical personnel is essential in developing an appropriate management plan for any given patient.

HIGHLIGHTS

- Intubation allows for controlled mechanical ventilation with operative and nonoperative indications.
- A detailed airway history and examination prior to intubation are critical in planning and executing the appropriate intubation technique and in avoiding complications.
- The decision to intubate or perform a tracheotomy is predicated on the anticipated duration of mechanical ventilation, the clinical condition of the patient, and the skill of the anesthetist and surgeon, respectively.
- A number of intubating aids and devices are available for managing the difficult airway.
- Fiber optic orotracheal or nasotracheal intubation is the cornerstones in management of the difficult airway.
- The Hunsaker Mon-Jet tube is an attractive option for microlaryngeal surgery because it is laser-safe, offers superior laryngeal visualization, and is associated with few complications.
- The LMA is a supraglottic airway device that is less invasive than ET intubation, easy to insert, can be used blindly, and is associated with few complications.
- Most complications related to intubation are preventable with careful planning, selection of the appropriate technique, and attention to technical detail.
- When cricothyrotomy is necessary, it should be converted to a tracheotomy within 48 hours in order to avoid subglottic stenosis.
- Emergency bedside open tracheotomy is a life-saving measure, which must be performed very quickly because death from anoxia occurs in 5 minutes.
- Preoperative planning prior to tracheotomy decreases the likelihood of complications and includes a thorough head and neck exam, optimizing comorbidities, and proper tube selection.
- Postoperative tracheotomy care includes careful vital sign monitoring, frequent suctioning, cleaning/changing of the inner cannula, humidification, and meticulous local wound care.
- A multidisciplinary tracheotomy team produces measurable results in terms of decreased postoperative morbidity: the frequency of tube obstruction decreases, the use of speaking valves increases, and patients are decannulated more rapidly.
- Percutaneous dilatational tracheotomy can be performed safely with appropriate training, careful patient selection, and attention to technical detail, especially continuous endoscopic visualization.
- Overall, complications rates for endoscopic percutaneous dilatational tracheotomy are comparable to those for open surgical tracheotomy in the operating room.

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Voice: Anatomy, Physiology, and Clinical Evaluation

65

Lucian Sulica

The Larynx is a biologic valve located at the junction of the respiratory and the digestive tracts. Its evolutionary origins lie in the need to protect the lungs of amphibious organisms from water, and airway protection remains its most important biologic task. The development of the larynx into a phonatory organ arose because its position atop the tracheobronchial tree and its valving function gave it a unique ability to regulate expiratory airflow. Human voicing is the result of complex interactions among all of the elements of the upper aerodigestive tract, but it depends on precise and finely modulated glottic closure for sound.

The human larynx has a number of features that are specially adapted to its role as a sound source, including unique tissues capable of sustained high-speed oscillation and neuromotor specializations for fine control of vocal fold movement. As laryngology grows increasingly sophisticated and ambitious, especially with regard to restoration and even enhancement of voice quality, these details of anatomy and physiology have taken on a new clinical relevance. Increased insight into these has developed hand in hand with a better appreciation of factors leading to dysphonia. To be most effective, the otolaryngologist must understand all of these elements—anatomy, physiology, and clinical evaluation as a reflection of both—as an integrated whole that forms the foundation of any effort to treat the patient with a voice disorder.

ANATOMY

The Laryngeal Framework

The supporting framework of the larynx consists of one bone, the hyoid, and four cartilages: the cricoid, thyroid, and paired arytenoids (Fig. 65.1). The external framework is formed by the hyoid, the thyroid, and the cricoid, linked together by the thyrohyoid and cricothyroid membranes. All of these elements are suspended from the skull base and mandible by means of soft tissue attachments. The mylohyoid, the geniohyoid, the hyoglossus, and the stylohyoid muscles; the stylohyoid ligament; and the sling of the digastric insert into the superior aspect of the hyoid and exert cephalad traction. This is counterbalanced by the caudad pull of the omohyoid, sternohyoid, thyrohyoid, and sternothyroid muscles, all except the last inserting into the hyoid as well. The larynx thus moves vertically as a unit, dependent from the hyoid, its most superior element. This displacement is important not only in protecting the airway during swallowing but also in modifying the shape of the supraglottal resonating tract in voice production.

The cricoid cartilage may be considered the base of the larynx. As the only complete ring in the entire airway, it is particularly important in maintaining airway patency. However, the rigidity of this segment appears to predispose it to mucosal injury from endoluminal pressure, such as that from an endotracheal tube cuff and consequent stenosis. The thyroid cartilage rests atop the cricoid. Its inferior horns articulate with the outer surface of the cricoid posteriorly, and its V-shaped body envelops the soft tissue of the glottis. The angle at which the two halves of the thyroid cartilage join at the anterior midline is more acute in men than in women, and this accounts for its increased prominence in the male neck.

The paired arytenoids rest on the cephalic rim of the posterior cricoid and are the anchors for the mobile ends of the vocal folds, each one stretching from an anterior projection known as the vocal process to the anterior midline of the thyroid cartilage, just below the root of the epiglottis. Functionally, the arytenoid serves to translate the vectors of force of all of the individual intrinsic laryngeal muscles (but for the cricothyroid) into adductory and abductory vocal fold motion. Its eccentric shape is well suited to the task. A posterolateral projection from its body constitutes its muscular process, receiving insertions from both the lateral cricoarytenoid and the posterior

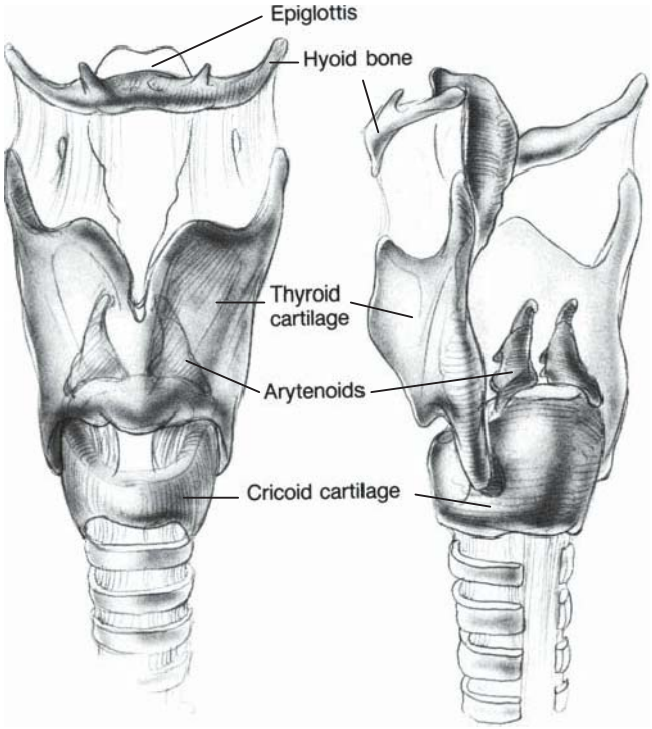


Figure 65.1 Laryngeal framework.

cricoarytenoid muscle and acting as a lever to amplify their actions. Its anterolateral face offers a broad attachment for the thyroarytenoid muscle, which functions to adduct and shorten the vocal fold. Scalloped facets face one another on the posteromedial surfaces of the arytenoids and house the attachments of the adductory interarytenoid muscle. The anteriorly projecting vocal process finally converts the action of laryngeal muscles into vocal fold motion.

The epiglottis, an elastic cartilage that has no structural role in the adult, is secured to the supporting elements of the larynx by means of the thyroepiglottic and hyoepiglottic ligaments. It is passively deflected to hood the laryngeal introitus during swallowing and serves as an accessory barrier to laryngeal entry. Finally, small cartilages of indeterminate and probably inconsequential function are found about the superior rim of the larynx. The corniculate cartilages (of Santorini) rest atop the arytenoid apices, and cuneiform cartilages (of Wrisberg) are contained within the superior rim of the aryepiglottic fold just anterolateral to the arytenoid mound. Whatever height and rigidity these may add to the aryepiglottic rim is probably not functionally significant in humans. Triticeal cartilages are sometimes found at the posterior border of the thyrohyoid membrane and are significant only because they may be mistaken for a foreign body on radiography.

In addition to bony and cartilaginous elements, two fibroblastic membranes are structurally important in the larynx (Figs. 65.2 and 65.3). The conus elasticus originates on the upper border to the cricoid cartilage and rises to the glottic aperture. Superiorly, its thickened free edges form

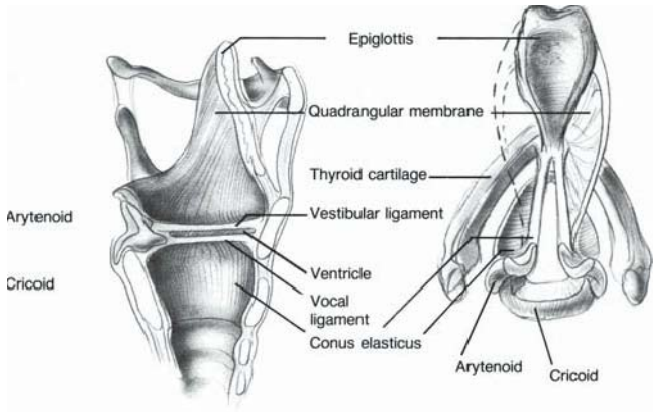


Figure 65.2 Fibroelastic membranes.

the vocal ligaments. The conus elasticus defines the convergent shape of the subglottis, which is of considerable physiologic importance in phonation. The supraglottic quadrangular membrane extends inferiorly from the aryepiglottic fold to the leading edge of the ventricular folds, similar to an inverted conus elasticus in shape, although not in functional importance. Both the conus and the quadrangular membrane, in addition to supporting the shape of the vocal fold and the ventricular fold, respectively, are barriers that may influence the spread of malignant disease.

Covered on the outside only by strap muscles and skin, the external bony and cartilaginous elements of the larynx are usually easily palpable. The most prominent points are the anterior arch of the cricoid and the superior notch of the thyroid in the anterior midline, and laterally,

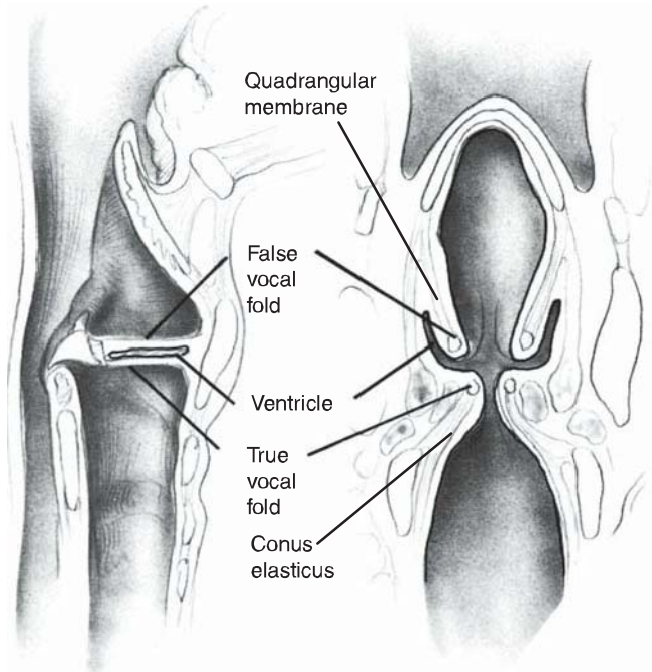


Figure 65.3 Vertical section through the larynx.

the superior horns of the thyroid and greater horns of the hyoid. From these landmarks, the location of most of the structures of the larynx can be extrapolated for purposes of manipulation, placement of surgical incisions, electromyography, injection, or other intervention. Tethered above and below by the strap muscles, the normal larynx may usually be rotated or displaced from side to side without difficulty or much discomfort. The latter motion normally produces a crepitus that is felt by the examiner's hand and the patient rather than heard and that results from the cartilaginous structures of the larynx sliding over the bony elements of the cervical spine.

The nature of the articulations of the laryngeal cartilages determines the range and trajectory of motion of the vocal folds and are thus worth some attention. Each cricothyroid joint consists of a shallow articulatory facet that seats the tuberculum of the inferior horn of the thyroid cartilage. These paired structures permit a rotatory motion between the thyroid and the cricoid cartilage, resulting in a visorlike approximation of their anterior portions on cricothyroid muscle contraction. As the anterior arch of the cricoid rises, the posterior plate drops, carrying with it the arytenoids. In consequence, the vocal folds lengthen and thin, which is a principal method of increasing phonatory pitch. The ligaments of the cricothyroid joint also seem to permit a ventrodorsal sliding motion, particularly when the articular facet on the cricoid cartilage is poorly defined or absent, as may be the case in as many as 70% of larynges (1). This sliding might account for as much as 40% of the increase of vocal fold length on cricothyroid contraction.

The cricoarytenoid joint is the principal articulation for vocal fold adduction and abduction. Arytenoid cartilage motion is sometimes presented as simple rotation around a vertical or helical axis, although it has long been known to be more complex. This oversimplification is likely the result of two factors. First, available means of clinical examination of the larynx, which renders vertical height differences between the vocal folds notoriously difficult to assess, create the impression of vocal fold motion in a single plane. Second, this misperception was of little or no practical consequence prior to relatively recent advances in laryngeal framework surgery.

Accounts also generally break down arytenoid motion into three axes, but this creates an artificially fragmented notion of the movement, which according to all evidence is smooth across its entire trajectory.

The arytenoid rests atop a convex articular surface on the cephalic edge of the cricoid. The joint surface faces more laterally at its posterior end and rotates superiorly as it extends anteriorly (2). It functions as a slipway for motion of the arytenoid body. The arytenoid body thus shifts anteromedially as it is pulled closed but posterolaterally when pulled open. The first motion depresses the vocal process, so that its adduction is not only medial but also inferior. Conversely, its abduction is lateral and superior, so that the vocal fold does not move into the body of the thyroarytenoid muscle but upward toward the ventricle. Vertical vocal process displacements, measured in cadavers, range up to 2.4 mm. The cricoarytenoid joint facets and consequently the paths of motion of the vocal process are often not symmetric, which should warn us against ascribing pathologic significance to small asymmetries of vocal fold motion. Wang (2) has noted correctly that symmetry is of functional importance only when the vocal folds are in adduction.

Understanding the three-dimensional nature of vocal fold motion is important to clinical evaluation and rehabilitation of glottic insufficiency because a denervated vocal fold may rest at any point along its normal sweep (3,4). (The classic terms for the position of an immobile vocal fold—median, paramedian, cadaveric, etc.—are purely descriptive; they have no physiologic or topognostic significance, contrary to time-honored belief.) In fact, with muscle traction diminished or even absent, it may even lie outside of this trajectory, as in the case of a so-called prolapsed arytenoid, when the vocal process may lie below the inferiormost extent of normal motion. Laryngoscopy may not readily reveal the height difference, and simple medialization, like that achieved by a thyroplasty implant alone, may not approximate the vocal folds at the same level.

The cricoarytenoid joint is remarkably stable for a structure that permits so many degrees of freedom in arytenoid motion. Dissection has revealed a layered network of articulatory ligaments that provide substantial stability in most directions. Multiple muscular and ligamentous attachments must be severed to produce subluxation (2). In cadaver experiments, even without active muscular support, the joint is extremely resistant to dislocation, both by endotracheal tube and direct manual manipulation (5,6). Available evidence suggests that cricoarytenoid joint dislocation is a very rare clinical condition.

Muscles and Nerves

The intrinsic muscles of the larynx—those that originate and insert on the laryngeal cartilages—are responsible for vocal fold motion (Fig. 65.4). The sole abductor of the vocal fold is the posterior cricoarytenoid muscle, which reaches from the posterior surface of the cricoid superolaterally to the muscular process of the arytenoid. Its principal antagonist is the thyroarytenoid muscle, which stretches from the inner surface of the thyroid to the arytenoid body. Together with the lateral cricoarytenoid muscle, it forms the principal adductory muscle complex of the vocal fold. It is aided in adduction by the interarytenoid, which is the only nonpaired laryngeal muscle. The thyroarytenoid also shortens the vocal folds by means of anterior traction on the arytenoid. The cricothyroid muscle, stretching from the external anterior surface of the cricoid to attach broadly on the caudal rim of the thyroid, functions as an antagonist to the thyroarytenoid in this respect. It elongates the vocal folds by effecting torsion at the cricothyroid joint, as

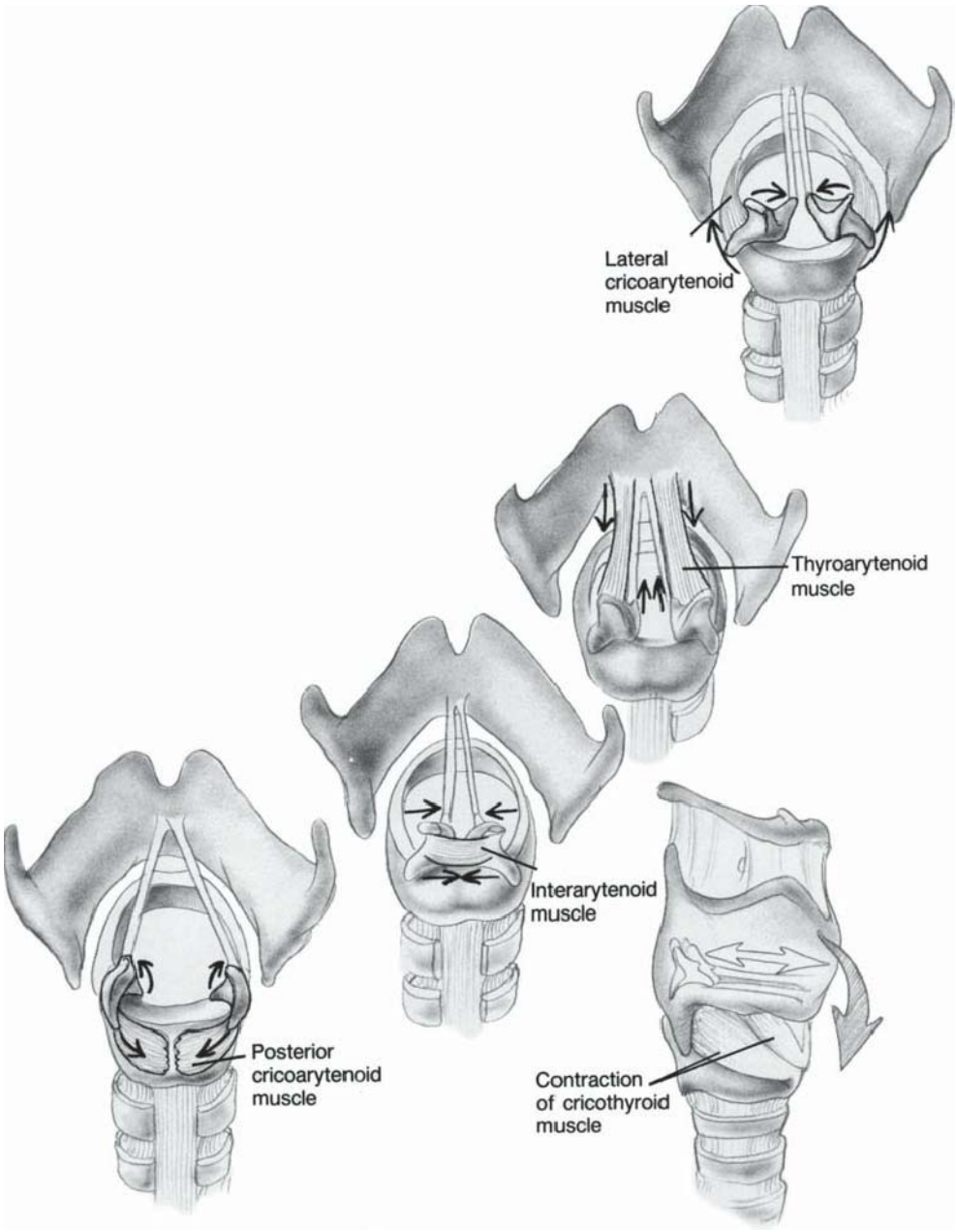


Figure 65.4 Intrinsic laryngeal muscles.

we have already seen. Minor aryepiglottic muscles, as well as a cephalad projection of the thyroarytenoid, serve to constrict the ventricular folds and supraglottic structures, which are accessory means of glottic valving that usually come into play during voicing only under pathologic circumstances.

There is considerable evidence that the thyroarytenoid–lateral cricoarytenoid muscle complex, the posterior cricoarytenoid muscles, and the cricothyroid muscles are divided into functionally separate compartments distinguished by fascial barriers and corresponding arborization patterns of laryngeal nerves (7–10). This impression is reinforced by differences in the concentration of muscle fiber types and specialized proprioceptors among these compartments (11). For instance, the medial division of the thyroarytenoid, known as the vocalis, contains fatigue-resistant slow-twitch fibers (12). These imply that it is especially suited to activity that requires fine-tuned tonic contraction, such as phonation. In contrast, the lateral compartment has a high concentration of fast-twitch fibers, better suited to rapid movement, such as that demanded by reflexive glottic closure for airway protection. A similar difference exists between the horizontal and the vertical compartments of the posterior cricoarytenoid. No muscle fiber distinctions seem to exist among the two compartments of the cricothyroid, but each exerts a different vector of force on the cricothyroid joint by virtue of differences in fiber origin, insertion, and direction (10,13).

Each hemilarynx receives its innervation from ipsilateral branches of the vagus. The superior laryngeal nerve arises from the bottom half of the nodose ganglion, about 36 mm below the jugular foramen (14). It travels medial to both the internal and external carotid arteries and splits into two branches after some 15 to 20 mm. The internal branch pierces the thyrohyoid membrane in company with the superior thyroid artery and ramifies to the mucosa of the ipsilateral laryngeal mucosa by means of a variable number of branches. The external branch runs lateral to the inferior constrictor muscle until it curves anteriorly at approximately the level of the inferior edge of the thyroid lamina to reach the cricothyroid muscle. Its path in relation to the apex of the thyroid lobe and its blood supply is of obvious clinical significance. Most nerves cross the superior thyroid artery well away from the superior pole of the thyroid. However, up to 30% cross that vessel within 1 cm of the gland, and up to 20% actually pass under the gland itself, representing the situation of considerable risk during thyroidectomy (15,16).

On the right side, the recurrent nerve arises from the main trunk of the vagus as it passes anterior to the subclavian artery and loops underneath that structure to travel toward the larynx. For purposes of investigation of right-sided vocal fold paralysis, it is important to understand that the course of the nerve can thus extend into the superior mediastinum; diagnostic imaging studies should not be restricted strictly to the neck. The left-sided nerve follows a similar path but loops around the aorta instead of the subclavian artery, as the result of differences in embryologic vascular development from one side to the other (17). These pathways in large part determine the vulnerability of each nerve to injury, be it from surgical manipulation, tumor compression, or other disease.

Classic descriptions hold that the recurrent nerve supplies motor input to all of the intrinsic muscles but for the cricothyroid, which receives its innervation from the external branch of the superior laryngeal nerve. Sensory information from the level of the glottis and above travels to the central nervous system via the internal branch of the superior laryngeal nerve and from below the glottis via the recurrent laryngeal nerve. This view, although essentially correct, may not capture the full complexity of the neuromuscular system of the larynx. Historically, the ansa of Galen, an extension of a branch of the internal branch of the superior laryngeal nerve running underneath the mucosa of the medial wall of the piriform sinus, has been regarded as the only anastomosis between the superior and recurrent laryngeal nerves. By means of neurospecific stains, inconsistent but relatively common connections have been found between the external branch of the superior nerve and the recurrent nerve within the thyroarytenoid muscle (7,18,19). Some investigators have asserted that the bilaterally innervated interarytenoid muscle contains anastomosis between the contralateral nerve populations, which may include contributions from the internal branch of the superior nerve (20,21).

The precise physiologic significance of such insights into nerve and muscle anatomy remains to be determined, but traditional concepts of laryngeal anatomy are being revised by an increased appreciation for fine muscular specialization and for the possibility of a more complex scheme of innervation, featuring more anastomotic pathways than previously suspected, interdigitating nerve branches, and terminal plexuses. This evolving picture may help to explain not only the robust tendency for reinnervation in the human larynx but also why such innervation is so often dysfunctional and why dynamic surgical reinnervation remains such a challenging clinical problem.

The Membranous Vocal Fold

The paired shelves of tissue formed by the thyroarytenoid muscles and their soft tissue cover, which extend from the vocal process of the arytenoids to the anterior midline of the thyroid cartilage, are known as the vocal folds. These form the principal valve for glottic closure and, of special interest to us, for glottic resistance necessary for phonation. This latter function is dependent on the unique and delicate microarchitecture of the leading edge of the vocal fold (Fig. 65.5).

The vocal fold is covered by a thin layer of stratified squamous epithelium, in contrast to the respiratory epithelium of other surfaces of the larynx and trachea. Below this lies the lamina propria, a pliable layer of fibrous proteins, including elastin, collagen, and other extracellular elements, which together account for its unique biomechanical properties. A sparse cell population composed principally of fibroblasts, thought to be responsible for the production and regulation of the components of the lamina propria, is also present (22,23). The superficial lamina propria lies immediately underneath the basement

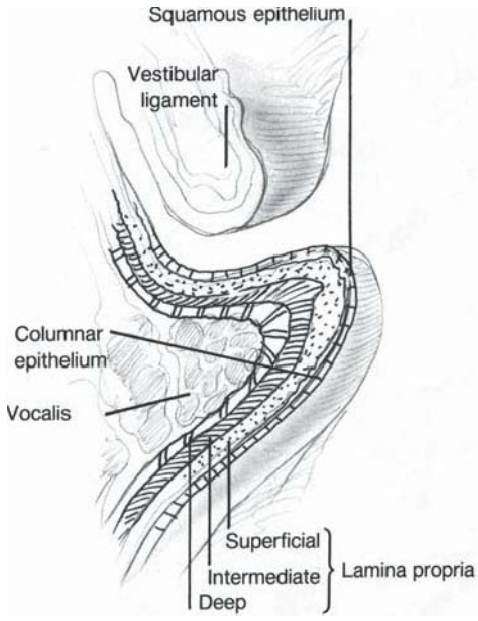


Figure 65.5 The vocal fold.

membrane of the epithelium and contains the lowest concentration of fibrous proteins. The superficial lamina propria has often been described, incorrectly, as a potential space. In reality, it has its own thickness and mass—about 0.5 mm at the middle of the adult vocal fold (24)—and is a distinct anatomic structure, not at all like the true potential space between the pulmonary pleura and the chest wall. It is true that it offers little resistance to injection of fluid, for instance, but this is a function of its loose structure rather than any anatomic separation. The time-honored eponym of "Reinke's space" is thus misleading and should probably be modified to "Reinke's layer" or not used at all. That the superficial lamina propria has depth and substance is a key point to grasp for anyone who would operate on lesions of the vocal fold.

Beneath the superficial layer of the lamina propria lie the intermediate and deep layers. These are not crisply distinct from one another; instead they represent a gradient along which elastin fiber concentration decreases and collagen fiber concentration increases as it sinks deeper. Stiffness increases in proportion to collagen fiber concentration. Taken together, these form the vocal ligament and are contiguous with the walls of the conus elasticus rising from below. Combined with the superficial lamina propria and the epithelium, these comprise the mucosa of the vocal fold (25). Deep to this mucosa lies the thyroarytenoid muscle, which likely consists of functionally distinct superficial and deep compartments, as we have seen.

For reasons that will become apparent in the discussion of phonatory physiology, the layers of the vocal fold structure have been divided into a "cover" and "body," each with fundamentally different physical properties that come into play during phonation. The cover of the vocal fold includes the epithelium and the superficial lamina propria. The ligament represents a transition zone, variably assigned by authors to either the body or the cover, and the body includes the thyroarytenoid muscle (25).

The anatomy of glottic closure is of considerable physiologic significance. Examined in cross-section, vocal folds do not taper to a sharp apex medially; they have a flattened, fairly blunt contour. As a result, the area of vocal fold contact in adduction has a vertical dimension (under most phonatory conditions), and the mucosa of one vocal fold approximates the other across a larger area than in a single plane. This is not entirely intuitive because laryngoscopy under continuous light (as opposed to stroboscopic light) tends to create the impression that vocal fold closure is a two-dimensional phenomenon, just as it distorts adduction and abduction in the same way. The contour of the vocal fold can be modified by the action of the muscles of the larynx, with consequences to the sound produced.

Laryngeal Changes with Age

At birth, the larynx rests considerably higher in the pharynx than it does in the adult (Fig. 65.6). In this position, the superior portion of the epiglottis overlaps with the

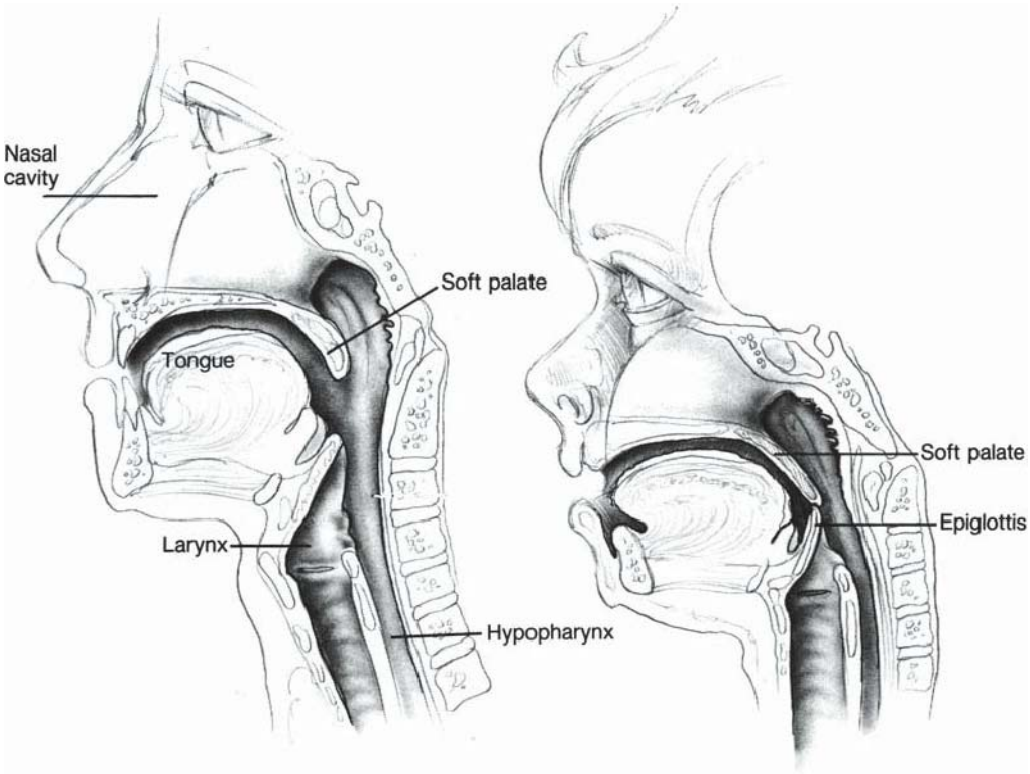


Figure 65.6 Laryngeal position in the adult and in the child.

caudal edge of the soft palate, effectively separating the respiratory from the alimentary tract. This is probably a necessary adaptation to breastfeeding, during which the infant must be able to breathe and suckle simultaneously. At the same time that it increases swallowing safety, this laryngeal position renders the newborn an obligate nosebreather until maturational laryngeal descent begins. The lower position of the larynx in the adult offers the capability of increased range and complexity of phonation by engaging the mouth and tongue in modification of sound, at the cost of an increased risk of choking and aspiration. That evolution has obviously favored such an arrangement hints at the biologic advantages of complex phonation.

The layered structure of the vocal fold is not present at birth; it develops throughout childhood from a homogenous and hypercellular mucosa (25,26). Lamina propria layering appears as early as 2 months, but the process is not complete until approximately 13 years of age, when the vocal fold assumes an essentially adult histologic configuration. This approximately coincides with the beginning of laryngeal framework growth at puberty. This growth is especially pronounced in males, in whom it is accompanied by an increase in vocal fold length and thickness, which largely accounts for characteristics of the adult male voice (27).

Assessing laryngeal changes purely as a result of aging is complicated by the difficulty in separating them from comorbidities such as neurologic disease and pulmonary parenchymal disease. Evidence suggests that much age-related change is not neurologic or even muscular in nature—it has to do with alterations in the lamina propria. In general, fibroblasts that produce superficial lamina propria elements become less metabolically active (28–30). In consequence, apparently, the lamina propria thins, principally as a result of a loss of elastin fibers (31). Its stiffness increases in large part because of the relative increase in the amount of collagen (32). Such changes are more typical in men. In women, edema of the lamina propria is a more salient feature for unclear reasons (29). In addition to gender differences, significant variation from individual to individual is present in the aging larynx (33). Much remains to be discovered in this domain, but it seems clear from available evidence that the bowing that has been accepted as the laryngoscopic correlate of laryngeal aging is not just a loss of muscular bulk, easily remediable by medialization, but also a change in the vibratory characteristics of the vocal fold cover.

PHYSIOLOGY

Airway Protection

The most important biologic function of the larynx is airway protection, achieved most simply by glottic closure. Comparative anatomy reveals that the crudest laryngeal structures are simple sphincters to protect the lungs from the entry of water (22) and suggests that the evolutionary origin of the larynx thus lies in the emergence of amphibious life. The human larynx is, of course, a much more sophisticated structure, but the redundancy of its mechanisms for closure—vocal folds, ventricular folds, and epiglottis—and apparent specializations in the lateral compartment of the thyroarytenoid muscle hint at the continued primary importance of this action. It is also no surprise to find that laryngeal sensory receptors are a varied population that responds to a wide number of different kinds of stimuli, both mechanical and chemical. There is evidence for specific sensitivity to pH, chloride ions, and ion salts, with stimulation resulting from detected deviations from physiologic norms (23). These trigger laryngeal closure via a reflex arc made up of the superior laryngeal nerve and the recurrent nerve. The automaticity of laryngeal closure has been adapted by investigators as a clinical test of the integrity of laryngeal sensation (24).

The phenomenon of laryngospasm likely represents an exaggeration or perpetuation of reflex laryngeal closure as a result of factors that are not yet completely described. Laryngeal receptors may also serve as triggers for extralaryngeal responses such as apnea, bronchoconstriction, bradycardia, and changes in peripheral vascular resistance, all of which may be mediated by generalization of the efferent response to the entire vagus, including sympathetics (23). There has been speculation that such a response, unchecked by an immature neural system and possibly in reaction to laryngopharyngeal reflux, may underlie sudden infant death syndrome (34,35).

Cough and throat clearing represent the addition and integration of a respiratory component into the basic mechanism for airway protection and may be voluntary. Glottic closure following inspiration permits the individual to raise subglottic air pressure and use high-pressure forceful exhalation to clear an irritant or obstruction.

Respiration

The larynx participates actively in respiration as a regulator of airway dimension. Respiratory activity in the larynx is focused in the posterior cricoarytenoid muscles (principally the horizontal belly), the sole abductors of the vocal folds, which generally activate to counteract and even slightly anticipate the negative intraluminal pressure generated by diaphragm contraction (inspiration) (36,37). The posterior cricoarytenoid muscles are not merely entrained with respiratory muscles to mirror phasic activity during the respiratory cycle, however. They appear to have the ability to respond independently to receptors monitoring air pressure, temperature, humidity, and CO_2 concentration (37,38).

There is disagreement on whether vocal fold adduction during expiration represents active adduction or merely passive relaxation of the posterior cricoarytenoid. It seems

clear that in some situations, adduction is indeed active and that the size of the glottic aperture is a major determinant of respiratory rate, by means of control of the duration of exhalation (39).

The Valsalva Maneuver

Relatively high-pressure glottic closure is needed for effective thoracic fixation in the Valsalva maneuver. A wide variety of effortful physical activity depends on or is enhanced by the integrity of the thoracic fixation maneuver, including lifting, pushing, rising from a sitting position, and climbing. This range of activities only grows with impairment of the physical condition of the individual. Clinically, compromise of the Valsalva maneuver may be one of the most misunderstood symptoms in conditions of glottic insufficiency such as vocal fold paralysis. It is often mistaken for shortness of breath related to obstruction and may thus steer the physician directly away from measures necessary to restore glottic competence.

Voice

In voicing, the larynx functions only as an integrated part of the larger respiratory system. The larynx rests atop the tracheobronchial tree and lungs, which are at the same time its evolutionary reason for being and its principal source of energy for phonation, air. Distal to the larynx are the resonating and articulatory structures of the pharyngeal, oral, and nasal cavities, which, although not strictly essential for phonation, modify laryngeal output to such a degree that it would not be recognizable to the listener were they not there. Phonation represents a complex interaction among all of these elements, the details of which are well beyond what can be covered in this text. Voicing, as discussed below, focuses on laryngeal function during sustained phonation in modal register as representative of the most typical clinical situation. Numerous important aspects are therefore not covered, and the interested reader is strongly urged to explore the topic further in works by Titze (27) and others (40,41).

Phonation results from a cyclic interaction between exhaled air and the unique biophysical properties of the vocal folds, as explained originally by the *myoelastic-aerodynamic theory of phonation* (42). The glottal cycle begins with the accumulation of air pressure against the convergent walls of the subglottis, the result of exhalation of air against closed or, ideally, nearly closed vocal folds. At a certain pressure threshold, the air column begins to push the bottom of the vocal folds apart. As discussed earlier, vocal fold closure has a vertical dimension, and the rising air column parts the vocal folds from inferior to superior in a progressive way (Fig. 65.7). As air passes through the constriction formed by the vocal folds, it accelerates until it reaches the widened supraglottic lumen, where it slows again. Total energy must remain constant, however, so this

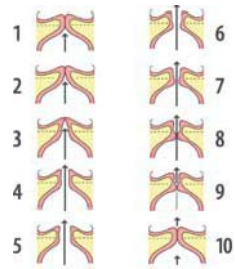


Figure 65.7 The phonatory glottic cycle. Courtesy of Voiceproblem.com.

increased velocity results in a drop in pressure in the area of constriction, according to the relationships set forth in the Bernoulli equation. This lower pressure (relative to the pressure immediately above the glottis) across the area of constriction is an important factor in glottic closure.

The glottal air column compresses the tissues of the vocal folds laterally as it passes through. These have an inherent elasticity, and their progressive deformation results in an equally progressive increase in the tissue forces favoring return to the midline. These forces combine with the decreased intraluminal pressure to begin the closure of the lower glottal edge, even as the upper edge is opened by the air column. This vertical phase difference is important in perpetuating the glottal cycle and corresponds to the mucosal wave seen on stroboscopic or high-speed photographic examination. Once the glottis is restored to its original configuration, the cycle repeats. The characteristics of the glottal cycle depend on inherent tissue properties, including the elasticity and viscosity of the vocal fold cover and the activity of the intrinsic laryngeal muscles, and the energy imparted by exhaled air.

The vocal fold oscillation of the glottic cycle changes an air column of constant pressure into one in which pressure varies regularly, and which is the physical correlate of what we perceive as sound. Like any periodic phenomenon, sound can be described in terms of the physical properties of its pressure waveform—amplitude, frequency, wave morphology, and periodicity. Each of these has a principal perceptual correlate—loudness, pitch, and voice quality, respectively. These may be altered by changes in either the aerodynamic contribution to the glottic cycle (air pressure) or the myoelastic contribution (tissue anatomy and stiffness), or, most commonly, both.

The amplitude of the pressure wave is perceived as loudness or sound intensity. The simplest means of increasing loudness is to raise the subglottic air pressure by using forced or active exhalation. However, tissue changes must occur to compensate for the raised pressure, or it will compromise the glottal cycle by overwhelming the elasticity of the vocal fold. This phenomenon is commonly seen in an individual with a denervated vocal fold. Because it is impossible to increase the stiffness of the paralyzed fold, the elevated pressure simply pushes it laterally, and a breathy break in the voice takes the place of the intended

shout. Under normal circumstances, increased tension of the vocal fold by means of appropriate muscle contraction (principally the thyroarytenoid but also the cricothyroid) increases the glottal resistance, restoring the balance of forces needed to maintain the glottal cycle.

The fundamental frequency, the rate of oscillation of the vocal folds, is mainly responsible for perceived pitch. This rate is a function of vocal fold tension on the one hand and mass on the other. The mechanism for controlling pitch involves an interaction between the cricoarytenoid, the thyroarytenoid muscle, and air pressure. Contraction of the cricothyroid muscle lengthens the vocal folds, increasing tension, decreasing mass per unit length, and thereby increasing frequency. Conversely, contraction of the thyroarytenoid shortens the vocal folds, decreasing tension, increasing mass per unit length, and thereby decreasing frequency. This relation is not true at all vocal intensities; however, because in louder phonation at lower frequencies, not only the mucosa but also the vocalis muscle is involved in vibration. As a result, its contraction increases tension and thus frequency.

It is principally in pitch control that the body and the cover of the vocal fold mentioned earlier in the discussion of anatomy play an important role. The body is a muscle with contractile properties that result in relatively large changes in mass and stiffness. The cover is a pliable, viscous, nonmuscular structure, the stiffness of which depends principally on its extracellular elements and extrinsic factors and varies a good deal less than that of the body. These two regions are decoupled—that is, they act as essentially separate oscillatory masses during phonation. Together, they act to preserve glottal elasticity, and thus the integrity of the glottal cycle, across a wider variety of vocal fold lengths and tensions than would otherwise be possible.

In reality, pitch and loudness are not separate phenomena; they are linked by aerodynamic and myoelastic phenomena. Greater air pressures tend to increase stretch of the vocal fold, which decreases mass and increases tension, resulting in higher frequency. Experimental work has shown that frequency rises together with sound intensity unless deliberate compensation takes place.

In general terms, hoarseness is the perceptual correlate of perturbations in the regularity of the glottal cycle and breathiness resulting from glottic insufficiency. A mental review of the clinical spectrum of voice disorders reveals the variety of ways in which this may occur. Edema, scars, and age-related changes alter the stiffness of the vocal fold cover, and if substantial enough, edema may alter mass as well. Mass lesions interfere with glottic closure and affect the elasticity and pliability of the vocal fold cover. Denervation impairs the ability to alter mass and stiffness of the vocal fold body, even when there is glottic closure at adduction. If the vocal folds cannot approximate, phonatory threshold pressure increases, sometimes beyond the capacity of the individual to sustain.

EVALUATION

History

Voice disorders have long resisted straightforward objective clinical characterization, despite the array of instrumental measures of acoustics and aerodynamics available. In most cases, important personal and subjective considerations influence not only the voice complaint but also the patient's treatment expectations. In consequence, medical evaluation of voice disorders requires attention to several factors not encompassed by the usual history solicited from patients with head and neck complaints. These include careful characterization of the complaint, both with respect to its nature and its severity, and an assessment of the patient's voice demands and habits. This approach emphasizes the functional limitations caused by the patient's voice problems.

Through the history, the otolaryngologist must first understand for what aspects of impaired voice production the patient seeks help. Patient perceptions of voice problems tend to be very individual and directly connected to the amount and type of vocal demands: for example, a school teacher's notion of "hoarseness" is likely to differ substantially from a singer's or a construction foreman's. "Hoarseness" is used broadly to describe a variety of phenomena and can refer to altered voice quality, phonatory fatigue, insufficient loudness, restricted pitch range, increased phonatory effort, breathlessness, impaired singing quality, or other features. It is not always the feature most obvious to the clinician that the patient finds troublesome.

The perception of the severity of these complaints is also subject to personal interpretation. Individuals have expectations and requirements of their voices that are not always a direct reflection of their occupational demands or other easily assessed factor and are often different from what the otolaryngologist might assume. Many people with dysphonia never seek medical attention, unaware that any problem exists. Others simply want to be reassured that their dysphonia is not caused by a malignancy. Still others complain of phonatory disturbances that are not apparent to the casual listener, and can even consider these crippling to professional or social activity. In part to help characterize the severity of an individual's voice problem, several standardized and statistically validated questionnaires have been developed. Among them, the Voice Handicap Index (VHI) (43) and the Voice Related Quality of Life (44) are the most widely used. The VHI-10 (45) is an abridgment of the former that makes it even easier to use without loss of statistical validity. Such inventories are useful to understand patient motivation and make appropriate treatment recommendations. Applied both before and after treatment, these can also form an important means of assessing outcome, which allows comparison among interventions, techniques, and studies.

We have seen that phonation depends on the integrity of the glottal cycle. Under typical circumstances, the glottal cycle repeats at approximately 100 cycles per second in men and 220 cycles per second in women. The physical stress on the tissues of the vocal fold cover is only beginning to be characterized by investigators, but it is considerable. This stress, known as *phonotrauma*, has the potential to cause changes to the oscillatory properties of the vocal folds and even to cause local tissue injury. When an individual uses the voice extensively or in adverse circumstances, phonotrauma and the potential for damage to the vocal apparatus grows. Because phonotrauma may be the single most important factor underlying most benign vocal fold lesions, assessing the particulars of voice use is an essential task of the voice history.

Independent of medical factors, phonotrauma is related to amount and intensity of voice use (which in turn may be the product of vocal demand, which usually results from an individual's professional requirements) and inappropriate or excessive voicing, usually resulting from an inherently talkative and extroverted personality. Teachers, for example, are notoriously overrepresented among voice patients, largely as a result of the relentless vocal demand of their work rather than any intrinsic behavioral factors. Distinguishing between demand and personal inclination is obviously important to making appropriate treatment recommendations. Otolaryngologists traditionally receive little or no training in the behavioral aspects of phonation. Probably as a result, "vocal abuse," like "hoarseness," is a term that has been used broadly and somewhat indiscriminately in otolaryngology as a synonym for phonotrauma. However, it is not always correct, and almost never helpful, simply to blame the patient for his or her vocal predicament.

A speech-language pathologist who is skilled and experienced in the management of voice problems may add considerable depth to the voice evaluation, especially with respect to its behavioral aspects. The speech-language pathologist is able to focus on factors of the history and individual voicing techniques that contribute to phonotrauma and may also experiment with therapeutic techniques during the initial visit. Not only can this help to determine how best to address behavioral factors, but it can also help to distinguish malingering or psychogenic disorders from organic ones and may facilitate the laryngeal examination itself by addressing compensatory behaviors such as ventricular fold hyperfunction in cases of glottic insufficiency.

Examination

The voice examination too has specialized elements, not least among them the use of the ear as a diagnostic instrument. It begins with a qualitative assessment of the voice prior to any attempt at laryngoscopy. Gross abnormalities will be readily apparent as the patient describes the complaint; more subtle ones require specific maneuvers and phonatory tasks to search for breakdowns of phonatory physiology. Low-intensity, high-pitched phonation, which results in voice breaks, irregularities, and delays in voice onset, suggests a small mucosal lesion. Reduced maximum phonation time (normally greater than 20 seconds) and limitations in volume point to poor glottic closure. It may require a sustained vowel to clearly reveal a tremor or other instability. The clinician should develop a diagnostic impression based on the contents of the history and the voice assessment prior to any visualization of the larynx. Discrepancy between the preliminary diagnostic and laryngoscopic findings should serve as a warning that the evaluation is not complete. A flexible fiberoptic examination that reveals no mucosal pathology when voice qualities suggest that it must be present is not a rare clinical situation. Rather than settling on a vague and nonspecific diagnosis—"chronic laryngitis" and "reflux" are the current favorites—the physician should pursue more specialized diagnostic techniques, including rigid or flexible distal-chip endoscopy and stroboscopy, or consider referral to a laryngologist if these are not available.

The well-known Grade, Roughness, Breathiness, Asthenia, and Strain scale (46) and, more recently, the Consensus Auditory-Perceptual Evaluation of Voice (47) represent efforts to systematize qualitative voice assessment and standardize the terminology used. These serve a principally descriptive purpose rather than a diagnostic one. Although not essential for routine clinical practice, they are useful to focus the assessment and for inquiry into clinical outcomes and efficacy.

The larynx may be directly examined in a number of ways. The venerable laryngeal mirror has the advantage of crisp optical resolution and color fidelity, but in practice, these do not offset the inability to record the examination and the occasional technical difficulty of the examination. The flexible fiberoptic laryngoscope is readily available in nearly every otolaryngologist's office and offers the surest means of visualizing the vocal folds. Only the very rare patient will find the examination intolerable. Flexible fiberoptic laryngoscopy also disturbs normal laryngeal dynamics least, permitting laryngeal visualization during connected speech, a feature that makes the flexible laryngoscope the instrument of choice for the evaluation of most neurologic disorders (see Chapter 70). The typical findings of spasmodic dysphonia, tremor, and other diseases may change or disappear when the tongue is pulled forward for peroral laryngoscopy. Similarly, glottic dynamics in cases of vocal fold paralysis or paresis may be more reliably evaluated without tongue traction. However, because of dependence of optic fibers, the flexible fiberoptic scope is optically inferior to every other means of examining the larynx, including the mirror, and will not reliably reveal small mucosal lesions. New designs that convert the optical signal to digital information at the tip of the endoscope (so-called "chip tip" devices) do away with

fibers and improve the picture. The rigid endoscope, which transmits the image to the eyepiece via a glass rod, offers high-resolution optical qualities at the price of increased technical skill, similar to that required to handle a laryngeal mirror. As a result, it is a superior means of evaluating mass lesions and other anatomic, as opposed to dynamic, abnormalities.

The limited depth perception offered by all commonly used techniques of office examination tends to obscure the three-dimensional nature of laryngeal function, as we have seen with gross vocal fold motion and glottic closure. Efforts to extrapolate this from careful examination have not always proved reliable and may lead to significant diagnostic confusion. The endoscopist should always keep this limitation in mind.

Stroboscopy uses a pulsed light source to create an illusion of continuous, slow-motion mucosal oscillation. The light pulses at a frequency just slightly different from that of the glottal cycle, generating a series of still images of the vocal fold at slightly different points across several glottal cycles, which are fused into an apparently fluid and continuous sequence by the examiner's eye. The stroboscopic effect depends on appropriate timing of the light pulses in relation to phonatory frequency and so is most reliable when vocal fold oscillation is periodic. Yet we have seen that aperiodicity is an important component of dysphonia. If severe, it tends to compromise stroboscopic light timing and thus the quality of the examination. Despite this limitation, stroboscopy is the only practical way of imaging mucosal oscillation routinely in the clinic and the optimal—occasionally the only—way of identifying abnormalities in mucosal pliability. It is likely the single strongest diagnostic instrument in most cases of dysphonia, especially for those disorders related to disturbances of mucosal vibration (e.g., scar and sulcus).

Stroboscopy is often considered synonymous with the rigid endoscope and video recording. Indeed, by virtue of the excellence of its optics, a rigid endoscope is an ideal vehicle for the stroboscopic examination. Although it is possible to perform stroboscopy via the flexible laryngoscope, the quality of the image will usually be inferior to that obtained with a rigid peroral endoscope. In all office laryngoscopy, but especially in stroboscopy, video recording is important for documentation and to enhance the diagnostic power of the examination. Review, both at normal and reduced speeds, can reveal aspects of pathology not seen in the initial examination, even if it is meticulous and unhurried. Video recording is essential for comparison across time and accurate and revealing assessment of the results of clinical interventions.

This text has reviewed only the most common among the tools available to assess laryngeal functions. Many more are available to complement the core evaluation, consisting of the history and perceptual and laryngoscopic assessment. Among these are additional means of vocal fold imaging such as high-speed photography; videokymography; and, more recently, three-dimensional computed tomography. Electroglottography and photoglottography allow assessment of glottic closure and opening, respectively, and a host of acoustic and aerodynamic measures provides further insight into phonatory dynamics and efficiency. The reader searching for more breadth and depth regarding instrumental laryngeal evaluation is referred to several standard works (48,49).

CONCLUSION

An understanding of anatomic features and physiologic processes involved in phonation is inextricably linked with the practice of laryngology. Most clinical advances in the last few decades have been based on corresponding advances in these areas, and this same body of knowledge now forms the basis of an effective clinical approach to voice disorders. Tools for routine evaluation of the anatomic and physiologic elements most important to voice production are commonly available, and the otolaryngologist must use these to reveal the problem and plan an appropriate clinical intervention. Modern laryngology, and particularly laryngeal surgery, has become a functional endeavor. The aim of treatment is no longer simply to excise pathology—it is to restore the normal physiology of phonation. For this to succeed, it is necessary that the clinician understand the laryngeal basic sciences thoroughly and strive to transform each new development and insight in those fields into an ever-higher standard of voice rehabilitation.

HIGHLIGHTS

- The laryngeal framework consists of four principal cartilages. The thyroid envelops the soft tissues of the larynx. The cricoid is the base of the larynx and is an important structural airway element. The arytenoids serve to translate the vectors of force of all intrinsic laryngeal muscles except the cricothyroid into vocal fold motion.
- The thyroarytenoid, lateral cricoarytenoid, and interarytenoid muscles are the principle adductors of the vocal folds. The posterior cricoarytenoid muscles are the sole abductors. The cricothyroid muscles elongate the vocal folds by effecting torsion at the cricothyroid joint.
- The arytenoid body shifts anteromedially as it is pulled closed and posterolaterally on being pulled open. Vocal fold adduction and abduction is thus a three-dimensional motion: adduction is medial and inferior, and abduction is lateral and superior.
- The recurrent laryngeal nerves are the principal sources of motor innervation to all of the intrinsic

laryngeal muscles except the cricothyroid and sensory innervation below the glottis. The superior laryngeal nerves are the principal sources of motor innervation to the cricothyroid muscle and sensory innervation above the glottis.

- The medial margin of the vocal fold consists of epithelium covering a layered matrix of fibrous proteins, known as the lamina propria, with unique biophysical properties essential for high-speed vocal fold oscillation necessary for phonation.
- The superficial lamina propria of the vocal fold is a distinct anatomic layer, rather than a potential space as the name "Reinke's space" implies. It is usually intimately related to mucosal pathology of the vocal fold, and its disruption leads to postoperative dysphonia.
- The larynx descends during human development so that the airway and swallowing passage are no longer separate. The capability for complex phonation thus comes at the price of an increased potential for choking and aspiration.
- The larynx functions as the sound source for voicing. Oscillation of vocal fold structures induced by exhaled air creates cyclic changes in air pressure perceived as sound.
- Loudness or sound intensity is the main perceptual correlate of the amplitude of the air pressure wave, generated principally by changes in exhaled air pressure. Pitch is the main perceptual correlate of the frequency of the pressure wave, generated principally by changes in mass and tension of the vocal folds.
- Evaluation of voice disorders consists of the history, including a characterization of individual vocal demand and behavioral elements contributing to the voice disorder, the perceptual assessment of the voice, and laryngoscopy.
- Stroboscopy is the only technique that allows routine clinical imaging of vocal fold oscillation, and as a result it is likely the single strongest diagnostic instrument in most cases of dysphonia.
- Dysphonia results from disruptions of phonatory physiology. To be most effective, treatment of dysphonia must focus on the restoration of normal physiology rather than excision of a specific lesion or alteration of laryngeal anatomy.

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66 Laryngopharyngeal Reflux

Joel H. Blumin *Nikki Johnston*

Reflux of gastric contents into the esophagus, gastroesophageal reflux (GER), is a normal physiologic phenomenon that occurs in most people, particularly after meals. Brief and infrequent exposure of the esophagus to gastric contents does not result in injury and disease, implying that there are intrinsic defense mechanisms that act to maintain mucosal integrity. In fact, based upon pH monitoring studies, up to 50 reflux episodes a day (below pH 4) are considered normal (1). It is thought that esophageal symptoms and complications arise when reflux is prolonged and/or there is a breakdown in the defense mechanisms. This is termed gastroesophageal reflux disease (GERD). GERD is accepted as possibly the most common chronic disease of adults in the United States affecting more than 30% of Western society (2).

When gastric reflux travels more proximal into the laryngopharynx, it is termed laryngopharyngeal reflux (LPR) (3). Other terms, such as gastropharyngeal reflux and esophagopharyngeal reflux (EPR), have been used synonymously. These are all considered as part of extraesophageal reflux (EER), reflux involving structures other than, or in addition to, the esophagus. LPR contributes to several otolaryngologic symptoms, inflammatory disorders, and perhaps also neoplastic diseases of the laryngopharynx (3–9) and appears to be as common in children and infants as adults (10). It is estimated that 10% of patients visiting otolaryngology clinic have reflux-attributed disease, and up to 55% of patients with hoarseness have reflux into their laryngopharynx (3,7). LPR is actually one of the most common factors associated with inflammation in the upper airways and is a common source of chronic laryngitis (3,4). Compared to the esophagus, where up to 50 reflux episodes (below pH 4) a day are considered normal or physiologic, the laryngopharynx appears to be more sensitive to injury by gastric refluxate. It has been shown experimentally that three reflux episodes per week or less into the laryngopharynx results in severe damage of the laryngeal epithelium (3). Recently published normative data utilizing impedance monitoring statistically demonstrated that one or more reflux events per 24-hour period are significant for diagnosis of LPR and that LPR events are indeed rare in an asymptomatic population (11).

Symptoms of LPR include dysphonia, throat clearing, postnasal drip, chronic cough, dysphagia, globus pharyngeus, excessive phlegm, heartburn, dyspnea, laryngospasm, and wheezing (12). Signs of LPR include those of laryngeal inflammation such as erythema and edema of the larynx, especially in the postcricoid and hypopharyngeal areas. Additional signs associated with LPR include vocal fold edema, diffuse laryngeal erythema and edema, pseudosulcus vocalis, obliteration of the laryngeal ventricles, thickened laryngopharyngeal mucus, and granulomata (12). One should consider that many of these signs are not specific to LPR and can be associated with other forms of laryngopharyngeal inflammation.

REVIEW OF GASTRIC REFLUX CONTENTS AND PHYSIOLOGY

Gastric Acid

Gastric acid is produced by parietal cells in the stomach. Parietal cells contain an extensive secretory network, called canaliculi, from which gastric acid is secreted into the lumen of the stomach. These cells are part of the fundic glands in the gastric mucosa. Gastric acid is approximately pH 2 in the human stomach lumen, the acidity being maintained by the proton pump H^+/K^+ ATPase. The resulting highly acidic environment in the stomach lumen causes proteins from food to denature, thus exposing the protein's peptide bonds. The chief cells of the stomach secrete inactive enzymes pepsinogen and renin for protein breakdown. Gastric acid then activates pepsinogen into pepsin—this enzyme then helps digestion by breaking the

bonds linking amino acids, a process known as proteolysis. In addition, the acidic environment of the stomach inhibits growth of many microorganisms; the gut's bacterial load is controlled and this helps prevent infection.

Secretion of Gastric Acid

Gastric acid secretion happens in several steps. Chloride and hydrogen ions are secreted separately from the cytoplasm of parietal cells and mixed in the canaliculi ultimately forming hydrochloric acid (HCl). This acid is then secreted into the lumen of the oxyntic gland and gradually reaches the stomach lumen. Chloride and sodium ions are secreted actively from the cytoplasm of the parietal cell into the lumen of the canaliculus. This creates a negative potential of −40 to −70 mV across the parietal cell membrane that causes potassium and sodium ions to diffuse from the cytoplasm into the parietal cell canaliculi. The enzyme carbonic anhydrase catalyzes the reaction between carbon dioxide and water to form carbonic acid. This acid immediately dissociates into hydrogen and bicarbonate ions. The hydrogen ions leave the cell through H^+/K^+ ATPase antiporter pumps. At the same time, sodium ions are actively reabsorbed. The majority of secreted potassium and sodium ions therefore return to the cytoplasm. The highest concentration that gastric acid reaches in the stomach is 160 mM in the canaliculi. This is about 3 million times that of arterial blood, but is isotonic with other bodily fluids. The lowest pH of the secreted acid is 0.8, but as the acid is diluted in the stomach lumen with other secretions, the intragastric pH will range between 1 and 3.

There are three phases in the secretion of gastric acid:

The cephalic phase: 30% of the total gastric acid produced is stimulated by anticipation of eating and the smell or taste of food.

The gastric phase: 60% of acid secreted is stimulated by the distension of the stomach with food. Digestion also produces proteins, resulting in even more gastrin production.

The intestinal phase: the remaining 10% of acid is secreted when chyme enters the small intestine, and is stimulated by small intestine distension.

Regulation of Secretion

Gastric acid production is regulated by both the autonomic nervous system and several hormones. The parasympathetic nervous system, via the vagus nerve, and the hormone gastrin stimulate the parietal cell to produce gastric acid, both directly acting on parietal cells and indirectly by stimulating secretion of the hormone histamine from enterochromaffin-like (ECL) cells. Vasoactive intestinal peptide, cholecystokinin, and secretin all inhibit production. The production of gastric acid in the stomach is tightly regulated by positive regulators and negative feedback mechanisms. Four types of cells are involved in this process: parietal cells, G cells, D cells, and ECL cells. In addition, the endings of the vagus nerve (CN X) and the intramural nervous plexus in the digestive tract also significantly influence secretion. Nerve endings in the stomach secrete two stimulatory neurotransmitters: acetylcholine and gastrin-releasing peptide. Their action is both direct on parietal cells and mediated through the secretion of gastrin from G cells and histamine from ECL. Gastrin acts on parietal cells directly and indirectly too, by stimulating the release of histamine. The release of histamine is the most important positive regulation mechanism of the secretion of gastric acid in the stomach. Its release is stimulated by gastrin and acetylcholine, and inhibited by somatostatin.

Neutralization of Acid

In the duodenum, gastric acid is neutralized by sodium bicarbonate. This also blocks gastric enzymes that have their pH optima in the acid range. The secretion of sodium bicarbonate from the pancreas is stimulated by secretin. This polypeptide hormone gets activated and secreted from S cells in the mucosa of the duodenum and jejunum when the pH in duodenum falls below 4.5 to 5.

This neutralization is described by the equation:

$$HCl + NaHCO_3 \rightarrow NaCl + H_2CO_3$$

The carbonic acid instantly decomposes into carbon dioxide and water, and is eliminated through the kidneys in urine.

Role of Gastric Acid in Disease

In hypochlorhydria and achlorhydria, there is low or no gastric acid in the stomach, potentially leading to problems as the disinfectant properties of the gastric lumen are decreased. In such conditions, there is greater risk of infections of the digestive tract (such as infection with *Helicobacter* bacteria). In Zollinger-Ellison syndrome and hypercalcemia, there are increased gastrin levels, leading to excess gastric acid production, which can cause gastric ulcers. Reflux of gastric acid into the esophagus and more proximally into the laryngopharynx and other extra-esophageal sites also cause significant injury and disease—to be discussed in more detail later in this chapter.

Pharmacology

The H^+/K^+ pump enzyme is the target of proton pump inhibitors (PPIs), used to increase gastric pH in diseases that feature excess acid. Histamine H_2 antagonists indirectly decrease gastric acid production. Antacids have high pH and neutralize existing acid.

Pepsin

Pepsin is expressed as a pro-form zymogen, pepsinogen, whose primary structure has an additional 44 amino

acids. In the stomach, chief cells release pepsinogen. The acid present in the stomach activates this zymogen. The hormone gastrin and the vagus nerve trigger the release of both pepsinogen and HCl when food is ingested. HCl creates the acidic environment that allows pepsinogen to unfold and cleave itself in an autocatalytic fashion, thereby generating pepsin, the active form of the enzyme. Pepsin then cleaves the 44 amino acids from pepsinogen creating more pepsin. Pepsin will digest up to 20% of ingested protein's amide bonds by cleaving preferentially after the N-terminal of aromatic amino acids such as phenylalanine, tryptophan, and tyrosine. Pepsin exhibits preferential cleavage for hydrophobic, preferably aromatic, residues in P1 and P1′ positions. Increased susceptibility to hydrolysis occurs if there is a sulfur-containing amino acid close to the peptide bond, which has an aromatic amino acid. Pepsin cleaves Phe–Val, Gln–His, Glu–Ala, Ala–Leu, Leu–Tyr, Tyr–Leu, Gly–Phe, Phe–Phe and Phe–Tyr bonds in the B chain of insulin. Peptides may be further digested by other proteases in the duodenum and eventually absorbed in the intestine. Pepsin is stored as pepsinogen; so it will only be released when needed and does not digest the body's own proteins in the stomach's lining.

Pepsin is maximally active at pH 2, but has activity up to pH 6.5. While inactive at pH 6.5 and above, it remains stable to pH 8. The enzyme is not irreversibly inactivated (denatured) until pH 8. While the stomach is designed to resist damage by pepsin, reflux of pepsin into the esophagus and laryngopharynx causes damage even above pH 4. Pepsin is considered an important etiologic factor in reflux disease of the aerodigestive tract and a biomarker for reflux, whose levels and acidity can be related to the severity of damage.

Bile

Bile is produced by hepatocytes in the liver, draining through the many bile ducts that penetrate the liver. During this process, the epithelial cells add a watery solution that is rich in bicarbonates that dilutes and increases alkalinity of the solution. Bile then flows into the common hepatic duct, which joins with the cystic duct from the gallbladder to form the common bile duct. The common bile duct in turn joins with the pancreatic duct to empty into the duodenum. If the sphincter of Oddi is closed, bile is prevented from draining into the intestine and instead flows into the gallbladder, where it is stored and concentrated up to five times its original potency between meals. This concentration occurs through the absorption of water and small electrolytes, while retaining all the original organic molecules. Cholesterol is also released with the bile, dissolved in the acids and fats found in the concentrated solution. When food is released by the stomach into the duodenum in the form of chyme, the duodenum releases cholecystokinin, which causes the gallbladder to release the concentrated bile to complete digestion.

The human liver can produce close to one litre of bile per day. About 95% of the salts secreted in bile are reabsorbed in the terminal ileum and reused. Blood from the ileum flows directly to the hepatic portal vein and returns to the liver where the hepatocytes reabsorb the salts and return them to the bile ducts to be reused, sometimes two to three times with each meal.

Action of Bile Salts in Digestion

Bile acts to some extent as a surfactant, helping to emulsify the fats in food. Bile salt anions have both a hydrophilic and hydrophobic side, and therefore tend to aggregate around droplets of fat (triglycerides and phospholipids) to form micelles, with the hydrophobic sides toward the fat and hydrophilic to the outside. The hydrophilic sides are positively charged due to the lecithin and other phospholipids that compose bile, and this charge prevents fat droplets coated with bile from reaggregating into larger fat particles. Ordinarily, the micelles in the duodenum have a diameter of around 14 to 33 μm.

The dispersion of food fat into micelles thus provides an increased surface area for the action of the enzyme pancreatic lipase, which digests the triglycerides, and is able to reach the fatty core through gaps between the bile salts. A triglyceride is broken down into two fatty acids and a monoglyceride, which are absorbed by the villi on the intestine walls. After being transferred across the intestinal membrane, fatty acids are reformed into triglycerides, then absorbed into the lymphatic system through lacteals. Without bile salts, most of the lipids in the food would be passed out in feces, undigested.

Since bile increases the absorption of fats, it is an important part of the absorption of the fat-soluble substances, such as the vitamins D, E, K, and A. Besides its digestive function, bile serves also as the route of excretion for bilirubin, a by-product of red blood cells recycled by the liver.

The alkaline bile also has the function of neutralizing any excess stomach acid before it enters the ileum, the final section of the small intestine. Bile salts also act as bactericides, destroying many of the microbes that may be present in the food.

Role of Bile in Reflux Disease

Reflux of bile is known to cause esophagitis and is likely to play a role in reflux-attributed laryngeal injury and disease (13). The mechanism of bile-induced mucosal injury is thought to be related to "intramucosal trapping" of bile acids that results in mucosal damage primarily by disorganizing membrane structure or interfering with cellular metabolism. Taurocholic acid does this at pH 2 and chenodeoxycholic acid at pH 7. Some bile acids cause damage at high pH due to their lipophilic properties at the pH at or near the pK_a value. For example, taurocholic acid (which is a conjugated bile acid with a $pK_a \sim 2$) and

chenodeoxycholic acid (which is an unconjugated acid with pK_a ~ 7) are unionized and therefore can enter the cell at an acidic and neutral pH, respectively. Once inside the cell, bile acids are trapped by ionization and subsequently cause mucosal damage.

Trypsin

Trypsin is secreted into the duodenum, where it acts to hydrolyze peptides into their smaller building blocks—amino acids (these peptides are the result of the enzyme pepsin breaking down the proteins in the stomach). This enables the uptake of protein in the food because peptides (though smaller than proteins) are too big to be absorbed through the lining of the ileum. Trypsin catalyzes the hydrolysis of peptide bonds.

Trypsin is produced in the pancreas in the form of inactive zymogen, trypsinogen. When the pancreas is stimulated by cholecystokinin, it is then secreted into the small intestine. Once in the small intestine, the enzyme enteropeptidase activates it into trypsin by proteolytic cleavage. The resulting trypsins themselves activate more trypsinogens (autocatalysis), so only a small amount of enteropeptidase is necessary to start the reaction. This activation mechanism is common for most serine proteases, and serves to prevent autodigestion of the pancreas.

Involvement of Trypsin in Reflux Disease

Studies have shown that trypsin can stimulate the production of inflammatory mediators. Chemokines and prostaglandins are increased in human esophageal epithelial cells when exposed to trypsin *in vitro* (14). Trypsin has also been shown to induce chronic esophageal inflammation in rats (15).

PATHOPHYSIOLOGY OF LPR

Gastric refluxate, containing acid, pepsin, bile, and trypsin, obviously passes through the esophagus (as in GER) and enters the laryngopharynx (as in LPR), yet patients with laryngeal symptoms and injury do not often have esophageal symptoms or injury. It is thought that LPR patients have intact esophageal defense mechanisms that prevent esophageal injury by the refluxate. For example, in the esophagus, peristaltic motility helps clear the refluxate, salivary bicarbonate neutralizes the refluxate, and mucus secretions prevent the refluxate from penetrating the epithelium. In addition, the upper esophageal sphincter (UES) closes to prevent refluxate from entering the laryngopharynx. It is thought that UES function is defective in many patients with reflux-attributed laryngeal symptoms and endoscopic findings. The larynx lacks many of the intrinsic defense mechanisms present in their esophageal counterparts, perhaps explaining its increased sensitivity to gastric refluxate compared to the esophagus.

Reflux is thought to cause laryngeal symptoms and induce extraesophageal pathology by several different mechanisms. First, by direct contact of acid and pepsin with the epithelium—the microaspiration theory (4). Second, the trauma theory suggests that exposure of the laryngeal epithelium to gastric refluxate alone is not sufficient to cause injury and that an additional factor, such as vocal abuse or concomitant viral infection, is necessary to induce mucosal lesions (3,16). Finally, the esophageal–bronchial reflex theory suggests that acid in the distal esophagus stimulates vagally mediated reflexes that cause chronic cough, which in turn causes laryngeal symptoms and lesions (17).

Differences between LPR and GERD

Ossakow et al. (18) compared symptoms of patients with reflux esophagitis with those of patients with laryngitis. They found that hoarseness was the most prevalent symptom of patients with LPR (100%), although none of the patients with GERD reported experiencing hoarseness. Heartburn was present in the majority of patients with GERD (89%), but only a small percentage of LPR patients (6%). Wiener et al. (19) demonstrated abnormal pH studies in 78% of patients with hoarseness, all of whom had normal esophageal manometry, and of these, 72% had normal endoscopy with biopsy. This supports the theory that the majority of LPR patients have normal acid clearance mechanisms (20). Although both esophagitis and laryngitis are likely to be caused by the damaging effects of the corrosive refluxate, significantly more damage occurs in the larynx compared to the esophagus following exposure to acid and pepsin. This may be because the esophagus has better defense mechanisms to counteract such damage, for example, peristalsis, saliva, and bicarbonate production (3,21). Therefore, although there may not be sufficient reflux to cause esophagitis, it may be enough to develop symptomatic LPR.

The pattern and mechanism of LPR and GERD are different. LPR patients typically have upright (daytime) reflux with good esophageal motor function and no esophagitis, whereas GERD patients have supine (nocturnal) reflux and esophageal dysmotility (3,22,23). GERD patients often have a dysfunction of the lower esophageal sphincter (LES), while the UES is a primary defect in LPR patients (24). The different pattern and mechanism of reflux may explain the different clinical manifestations observed in LPR and GERD.

Role of Nonacid and Weakly Acid Reflux in Laryngeal Inflammation and Disease

Studies using combined multichannel intraluminal impedance with pH monitoring (multichannel intraluminal impedance-pH [MII-pH]; discussed later in this chapter) reveal a positive symptom association with nonacidic

reflux and a significant association between nonacidic and weakly acidic reflux and persistent symptoms on PPI therapy (25–27). Using MII-pH monitoring, Tamhankar et al. (25) showed that PPI therapy decreases the H^+ ion concentration in the refluxed fluid, but does not significantly affect the frequency or duration of reflux events. Kawamura et al. (28) reported on a comparison of GER patterns in 10 healthy volunteers and 10 patients suspected of having reflux-attributed laryngitis. Using a bifurcated MII-pH reflux catheter, the investigators found that gastric reflux with weak acidity (above pH 4), is more common in patients with reflux-attributed laryngitis compared to healthy controls. Oelschlager et al. (29) demonstrated that the majority of reflux episodes into the pharynx are in fact nonacidic. Sharma et al. (27) reported that 70/200 (35%) patients on at least twice daily PPI had a positive symptom index for nonacidic reflux. Finally, Tutuian et al. (26) also recently reported that reflux episodes extending proximally are significantly associated with symptoms irrespective of the pH of the refluxate. Patients with signs and symptoms associated with nonacidic and weakly acidic reflux would likely have a negative pH test and would not benefit from PPI therapy. Diagnosis and treatment has focused on the acidity of the refluxate because it was thought that the other components of the refluxate would not be injurious at higher pH. However, it is now known that certain bile acids are injurious at higher pH (30,31), and recent data supports a role for pepsin in reflux-attributed laryngeal injury and disease, independent of the pH of the refluxate (32,33). Given these data, it seems that a treatment regimen based on acid suppression alone would be bound to fail. Much of the controversy that has revolved around LPR management can easily be explained by this inflammation caused by weakly or nonacidic agents.

Antireflux surgery, such as fundoplication, is one of the few options for patients with persistent reflux-attributed symptoms and endoscopic findings. Unlike medical therapy, which does not stop reflux from occurring but only increases the pH of the refluxate, surgical therapy restores the physiologic separation between the abdomen and thorax and strengthens the LES, preventing refluxate from coming up the esophagus. Iqbal et al. (34) recently reported a study in which 85% of patients who had a fundoplication for extraesophageal symptoms of reflux had a positive outcome. The majority of these patients had refractory symptoms on maximal acid suppression therapy. These data additionally question the role of acid alone in the development of reflux-related pathology and highlight a potential role for the other components of the refluxate.

A role for pepsin in nonacid reflux has been postulated in the recent literature. As already stated, this enzyme is maximally active at pH 2, but can cause tissue damage above this pH, with complete inactivation not occurring until pH 6.5 (33,35,36). While pepsin is inactive at pH 6.5, it remains stable until pH 8 and thus can be reactivated when the pH is reduced. Pepsin is not irreversibly inactivated until pH 8 (33,36). Thus, even if the pepsin, which has been detected in, for example, laryngeal epithelia, is inactive (37,38) (mean pH of the laryngopharynx is 6.8), it would be stable and thus could sit inactive/dormant in the laryngopharynx and have the potential to become reactivated by a decrease in pH, either by a subsequent acid reflux event or perhaps once taken up by laryngeal epithelial cells and transported through intracellular compartment of lower pH (33,39–41).

Johnston et al. described how pepsin causes laryngeal epithelial cell damage at pH 7, and thus in nonacidic refluxate. These data may help explain why some patients have refractory symptoms on maximal PPI therapy, and help explain the reported symptom association with nonacidic reflux events. The authors report mitochondrial and Golgi damage in laryngeal epithelial cells exposed to pepsin at pH 7 (40). Cell toxicity was also demonstrated using the MTT cytotoxicity assay. Pepsin at pH 7 was also found to significantly alter the expression levels of multiple genes implicated in stress and toxicity. Of most clinical significance, they report that pepsin (0.1 mg/mL, pH 7) induces a proinflammatory cytokine gene expression profile in hypopharyngeal FaDu epithelial cells *in vitro* similar to that which contributes to disease in GER patients (42). Collectively, these data suggest a mechanistic link between exposure to pepsin, even in nonacidic refluxate, and cellular changes that lead to laryngopharyngeal inflammatory disease. In this context, the unexpected finding that pepsin is taken up by human laryngeal epithelial cells by receptor-mediated endocytosis is highly relevant. Pepsin has been previously assumed to cause damage by its proteolytic activity alone, but the discovery that pepsin is taken up by laryngeal epithelial cells by receptor-mediated endocytosis opens the door to a new mechanism for cell damage. It is possible that inactive, but stable, pepsin at pH 7 taken up by laryngeal epithelial cells becomes reactivated once inside the cell in compartments of lower pH such as late endosomes and the trans-reticular golgi where pepsin presence has been confirmed (32). The therapeutic potential of receptor antagonists and irreversible inhibitors of peptic activity to prevent pepsin uptake and/or reactivation are currently being studied.

OTHER CLINICAL MANIFESTATIONS OF EER

EER has been implicated as a source or cofactor of inflammatory disease of the mucosa of the entire head and neck. Subsites affected by reflux include mucosa of the nose, paranasal sinuses, eustachian tube and middle ear, nasopharynx, oropharynx, hypopharynx, larynx, subglottis, trachea, and lower airway. Connection of EER to specific disease states has been demonstrated in an ever expanding list of conditions of the aerodigestive tract including otitis media (OM), sinusitis, cough, sleep disordered breathing,

laryngitis, laryngospasm, airway stenosis, and lower airway problems such as asthma, chronic obstructive pulmonary disease, interstitial pulmonary fibrosis, and chronic lung transplant rejection. Evidence for these has been based largely on clinical findings that correlate to pH probe studies confirming EER or detection of elements of refluxate in the subsite in question. Animal and basic science studies have been used to propose or confirm a mechanism, but in most cases, direct cause and effect in the human condition has yet to be confirmed. Mechanism for disease is typically explained as occurring either by direct contact of refluxate and resulting inflammation of the mucosa or via a vagally mediated neurogenic process as previously discussed.

Extraesophageal Reflux and the Middle Ear

It has been proposed that refluxate that reaches to the nasopharynx can induce an inflammatory cascade that leads to middle ear dysfunction and OM. This can occur from direct inflammation and obstruction of the eustachian tube or by flow through the eustachian tube into the middle ear (43,44). Ambulatory pH probe studies of children with OM show a high rate of acid reflux (45). The presence of pepsin within the middle ear has also been shown in children with OM (46,47). The relatively neutral pH environment of the middle ear has led to criticism of the role of reflux in OM. Data showing presence of bile acids in effusions (48) as well as the recent expansion of our understanding of pepsin-induced mucosal injury at weakly or nonacidic pH provides another possible explanation (49). There have been limited evaluations of the effects of acid suppressive treatment in OM. In two small studies (50,51), there were significant clearing of effusions with antireflux therapy alone.

Extraesophageal Reflux and the Nose and Paranasal Sinuses

Although an association between sinonasal disease and gastric hypersecretion was first documented in 1950, only more recently has the awareness of this association been more fully investigated. In the late 1990s, several studies revealed a high association between EER and sinonasal disease. DiBaise et al. (52) performed pH probe studies on a group of patients with chronic rhinosinusitis (CRS) and noted 78% of patients had evidence of reflux. A larger epidemiologic study by El-Serag et al. (53) demonstrated that adults with GER were more likely to also have a history of sinusitis. In another study, patients with sinusitis were evaluated for reflux and those with objective findings of reflux were treated with acid suppression with a PPI. The majority of patients in this small noncontrolled study demonstrated improvement in their sinonasal symptoms following treatment for reflux. More recent studies of acid detection by pharyngeal probe have demonstrated its presence in the nasopharynx and multiple studies have demonstrated a high prevalence of GER with sinusitis in the pediatric population; however, cause and effect have yet to be proved (54).

The mechanism for disease is similar to other sites of the head and neck and can be explained by direct mucosal contact of refluxate or via a vagally mediated neurogenic process. With respect to the neurogenic mechanism, abnormalities of the autonomic system have been demonstrated in those with sinusitis and reflux. These abnormalities have been proposed to affect sinonasal mucosal edema and ostial function (55).

As with OM, there have been attempts to evaluate the effect of acid suppression and CRS (56). Results have been positive, but study design has been questioned. Bothwell noted that children with medically refractive CRS experienced relief of symptoms and avoided operation after acid suppressive therapy (57). Patients with CRS and a positive pH probe study tend to respond better to acid suppressive therapy then their cohorts without positive pH studies (52,58).

Extraesophageal Reflux and Stenotic Lesions of the Larynx and Airway

Stenotic lesions of the larynx and trachea continue to be a challenge to the otolaryngologist and patient. Although many of these lesions are posttraumatic or related to collagen-vascular disease, a subset remains idiopathic. Reflux has long been suggested to have a significant role in development of and worsening of laryngotracheal stenosis (LTS).

Bogdasarian and Olson (59) first suggested that reflux of gastric acid might play a significant role in the cause of posterior glottic stenosis. Later, Bain et al. (60) reported a case of subglottic stenosis (SGS) in a 57-year-old woman without a history of operation, trauma, or intubation. Her preoperative airway was described as being the size of a pencil eraser and then 5 months after a Nissen fundoplication and endoscopic airway management, her airway returned to a normal caliber. Little et al. (61) reported a case of a 12-year-old girl with recalcitrant SGS who continued to produce exuberant granulation tissue. During an endoscopic procedure, she was noted to have gastric contents in her larynx and hypopharynx. This patient was then treated with H_2-receptor blockers and antireflux behavioral management; she was subsequently decannulated and there was no further formation of granulation tissue.

In Koufman's widely cited manuscript on the description of EER, 225 patients with a variety of laryngeal disorders were systematically evaluated for reflux (3). Ambulatory 24-hour pH monitoring was preformed in 182 patients of whom 32 had LTS. Over three-quarters of those with LTS had abnormal pH studies. This group also had the highest rate of acid reflux identified of the seven categories of EER that were evaluated. In 1997, Little et al. (10) evaluated 222 children with a 24-hour dual probe pH monitoring.

About one-quarter of these patients had laryngeal findings and those with laryngomalacia or laryngeal stenosis had the highest number of pharyngeal reflux events. Maronian et al. (62) studied nineteen patients with SGS and was able to test fourteen with a three or four port pH probe monitor. Only two patients did not demonstrate pharyngeal reflux events. About one-half of the studied patients had idiopathic SGS and they concluded that reflux was the probable cause. The remaining group had concomitant disease states including sarcoidosis, Wegener's granulomatosis, laryngeal trauma, and intubation. Reflux was involved in all tested patients and it was concluded that it acts as a synergistic factor that stimulates granulomatous disease to react and subsequently result in the development of stenosis.

Clinical evaluations of acid suppression and management of LTS have been overwhelmingly positive. In most studies, patients taking H_2 blockers or PPIs show enhancement of surgical outcomes (63). Antireflux operation in the form of Nissen fundoplication is commonly recommended for those with LTS and confirmed EER as demonstrated from pH probe or MII-pH studies.

DIAGNOSIS

The diagnosis of LPR is based on a constellation of patient symptoms, clinical evaluation with visualization of the laryngopharynx, and specific invasive testing procedures (16). Many paradigms for diagnosis and treatment exist. The best diagnosis is based on a specific testing procedure, but many patients forego this and elect to undergo empiric therapy with acid suppression (such as a PPI, available now in the United States over the counter) as it is safe and effective. Response to treatment has been questioned as placebo effect (64). Given long-term treatment costs and potential risks, an objective test should be recommended for those undergoing long-term therapy (65). At the time of this writing, dual-probe ambulatory 24-hour pH monitoring is considered by many as the gold-standard evaluation, however, this accolade is not without debate, and indeed may soon be superseded by MII-pH monitoring (29,66).

Quality of Life Instrument

The most widely used quality of life (QOL) instrument related to LPR in the otolaryngologic literature is the *reflux symptom index* (RSI) developed by Belafsky et al. (67) This instrument (Table 66.1) consists of nine questions related to symptoms of irritation of the aerodigestive tract and was validated with ambulatory pH probe monitoring and appropriately controlled. A total score greater than 13 suggests the presence of LPR.

Laryngopharyngoscopy

When evaluating disorders of the upper aerodigestive tract, visualization of the organ of interest is imperative. While indirect laryngoscopy with a mirror may be adequate, endoscopy of the larynx and pharynx is an easily implemented and well-tolerated procedure that all otolaryngologists are well versed in performing (68). Visualization of the structures in question is superior and often times there is an opportunity for recording and photodocumentation. Signs of inflammation of the laryngopharynx are considered significant toward the diagnosis of LPR. The clinician needs to be careful, however, as these signs may also be considered nonspecific of a particular disease. Posterior laryngitis with thickening and pachyderma of the laryngeal posterior commissure and postcricoid mucosa has been classically associated with LPR (69,70). Signs of LPR, however, have been demonstrated to be more extensive and involve other subsets of the larynx. Granuloma of the vocal process is highly associated with LPR (71) as are stenoses of the larynx or subglottis (3). Changes within the endolarynx include pseudosulcus, vocal fold edema, and thickened

TABLE 66.1 THE REFLUX SYMPTOM INDEX

Within the last month, how did the following problems affect you? *Circle the appropriate response.*	0 = No Problem 5 = Severe Problem					
1. Hoarseness or a problem with your voice	0	1	2	3	4	5
2. Clearing your throat	0	1	2	3	4	5
3. Excess throat mucus or postnasal drip	0	1	2	3	4	5
4. Difficulty swallowing food, liquids, or pills	0	1	2	3	4	5
5. Coughing after you ate or after lying down	0	1	2	3	4	5
6. Breathing difficulties or choking episodes	0	1	2	3	4	5
7. Troublesome or annoying cough	0	1	2	3	4	5
8. Sensations of something sticking in your throat or a lump in your throat	0	1	2	3	4	5
9. Heartburn, chest pain, indigestion, or stomach acid coming up	0	1	2	3	4	5
TOTAL						

A score >13 suggests the presence of LPR.
From Belafsky PC, Postma GN, Koufman JA, Validity and reliability of the reflux symptom index (RSI). *J Voice* 2002;16(2):274–277, with permission.

TABLE 66.2 THE REFLUX FINDING SCORE

Subglottic edema	0 = absent 2 = present
Ventricular	2 = partial 4 = complete
Erythema/hyperemia	2 = arytenoids only 4 = diffuse
Vocal fold edema	1 = mild 2 = moderate 3 = severe 4 = polypoid
Diffuse laryngeal edema	1 = mild 2 = moderate 3 = severe 4 = obstructing
Posterior commissure hypertrophy	1 = mild 2 = moderate 3 = severe 4 = obstructing
Granuloma/granulation tissue	0 = absent 2 = present
Thick endolaryngeal mucus	0 = absent 2 = present

A score of >7 suggests LPR.
From Belafsky PC, Postma GN, Koufman JA. Title the validity and reliability of the reflux finding score (RFS). *Laryngoscope* 2001;111(8): 1313–1317, with permission.

mucus. The *reflux finding score* (RFS) is a validated checklist of items to look for in the laryngopharynx when considering LPR (Table 66.2; Figs. 66.1 to 66.4) (72).

Esophagoscopy

The role of esophageal endoscopy is different than that of laryngopharyngeal endoscopy in the diagnosis and management of LPR. While visualization of the laryngopharynx is considered paramount in making a diagnosis, esophageal visualization is more useful to rule out other pathology that either mimics the symptoms of LPR, or pathology that is associated with LPR (73). Some recommend an esophageal evaluation in those with known LPR to rule out important phenomena such as Barrett's intestinal metaplasia (74). This is important to consider even in those with well-treated LPR given a high association of esophageal pathology in those with laryngopharyngeal symptomology.

Endoscopy can be performed with either of two methods—flexible large bore transoral or flexible small bore transnasal telescopy. Transoral rigid esophageal endoscopy is not typically applied in reference to LPR and holds a more traditional role in management of anatomic abnormalities of the esophagus. Transoral flexible esophageal endoscopy with a large bore telescope is performed under sedation (monitored anesthesia) and is usually considered an outpatient operation or procedure. Transnasal endoscopy (TNE) has been well accepted in the otolaryngologic literature as a diagnostic and screening tool. It is very safe and effective. Most complications from upper endoscopy are associated with anesthesia and sedation (75). In the TNE procedure, the patient is ambulatory and awake. There is no sedation and only topical anesthetics are used. The procedure can be performed in the office and is well

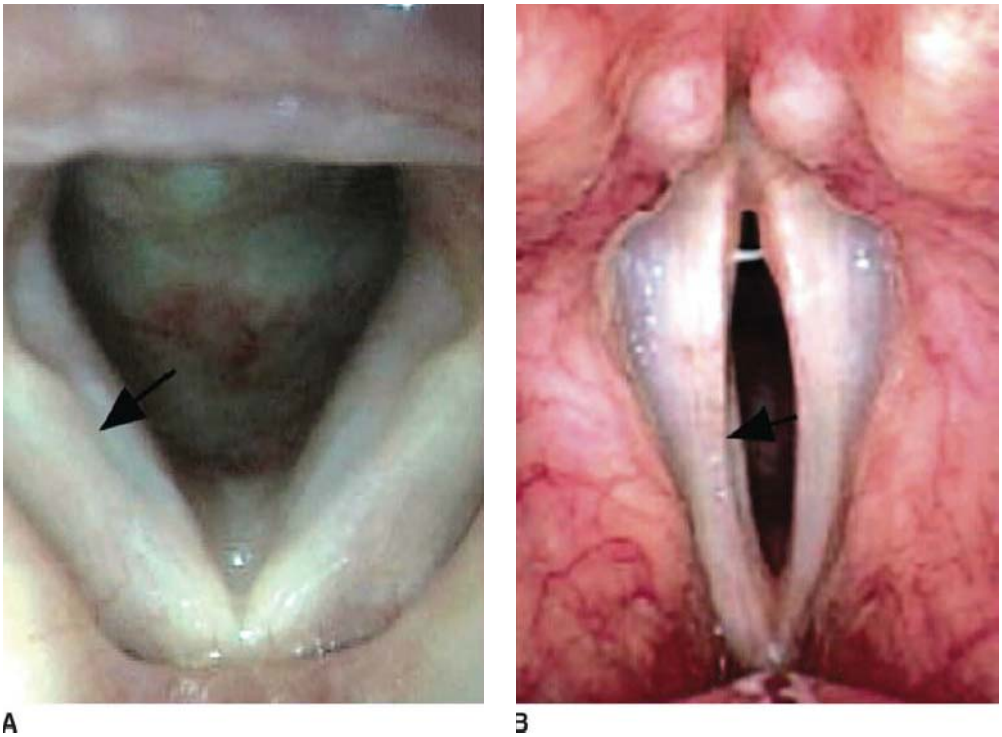


Figure 66.1 Comparison of pseudosulcus versus true sulcus vocalis. **A**: Bilateral pseudosulcus vocalis (*arrow*). Notice the subglottic edema extends past the vocal process all the way to the posterior larynx. Also present are posterior commissure hypertrophy, vocal fold edema, diffuse laryngeal edema, and partial ventricular obliteration. **B**: True sulcus vocalis of the right vocal fold (*arrow*). Notice that the sulcus is present in the midportion of the striking zone and stops at the vocal process of the arytenoid. From Belafsky PC, Postma GN, Koufman JA. Title the validity and reliability of the reflux finding score (RFS). *Laryngoscope* 2001;111(8):1313–1317, with permission.

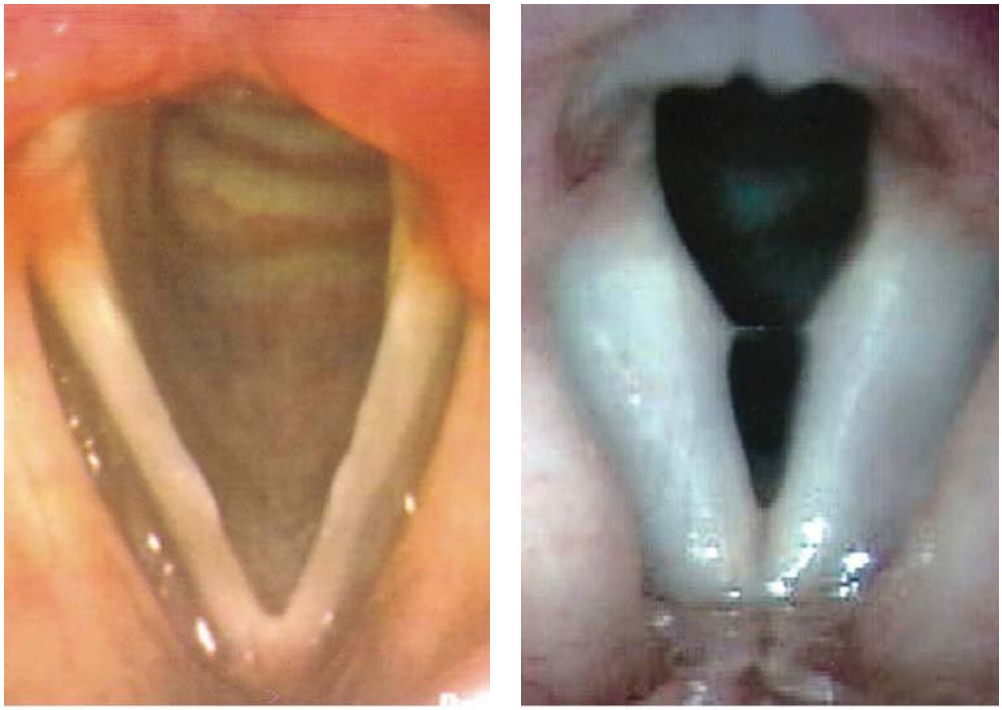


Figure 66.2 Ventricular obliteration. **A**: Open laryngeal ventricles. Note the sharp ventricular bands and the open space between the true and false vocal folds. Note small prenodules. **B**: Ventricular obliteration. Both the true and false vocal folds are swollen, thus obliterating the ventricles. Also present is mild posterior commissure hypertrophy. From Belafsky PC, Postma GN, Koufman JA. Title the validity and reliability of the reflux finding score (RFS). *Laryngoscope* 2001;111(8):1313–1317, with permission.

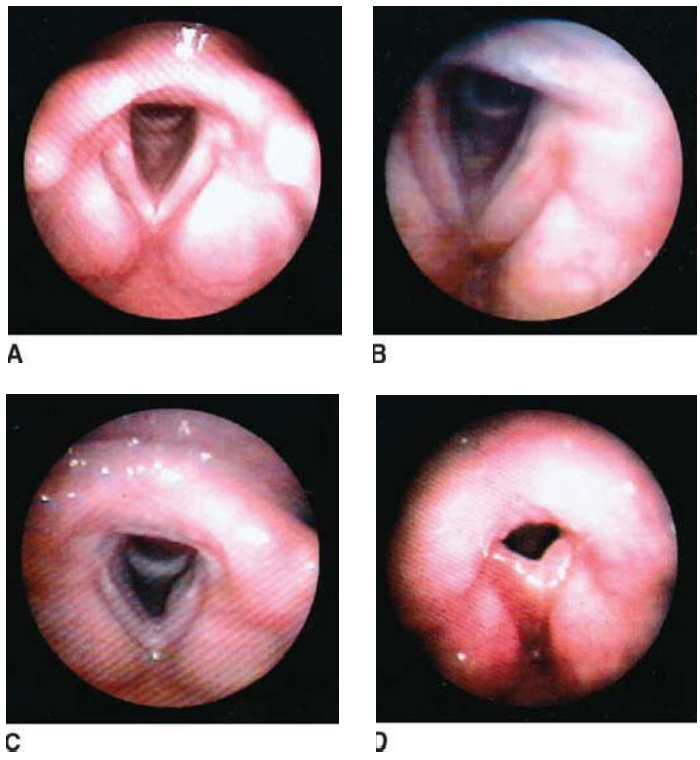


Figure 66.3 Vocal fold edema. **A**: Mild vocal fold edema. **B**: Moderate vocal fold edema. Pseudosulcus vocalis, posterior commissure hypertrophy, and partial ventricular obliteration are also present. **C**: Severe vocal fold edema. Sessile changes are noted. Also present are pseudosulcus vocalis, posterior commissure hypertrophy, and partial ventricular obliteration. **D**: Polypoid degeneration of the true vocal folds. Also present are severe posterior commissure hypertrophy, total ventricular obliteration, and diffuse laryngeal edema. From Belafsky PC, Postma GN, Koufman JA. Title the validity and reliability of the reflux finding score (RFS). *Laryngoscope* 2001;111(8):1313–1317, with permission.

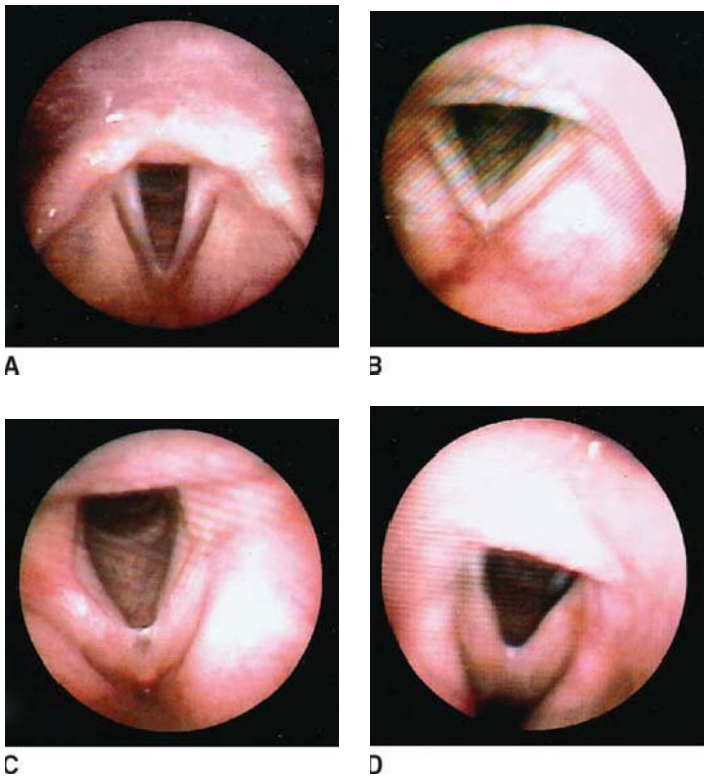


Figure 66.4 Posterior commissure hypertrophy. **A**: Normal posterior commissure. Cuneiform cartilages can still be visualized. **B**: Mild posterior commissure hypertrophy. Slight mustache-like configuration of posterior commissure. Also present are moderate vocal fold edema, pseudosulcus vocalis, and partial ventricular obliteration. **C**: Moderate posterior commissure hypertrophy. Straight line across the posterior larynx. Also present are moderate vocal fold edema, pseudosulcus vocalis, partial ventricular obliteration, and diffuse laryngeal edema. **D**: Severe posterior commissure hypertrophy Also present are several vocal fold edema, total ventricular obliteration, and diffuse laryngeal edema. (From Belafsky PC, Postma GN, Koufman JA. Title the validity and reliability of the reflux finding score (RFS). *Laryngoscope* 2001;111(8):1313–1317, with permission.)

tolerated by patients because of little down time and no need for a driver or companion's assistance in the periprocedural period. In their review of over 700 cases, Postma et al. (73) noted no major complications. In this and other reviews, only minor epistaxis and rare vasovagal response has been reported.

Reflux Detection

Detection of retrograde transport of liquid and gas from the stomach to the upper aerodigestive tract is considered the current gold standard of reflux testing. A variety of tools have been used to detect refluxate. The most widely used is a pH monitor and this tool comes in several varieties. Wired varieties are equipped with antimony probes that detect a change in endoluminal pH. These are commercially available with single (esophageal) and dual (esophageal and pharyngeal) acid detection capability. Triple and quadruple probes have been used experimentally. The coated wire probe is placed transnasally after calibration to the desired level in the esophagus. Single probes are commonly used in the gastroenterology literature to detect GER. As GER is quite different from LPR, single (distal esophageal) pH probe monitoring has little to no role in detection of LPR. For detection of LPR, the dual pH probe is most commonly used and placed for 24 hours while the patient is ambulatory, and at least theoretically, going about their normal routines. An intake log of food, drink, position (supine or upright), and any symptomology is kept by the patient and used for later interpretation of the study. Placement of the dual probes is not without controversy. The distal LES can be measured by pH pullback or by manometry (76). The upper probe can be placed just below, at, or just above the cricopharyngeus (77). Interpretation is also subject to debate. Distal esophageal events are defined as pathologic if they exceed a certain Johnson-DeMeester score (78). A similar scoring system does not exist for the upper probe interpretation. At the upper probe, pathologic reflux is considered by some as a single event while others suggest an acid exposure of 0.1% of the study less than pH 4 (3,79). Recent normative data demonstrate that as little as one reflux event to the pharynx is significant enough to diagnose LPR (11). Additional controversy and debates are made about consideration of a pH of less than 4 as significant as defined by convention in the gastroenterology literature. Data discussed earlier in this chapter suggest that peptic activity of refluxate exists at higher pH. Some have incorporated this and suggest that pH studies be interpreted at a cutoff of pH 5 or higher (80).

Many consider traditional wired transnasal pH probes encumbering to the patient in the clinical setting. A wireless probe system was developed to overcome this issue (81). The Bravo pH Monitoring System (Given Imaging Ltd., Yokneam, Israel) utilizes a capsule-contained pH probe coupled to a wireless transmitting system. This small capsule is attached to the esophageal mucosa under endoscopic guidance and then transmits data to a wireless device held at the patient's waistband. The probe usually stays in place for 3 to 5 days before it self-detaches with normal sloughing of the esophageal epithelium. Data is

collected for 48 hours. Criticism of this technique lies in its application to LPR. The probe must be placed in the esophagus and therefore upper esophageal or pharyngeal measurement cannot be performed.

Another limitation of the more traditional antimony pH electrodes is their need for a moist environment to remain accurate. One of the major obstacles in pH monitoring of the pharynx is the risk of the electrode drying as it frees itself from the liquid film at the mucosa. The Dx-pH Measurement System (Restech Corporation, San Diego, CA) was designed to overcome some of this limitation (82). This is a wired short probe that is placed transnasally at the level of the oropharynx and is capable of detection of both gaseous and liquid acid refluxate. It is also considered more comfortable than a standard pH probe because of its short length. Data on its application to LPR is still emerging, but at the time of this writing, it seems like a useful screening tool for LPR.

One of the major shortfalls of pH testing alone is the relative inability to detect reflux events at weakly acidic or neutral pH. The Bilitec 2000 system (Medtronic, Shoreview, MN) is a transnasal system that detects the presence of bile pigments via spectrophotography (83,84). Tack et al. (85) have recommended simultaneous pH and Bilitec monitoring in patients with refractory esophagitis after demonstrating a high degree of duodenal reflux in patients that failed PPI therapy. With respect to LPR, Poelmans et al. (86) demonstrated bile in throat phlegm utilizing a similar dual pH and Bilitec monitoring trial.

MII-pH monitoring now represents perhaps the ultimate in reflux detection (87). This device has the capability of detecting acid, weakly acidic, and nonacid events occurring at multiple stations within the esophagus, stomach, and pharynx. Furthermore, both contents and direction of flow can be differentiated—events can be separated into liquid or gas and can be identified as anterograde (swallow) and retrograde (reflux) direction. Patients who are acid suppressed on a PPI can still be evaluated for reflux (27,88).

The impedance detection device looks similar to a standard wired pH probe system, and indeed, many commercial models have an integrated pH probe system; hence the moniker of combined MII-pH probes. Impedance is a measure of electrical resistance. Multiple impedance electrodes are present along the length of the catheter probe system. Each probe is capable of detecting a rise or drop in intraluminal impedance. Gas has a very high impedance, normal mucosa is somewhat lower, and liquids such as saliva and refluxate are even lower. With multiple electrodes, directionality of an impedance delta can be ascertained, and if anterograde, is considered a swallow, and if retrograde, is considered a reflux or eructation.

Data with MII-pH testing and LPR are still emerging. The most recent studies have confirmed weakly and nonacidic reflux in those with LPR and those that fail acid-suppressive medical therapy (11,25–27,89). MII-pH seems to have an emerging role in identifying those who may benefit from operative therapy given the current limitations of medical therapy (90).

Radiologic Imaging

There exists a variety of imaging techniques available to image the esophagus including the barium swallow, modified barium swallow, and other techniques of videofluoroscopy. In general, a contrast material such as liquid barium is swallowed under fluoroscopic visualization (91). Although this method has a traditional application toward detection of reflux, in studies that compared imaging to pH probe monitoring, the sensitivity of reflux detection only ranged from 25% to 33% (92). Superficial mucosal pathology including esophagitis, dysplasia, and metaplasia may not be successfully seen on imaging. Most would recommend esophagoscopy and biopsy toward specific diagnosis of epithelial disease. Imaging, on the other hand, does have a significant role in diagnosis of anatomic or structural abnormalities such as tumor, rings, slings, and strictures. Manometry is thought to be a superior method of detecting motility disorders, however, there is a zone at the transition of striated to smooth muscle in the proximal esophagus that is not well detected on manometry. Videofluoroscopic studies can demonstrate EPR that is thought to be associated with LPR. This phenomenon is best assessed with an imaging study (93).

Tissue and Fluids Assay—Pepsin Detection

Pepsin has been posited to be a reliable marker for the diagnosis of EER (38). Synthesized only by the chief cells of the gastric fundus as the zymogen pepsinogen and subsequently converted to active pepsin via autolysis in the acidic environment of the stomach, pepsin is the primary proteolytic enzyme of the digestive system and one of the key deleterious agents of gastric refluxate (3,94). While the constitution of gastric refluxate is variable and components such as acid or bile salts may or may not be present, all refluxate contains pepsin. Like MII, pepsin assay has the capacity to detect nonacidic reflux and may be used to monitor reflux in patients undergoing treatment with PPIs. Superior to pH and MII testing, pepsin analysis may be performed on easily obtainable samples of saliva and sputum thereby facilitating testing of all patients including children or the neurologically impaired, as this would require no transnasal catheter placement or other invasive procedure. Patients could also be evaluated in their more normal state without dietary or lifestyle alteration that comes with the more invasive testing. Pepsin assay also offers the advantage of direct detection of refluxate at sites of airway damage potentially attributable to EER. Although pepsin assay alone does not indicate a causal relationship to airway damage, presence of pepsin outside of the stomach does indicate reflux and refluxate reaching the tested tissue or fluid. To date, this technique has demonstrated the

presence of pepsin in the laryngopharynx, esophagus, trachea, lung, sinus, middle ear, sputum/saliva, and exhaled breath (37,38,43,49,94–97). At the time of this writing, a pepsin diagnostic test remains confined to research laboratories and is not commercially available; however, it is anticipated that a pepsin in-office clinical test will be commercially available in the near future.

TREATMENT OF LARYNGOPHARYNGEAL REFLUX

When treating LPR, the goal is to eliminate symptoms, heal mucosal lesions, manage complications, and maintain symptom remission. It is thought that control of intragastric acid secretion and reduction of pharyngeal and laryngeal acid exposure is directly related to mucosal healing and symptom relief. Dietary and lifestyle adjustment (Table 66.3), medicines, and operations have been used to manage those with LPR.

LPR is often treated empirically, that is, based on symptoms and findings consistent with the disease (16). These symptoms and findings, however, can also be considered nonspecific and encompass a variety of etiologies of chronic laryngopharyngitis. Controversy exists whether to begin treatment based on a clinical diagnosis alone, or to defer this treatment until after confirmation by more objective data such as a pH probe study (98). Because behavioral maneuvers and acid suppressive medicines are considered safe and possibly effective, many recommend a 3 month period of empiric treatment and then evaluating again for treatment response before objective testing (i.e., pH monitoring) is employed. Others however recognize the limitations and potential risks of empiric treatment and suggest that medical management be delayed until after objective testing (65,99). One should keep in mind that the contemporary practice of medical therapy for LPR is not specifically U.S. FDA approved. Although clinical practice guidelines exist for treatment of GERD, no evidence-based guidelines truly exist (at the time of this writing) for LPR. Treatment of LPR and EER is largely based on uncontrolled observational studies or physiologic pH data (98,100). With LPR, the evidence-based definition of who receives empiric treatment with medicines and who has an esophageal endoscopy has yet to be completely established (Fig. 66.5).

TABLE 66.3 RECOMMENDED LIFESTYLE MODIFICATIONS FOR REFLUX

Weight loss (≤25 kg/m^2)
Small meal size
Avoid lying down within 3 h of eating a meal
Eat a low fat, low acid diet
Avoid carbonate beverages
Avoid spicy food and chocolate
Stop smoking
Reduce alcohol intake
Avoid tight-fitting clothes

These lifestyle modifications may be helpful in managing reflux disease, however, scientific data proving the effectiveness of these changes is still needed.

Weight Loss

The relationship between obesity and LPR is not well defined. Some studies show an increased risk of reflux symptoms in obese individuals (101), but other studies show no such association (102). However, patients with LPR are recommended to make dietary and lifestyle modifications. Diet and weight loss will decrease intra-abdominal pressure, stomach distension, and LES relaxations. Thus, most physicians advocate weight loss to help control reflux, with the goal of a body mass index of approximately 25 kg/m^2.

Dietary Factors

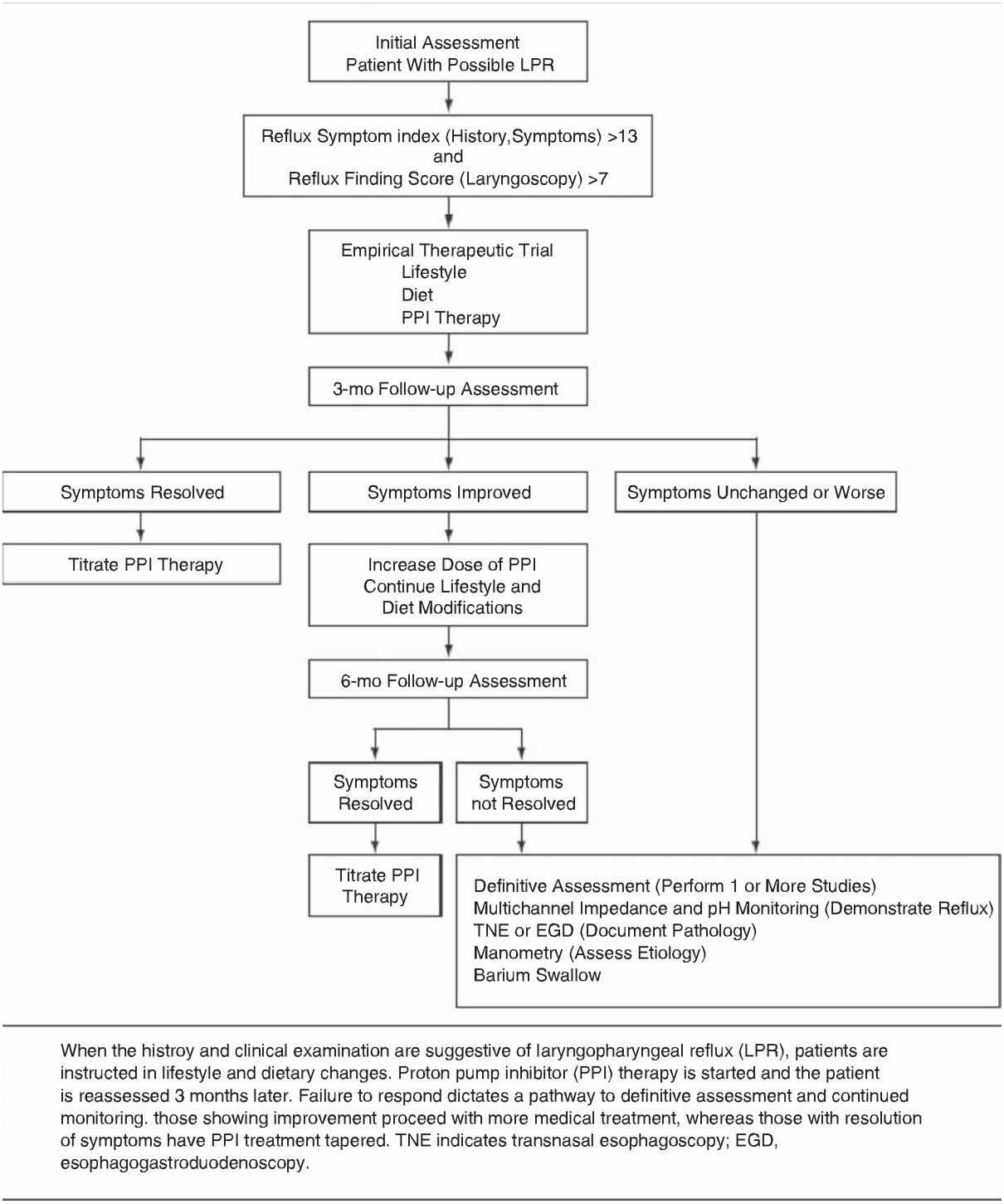
Patients with LPR often report worsening of symptoms with acidic and spicy foods. If patients report exacerbation of symptoms with certain foods they should decrease or eliminate them from their diet. Common mucosal irritants include citrus juices, tomato products, coffee, tea, cola, spicy foods, and alcohol. Carminatives such as chocolate or peppermint will lower LES pressure, increasing the frequency of reflux, and therefore should also be avoided. Carbonate beverages are not only acidic, but also promote reflux by gaseous gastric distension (103). It is likely that meal volume and subsequent gastric distension will affect reflux (104). Fatty or fried foods are also thought to promote reflux. Finally, reflux often occurs postprandially, so the supine position should be avoided for at least 3 hours after a meal. It is therefore recommended that patients eat small meals that are low in fat, low acid, and avoid lying down after a meal.

Medications

Medications such as anticholinergics, sedatives, tricyclic antidepressants, potassium tablets, iron sulphate, and nonsteroidal anti-inflammatory drugs decrease LES pressure promoting reflux and thus should be avoided when possible.

Smoking

Smoking tobacco is associated with reflux disease. Smoking decreases LES pressure, promoting reflux. The toxic irritants in tobacco also affect laryngeal mucous membranes and increase mucous viscosity causing excessive throat clearing. Furthermore, smoking-associated cough will increase intra-abdominal pressure thereby increasing reflux events.



When the histroy and clinical examination are suggestive of laryngopharyngeal reflux (LPR), patients are instructed in lifestyle and dietary changes. Proton pump inhibitor (PPI) therapy is started and the patient is reassessed 3 months later. Failure to respond dictates a pathway to definitive assessment and continued monitoring. those showing improvement proceed with more medical treatment, whereas those with resolution of symptoms have PPI treatment tapered. TNE indicates transnasal esophagoscopy; EGD, esophagogastroduodenoscopy.

Figure 66.5 Algorithm for assessment and management of LPR (from Ford CN. Evaluation and management of laryngopharyngeal reflux. *JAMA* 2005;294(12):1534–1540, with permission. Copyright © 2005 American Medical Association, all rights reserved)

Alcohol

Alcohol intake is also associated with reflux disease. Like tobacco, alcohol decreases LES pressure, but also increases gastric acid secretion and negatively affects esophageal motility and gastric emptying (105).

Tight-Fitting Clothes

Tight-fitting clothes will increase intra-abdominal pressure and thus should be avoided in patients with reflux disease.

Elevation of the Head of the Bed

As already mentioned, most LPR patients reflux during the daytime and have little to no reflux when supine (8). However, if the patient reports night-time symptoms, or has pH-documented supine reflux, elevation of the head of the bed by 6 inches may help decrease reflux by the action of simple gravity.

MEDICAL TREATMENT

Treatment of LPR is largely focused on increasing the pH of the refluxate. The harmful effects of pathologic reflux are controlled by neutralizing the stomach acid and suppressing its production. While acid neutralization and suppression therapies are effective for the treatment of GERD, their role in the treatment of LPR remain controversial. Studies performed to date report variable results to medical therapies.

Bicarbonate Gum

Chewing sugar-free bicarbonate gum will directly increase esophageal and pharyngeal pH by buffering acid and will indirectly increase pH via saliva production (106).

Prokinetic Agents

Prokinetic agents such as metoclopramide and cisapride are used in reflux patients who have dyspeptic symptoms such as nausea, vomiting, and abdominal bloating. These drugs increase LES pressure and accelerate esophageal acid clearance and gastric emptying. Their use has fallen out of favor in recent years (107). Problems with cardiac arrhythmias and drug-associated deaths led to removal of cisapride from the US market in 2000 (108). Their results as single agent therapy for GER or LPR have been disappointing. Some patients are intolerant of the medicines side effect profiles including diarrhea or cramping, and treatment success with acid suppression has been variable and limited.

Sucralfate

Sucralfate is used in the treatment of GERD and stress ulcers and may be useful in the treatment of LPR; however, there are no specific data to support this as a treatment of LPR. Sucralfate is a locally acting substance that reacts with HCl to form a cross-linking viscous material that acts as an acid buffer for up to 8 hours. It attaches to proteins on the surface of ulcers, such as albumin and fibrinogen, to form stable and insoluble complexes, creating a barrier against gastric refluxate. In addition, it prevents back diffusion of hydrogen ions and absorbs both pepsin and bile acids further preventing esophageal damage by reflux.

Alginate

Alginate antireflux preparations are widely used for the treatment of GERD. They react with stomach acid to form a gel raft that floats on top of the stomach, helping to keep gastric contents in the stomach and preventing GER. Several studies have shown the efficacy of Gaviscon Advance (Reckitt Benckiser, Kingston-upon-Thames, UK) in the treatment of LPR. This alginate preparation is licensed in the United Kingdom for the treatment of LPR, but is not currently available in the United States. Treatment with Gaviscon Advance, either alone or in conjunction with a PPI, was found to be significantly beneficial in improving symptoms, laryngeal findings, and patient QOL compared to control (109).

H_2 Receptor Antagonists

H_2 receptor antagonists, such as cimetidine, famotidine, ranitidine, and nizatidine, inhibit gastric acid secretion by blocking stimulation of the parietal cell. They competitively inhibit the binding of histamine to the basolateral membrane of parietal cells to suppress acid production. H_2 receptor antagonists are best used for "situational" relief of reflux symptoms induced by certain activities, for example, in patients who experience heartburn during running. It is recommended that H_2 receptor antagonists are taken 1 hour prior to the activity that causes reflux symptoms. While they are effective in up to 80% GERD patients (110), they are only effective in approximately 50% LPR patients (111). This is because H_2 receptor antagonists merely reduce acid production by blocking stimulation of the parietal cell. The laryngeal epithelium is more sensitive to injury from gastric acid compared to the esophagus and thus more complete acid suppression is required (3,10).

Proton Pump Inhibitors

PPIs (omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole, and dexlansoprazole) irreversibly inhibit the H^+/K^+ ATPase enzyme that catalyses acid secretion in the parietal cells. By targeting the terminal step in production they prevent secretion of HCl and thus are potent gastric acid-suppressing agents, which are very effective for the treatment of GERD. Studies investigating the efficacy of PPIs for the treatment of LPR have shown variable results and thus their use continues to be of much debate in otolaryngology and gastroenterology. Nonetheless, empiric therapy with PPIs remains the backbone of medical management of LPR.

Early studies investigating the efficacy of PPIs for the treatment of LPR revealed promising response rates. For example, Shaw et al. (112) reported objective improvement in two-thirds of reflux-laryngitis patients after 3 months of omeprazole. However, these early studies were uncontrolled and did not compare the effect of PPI to placebo.

Several groups then compared once-daily to twice-daily dosing of PPIs since the laryngeal epithelium is thought to be more sensitive to damage by gastric refluxate compared to the esophagus. They found a significant response rate in nonresponders when elevated to a twice daily dosing regimen (23,113). El-Serag et al. (114) performed the first prospective placebo-controlled trial of PPIs for the treatment of LPR, reporting significant improvement with BID PPI compared to placebo. Later in 2006, Vaezi et al. (64) reported a prospective multicenter randomized study evaluating the efficacy of PPIs in treating LPR. They found no difference in LPR response to PPI or placebo. However, these data may be inconclusive because the inclusion criteria likely produced a dilution effect. The majority of patients included in this study were marginal cases with minimally troubling symptoms based on their LPR Health-Related Quality of Life assessment and absence of pharyngeal acid on pH monitoring. In contrast, in 2008, Reichel et al. (115) reported that patients with symptoms and endoscopic signs of LPR showed a statistically significant improvement in both symptoms and findings on omeprazole for 12 weeks compared to placebo. A substantial placebo effect was noted at 6 weeks; however, this was no longer evident at 12 weeks. Qadeer et al. (116) performed a meta-analysis that included 8 double-blind randomized controlled trials with a total of 344 patients. The authors concluded no significant benefit of PPI over placebo. However, it should be noted that there was greater than 50% reduction in self-reported laryngeal symptoms with PPI treatment in five of the eight studies included in the analysis. It has been suggested that the high placebo response in the other three trials dampened the significance of PPI therapy for LPR. There is a clear discrepancy in the results of the studies performed to date investigating the efficacy of PPIs for LPR. It is thought that this is due to the different inclusion used and because the majority of these studies included patients with mild LPR. Studies with more stringent inclusion criteria, with patients with moderate to severe LPR, are needed. In support of this, in a Cochrane Database review of the use of PPIs for the treatment of hoarseness, none of 302 studies met the inclusion criteria (117). It is hoped that multicenter studies, which include moderate to severe LPR patients, will give more consistent results. A better diagnostic test is also desperately needed for LPR to ensure all patients entered into these clinical trials do actually have LPR. It has been suggested that the lack of a true gold standard diagnostic test for LPR results in many patients being misdiagnosed with LPR, which in turn weakens the treatment arm of studies investigating the efficacy of PPIs. While we await a better diagnostic and multicenter trials with more stringent inclusion criteria, most physicians continue to recommend empiric acid suppression with PPIs for 3 and up to 6 months for LPR.

In both empiric and long-term management of LPR with a PPI, one should consider the potential adverse effects of therapy (118). Relatively benign side effects of PPIs include bloating, constipation, or diarrhea. In the affected patient, these may limit therapeutic efficacy of medical management. Long-term sequelae of acid suppression may include malabsorption of vitamin B_{12} and calcium (119). An increased rate of hip fracture has been seen in patients with long-term high-dose twice-a-day PPI therapy (120). Acid suppression may also lead to an alteration of the gastric milieu and bacterial flora (119,121,122). Some studies have demonstrated an increased risk of pneumonia in those taking PPIs chronically (123). Lastly, drug–drug interactions need to be considered. There is emerging evidence that links PPI use to decreased anticoagulant activity of clopidogrel (Plavix) (124–126). This agent is commonly used in the management of cardiac and cerebrovascular disease and recent studies have demonstrated an increased rate of adverse events in those taking PPI and clopidogrel versus clopidogrel alone. Although PPIs are often considered safe medicines, one should exercise caution and attention to side effects when prescribing these medicines, especially on a long-term high-dose basis.

Surgical Management of Reflux

A surgical approach to EER and LPR is the most effective method of decreasing volume reflux of materials to the proximal esophagus or laryngopharynx, eliminating both acidic and nonacidic events. Fundoplication has been demonstrated to ablate reflux to the level of the pharynx (127). Airway symptoms can be eliminated even in patients who do not respond to medical therapy (128). A favorable outcome for surgical therapy has been shown to be more likely if (a) extraesophageal symptoms are nocturnal; (b) esophageal and laryngeal acid exposure is identified by pH monitoring; (c) there is an association between extraesophageal symptoms and reflux (both acidic and nonacidic); and (e) there is a positive response to medical therapy. Although it is preferred that there is an association between a patient's extraesophageal symptoms and reflux events and there is some response to medical therapy, this is not an absolute requirement to proceed with surgical management since it is well-known that many patients with symptoms associated with weak acid and nonacid reflux will not benefit from acid suppression medical therapy alone.

Surgical reconstitution of a physical and functional gastroesophageal (GE) junction can be accomplished using a variety of techniques (117). In a fundoplication procedure, a portion of the stomach is wrapped around the distal esophagus in an effort to reduce reflux through the GE junction by improved competence of the LES. Fundoplication may be complete (i.e., 360 degrees) wrap, as in the Nissen or Rossetti procedure, or partial (i.e., 270 degrees) wrap, as in the Toupet or Bore procedures. The most common reported GE junction operation for EER is the laparoscopic Nissen fundoplication (LNF).

The effectiveness of LNF as treatment for LPR has been evaluated in several studies in both adult and pediatric

cohorts (127,129–137). The majority of studies also demonstrate significant improvement of symptoms and signs of LPR in medically refractory patients treated with LNF. In a recent study (135), however, Swoger et al. were not able to demonstrate significant differences in symptom improvement in a small group of patients that underwent LNF who were prospectively compared to a control cohort that continued aggressive PPI therapy. This study however did show an 80% improvement in LPR signs in the LNF cohort that was not seen in the control group that continued on the PPI.

Ogut et al. (136) evaluated changes in scores of symptoms and signs of LPR using previously validated instruments. RSI and RFS were calculated in 38 patients with LPR who underwent LNF. Scores were taken at a presurgical baseline as well as 6 and 12 months postoperative. Additionally, voice-related acoustics were measured using a standardized method. This group of patients was compared to a larger cohort that underwent LNF but who did not have a baseline RSI that would support the LPR diagnosis. Significant differences with improvement in all measured parameters were noted. Symptoms and signs of LPR improved, as did the acoustic measures associated with dysphonia. As with the Swoger study (135), this group noted that symptoms improved but they did not completely disappear following LNF.

Although LNF seems to be an effective option for treatment of LPR, it is not without problems. As with any other surgical option, risks related to an operative approach are inherent. As the procedure is performed electively, the patient needs to be appropriately selected and other chronic medical conditions need to be considered. A patient with advanced cardiac or pulmonary disease may not be medically stable for an operative approach. Patients need to be informed of problems that may develop after creation of the fundoplication. There may be difficulty with vomiting or burping that can be distressing and uncomfortable. Some patients complain of solid dysphagia, bloating, or increased flatulence. It has been suggested that these adverse symptoms may be less evident with partial fundoplication procedures; however, while these have been demonstrated to be effective for GER, utility toward treatment of LPR have not been critically evaluated. Long-term analysis of LNF is generally positive, however, revisions are occasionally necessary (138,139). It is important to note that up to 20% of patients may need to return to PPI treatment of their condition after 10 years (140).

LNF is safe and effective at controlling volume reflux, however, given long-term recidivism of EER and LPR, it is not recommended for the typical LPR patient with benign symptoms such as throat clearing. A surgical approach is generally reserved for those with medically refractory EER, and those who experience the more severe sequelae of EER such as airway stenosis, reflux-associated asthma, dysplasia, or cancer, and should be considered as part of the spectrum of treatments available to the patient.

SUMMARY

LPR is a common disease of the upper aerodigestive tract heralded by chronic laryngopharyngitis. Symptoms are associated with chronic inflammation and include hoarse voice, throat clearing, cough, and globus sensation. Heartburn and other symptoms common to GERD are less associated with LPR as these are two distinct diseases. Patients with LPR tend to be upright refluxers with normal esophageal acid clearance; patients with GERD typically reflux while supine and have impaired esophageal clearance and motility. Diagnosis of reflux is often based on a constellation of symptoms and findings on indirect laryngopharyngoscopy. The clinician should be careful, however, and recognize that these symptoms and findings can also be considered nonspecific of a particular disease. More objective testing with dual pH or MII-pH probe studies is often initially deferred, but is more widely accepted as diagnostic of LPR. Treatment of LPR is typically empiric and based on suppression of acid, however, this concept incompletely addresses the nonacidic and weakly acidic components of reflux. Additionally, medical management has failed to demonstrate significant efficacy of symptom control over placebo in double-blinded studies. Antireflux surgery in the form of gastric fundoplication is the only treatment capable of reducing all components of reflux. Recommendation for this treatment is often reserved for those with advanced or more life-threatening sequelae of EER or LPR.

HIGHLIGHTS

- LPR is a common source of chronic laryngopharyngitis.
- LPR is different than gastroesophageal reflux (GER or GERD). Common symptoms of LPR include hoarseness, cough, throat clearing, globus sensation, and dysphagia. GER is more commonly associated with dyspepsia or heartburn.
- There are several mechanisms for disease in LPR. First, is the more obvious direct contact of refluxate to epithelium that leads to an inflammatory cascade. Unlike the lower esophagus or stomach, the upper aerodigestive tract has poor mechanisms of acid defense and clearance. Another mechanism suggests a neural basis, and is defined as an increase in vagal irritability secondary to distal esophageal reflux disease.
- EER has been implicated as having a major role in development of multiple conditions or diseases of the head and neck including OM, sinusitis, pharyngitis, laryngitis, chronic cough, airway stenosis, asthma, and other lower respiratory diseases.

- Laryngoscopy is required to make a diagnosis of chronic laryngitis associated with LPR. RSI and RFS can aid in diagnosis and monitoring of response to treatment.
- The current gold standard of reflux diagnosis is 24-hour ambulatory dual-probe pH monitoring. This may be supplanted in upcoming years with MII-pH monitoring, which can detect both acidic and nonacidic reflux events.
- Most treatment is based on acid suppression with oral medications; however, there is a reasonably high placebo rate and treatment failure rate. Most data show that acid suppression alone is insufficient to control reflux and only antireflux surgery is effective in this endeavor. Generalizable evidence is still lacking to recommend antireflux surgery to a broad group of patients with LPR.

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67 Infection, Infiltration, and Benign Neoplasms of the Larynx

Craig R. Villari *Melissa M. Statham*

Multiple infectious and benign conditions can affect laryngeal biomechanics and detrimentally affect laryngeal function and vocal performance. A variety of clinical presentations is possible ranging from dysphonia or dysphagia to airway compromise depending on pathology, the affected laryngeal subsite(s), and premorbid laryngeal anatomy. Treatment is targeted to the specific pathology, which is usually diagnosed from a thorough history, physical examination, and detailed laryngoscopy, but may also require more specific laboratory or radiologic examination.

INFECTIONS OF THE LARYNX

Viral Laryngitis

The most common cause of infectious laryngitis is viral (1). Viral laryngitis is typically self-limited with a normal duration of 5 to 7 days (2). Patients are usually dysphonic but may also present with odynophagia. History may include a viral prodrome with upper respiratory tract symptoms and physical examination usually demonstrates edematous, erythematous vocal folds (Fig. 67.1) with loss of normal vibratory pliability. Treatment includes supportive care with hydration and removal of laryngeal phonotory trauma (phonation and coughing, pollutants). The most common viral pathogens in the upper respiratory tract include rhinovirus, influenza A, B, C, and parainfluenza viruses. Patients with substantive vocal fold edema from viral laryngitis are at increased risk of repetitive phonotrauma leading to more significant vocal fold injury, such as midmembranous vocal fold lesions, epithelial and subepithelial trauma/ulceration, and scar (3). As such, these patients should ideally be limited to relative or absolute voice rest. Evidence suggests that anti-inflammatory medication may decrease subjective discomfort and decrease odynophagia, but one would not expect such treatment to decrease duration of illness as it could not affect the underlying viral etiology (4). Systemic corticosteroids may be utilized judiciously to treat moderate to severe laryngeal edema associated with very substantial symptoms, especially in patients with significant vocal demands that cannot be mitigated with behavioral modification. Antibiotics are not indicated in patients presenting with symptoms typical of viral laryngitis (1). Acute dysphonia lasting longer than 2 weeks is unlikely to result from viral laryngitis, and other etiologies should be investigated, including a detailed laryngoscopy.

Bacterial Laryngitis

Although rare, the physician should begin to consider a bacterial etiology when the supportive measures discussed above fail to decrease symptoms or if symptoms worsen after an initial plateau of symptoms. Initial clinical presentation may be similar to that of viral laryngitis, but supraglottitis and epiglottitis may result. As with the pediatric population, these conditions require escalated care, given the potential for airway demise. The causative bacteria are also similar to those in the pediatric population and include *Haemophilus influenzae*, *Streptococcus* species, and *Staphylococcus* species. *Haemophilus* species remain the most common but methicillin-resistant *Staphylococcus aureus* infections have been reported (1,5–7).

Diagnosis relies on endoscopic examination (Fig. 67.2) of the larynx. Radiologic imaging may be used to supplement endoscopic evaluation, and findings can include the classic "thumb-print" sign of supraglottic inflammation. Treatment depends on the clinical presentation with attention focused on airway competence. In a recent study, only 2 of 10 adult patients with supraglottitis evaluated over a 6-month period required airway intervention (8). Despite the majority of patients not needing airway protection, increased work of breathing and/or stridor must



Figure 67.1 Acute laryngitis: note global laryngeal edema and erythema.

be given proper credence. Medical treatment is targeted to the pathogen identified by culture. Additional supportive measures such as hydration and steroids are indicated (9).

Though not common in the United States, rhinoscleroma can also affect the larynx. Caused by *Klebsiella rhinoscleromatis*, patients tend to have laryngeal involvement (13/22 patients) and may need emergent tracheotomy to maintain airway patency (3/13 with laryngeal involvement) (10). In that series, all tracheotomy patients were decannulated with appropriate antibiosis. Pathologic examination demonstrates the gram-negative coccobacillus of *Klebsiella* on culture, as well as Mikulicz cells on mucosal biopsy.

Fungal Infection

Fungal laryngitis often occurs in immunocompromised patients, such as patients with systemic causes for immunosuppression (HIV, chemotherapy, diabetes, etc.) and individuals who are locally immunocompromised because of steroid inhaler use (11). Such infections are overwhelmingly candidal in etiology and will respond to systemic antifungal treatment (11,12). Patients will present with laryngopharyngeal symptoms, such as dysphagia and dysphonia. Physical examination demonstrates white plaque-like epithelial lesions of the mucosa surfaces, which may be focal or diffuse (Fig. 67.3). Conservative treatment with a systemic antifungal and a topical antifungal are appropriate, but short-interval evaluation is necessary to assess resolution as persistent lesions merit biopsy and possible culture of lesions.

Though the majority of fungal infections are *Candida sp.*, other fungal organisms, such as blastomycosis, coccidioidomycosis, and histoplasmosis may also infect the larynx. These infections target immunocompromised patients as seen with *Candida sp.* infections but tend to occur in endemic geographic regions. Blastomycosis and histoplasmosis are prevalent in the Mississippi and Ohio River valleys, and coccidioidomycosis is endemic in the southwestern United States and Central America. However, patients may become infected outside of endemic areas (13). Biopsied lesions require culture with periodic acid Schiff and histologic examination to evaluate possible granulomatous conditions such as tuberculosis (14). Hematoxylin and eosin (H&E) staining demonstrates pseudoepitheliomatous hyperplasia with possible ulceration. Microscopic broad-based budding cells are a pathognomic feature of blastomycosis. Clinically, patients can present with a range of symptoms and physical exam findings, spanning from dysphonia to occult airway compromise (15,16). Treatment involves long-term systemic antifungal therapy with agents such as amphotericin or triazole.

Mycobacterial Infection

Laryngeal tubercular infection from *Mycobacterium tuberculosis* is classically associated with active pulmonary disease but can present as isolated laryngitis (17,18). Laryngeal



Figure 67.2 Bacterial laryngitis: note posterior glottic purulence.



Figure 67.3 Fungal laryngitis: note white fungal plaques with marginal erythema on midmembranous vocal folds.

M. tuberculosis infections follow similar natural history to pulmonary tuberculosis and most commonly present as lesions in the posterior glottis. Patient factors include increased prevalence in underdeveloped countries, areas of over-crowding and communal living, and immunocompromised populations. While laryngeal infections present with similar symptoms as pulmonary infections (cough, hemoptysis, unintentional weight loss, fever, night sweats), patients may also present with laryngopharyngeal symptoms such as dysphonia, dysphagia, and odynophagia. Physical examination can demonstrate exophytic masses that mimic malignancy (19,20). Pathologic examination demonstrates caseating granulomas that are pathognomonic to *M. tuberculosis* infection. Treatment is targeted with multidrug regimens with culture guidance, as multidrug resistant *M. tuberculosis* strains are on the rise.

Other Infections

Less common infections of the larynx include leprosy and syphilis. *Mycobacterial leprae* and *Mycobacterium lepromatosis*, the causative infectious agents of leprosy, cause dramatic systemic and laryngeal epithelial changes. As with the other laryngeal infections, patients can present with variable severity in symptoms, with the most severe being occult aspiration or complete upper airway obstruction requiring tracheotomy (21,22). The World Health Organization recommends multidrug treatment with combinations of dapsone and rifampin with possible adjunctive clofazimine.

Syphilis is caused by *Treponema pallidum* infection and generally presents in stages. The primary stage generally presents to the otolaryngologist as a painless oropharyngeal chancre. During the secondary stage, patients can present with laryngeal manifestations, including leukoplakia, exophytic mass(es), and very rarely, decreased vocal fold mobility (23,24). Diagnosis involves serologic studies (venereal disease research laboratory or rapid plasma regain) and/or dark-field microscopy to visualize the pathopneumonic spirochetes sampled from suspect mucosal lesions. The mainstay of treatment is penicillin. For those patients with penicillin sensitivities, definitive allergy testing and desensitization may be required prior to treatment.

Idiopathic Ulcerative Laryngitis

Idiopathic ulcerative laryngitis (IUL) was first described in 2000 and a large clinical series was presented in 2011 (3,25). This condition involves dysphonia and severe cough following an upper respiratory tract infection and ulceration(s) of the midmembranous vocal fold. IUL appears to occur more in females than males (3). An etiologic agent(s) has not been identified and medical therapy with antibiotics, antifungal, and proton pump inhibitors are typically used but without an obvious positive response. These patients should be observed with serial office endoscopy (preferable video recorded) and the urge to perform a biopsy should be resisted. Biopsy will most likely be nondiagnostic and result in scar formation at the ulcer site. Patients should be counseled regarding the duration of the condition (average 3.3 months with a range from 2 to 10 months) and the possibility of vocal fold scar formation following the resolution of the ulcer(s) (3). If progression of the ulcer(s) occurs during serial examination a biopsy may be warranted.

INFILTRATION OF THE LARYNX

Multiple inflammatory processes can affect the larynx. These differ in their underlying presentation and pathologic and histologic features. As a group, these conditions generally cause decreased vocal fold pliability and/or lesions of the vocal folds, supraglottis, or subglottis. Symptoms correspond to the severity of vocal fold infiltration and potentially degrees of airway compromise.

Wegener Granulomatosis

Wegener granulomatosis is associated with necrotizing granulomatous inflammation and vasculitis of small blood vessels. The disease tends to affect the upper airway, the lungs, and the kidneys (26). The otolaryngologist may identify a patient because of nonhealing ulcers in the nasal cavity or, more rarely, subglottic airway stenosis. Diagnosis relies on thorough physical examination, nasal and laryngeal endoscopy, and testing for classical antineutrophil cytoplasm antibody (c-ANCA). Interestingly, 10% to 20% of those with airway symptoms have been reported to have a negative c-ANCA test (26).

The best treatment for these patients involves a multidisciplinary approach. Medical management with systemic corticosteroids and/or cyclophosphamide is used to obtain remission, and medications such as methotrexate, trimethoprim methoxazole, or azathioprine are used for maintenance therapy (26). Surgical treatments include subglottic expansion (subglottic releasing incisions with balloon or rigid dilation) and intralesional injection of corticosteroids (27). Subglottic stenting is generally avoided in favor of tracheotomy for recalcitrant presentations (28). In the setting of inactive Wegener granulomatosis with resultant subglottic stenosis, cricotracheal resection is also a viable treatment option.

Rheumatoid Arthritis

Rheumatoid arthritis affects millions of people worldwide with a predilection for females. It affects the larynx in just over one-fourth of cases (29). In comparison to unaffected control subjects, patients with rheumatoid arthritis had more frequent loss of higher frequency phonation, generalized dysphonia, decreased vocal fold mobility, and

laryngeal edema (30). These symptoms are modulated by the active status of the patient's disease. Active rheumatoid arthritis tends to present with a substantial laryngitis with erythematous arytenoid mucosa (30–32). Chronic rheumatoid arthritis also selectively targets the arytenoid cartilages, but more specifically seems to affect the cricoarytenoid joint causing ankylosis and possible joint fixation (26). Patients may also present with rheumatoid nodules, also known as bamboo nodes, which are focal subepithelial lesions, typically on the superior surface of the membranous vocal fold. Treatment of rheumatoid arthritis relies upon medical management with immunomodular and anti-inflammatory treatments. Although outcomes data are sparse, surgical management may be indicated to manage airway symptoms or to judiciously remove rheumatoid nodules to improve phonation (32,33). (See Chapter 68) Alternatively, serial vocal fold steroid injections are a less-invasive treatment that may improve vocal outcome (34).

Amyloidosis

Amyloidosis is an autoimmune condition characterized by extracellular deposition of fibrillar proteins in affected tissue. Laryngeal involvement is rare and may not be associated with primary systemic amyloidosis. However, laryngeal amyloidosis may be present in conjunction with other systemic conditions such as multiple myeloma (35,36). Patients usually present with bulky deposition of amyloid protein with variable degrees of infiltration of the vocal fold, paraglottic space, and the supraglottis. Presenting features include cough, dysphonia, dysphagia, and possible stridor. Biopsy is required for diagnosis as amyloid has a pathognomonic apple green birefringence after staining with Congo red (Fig. 67.4). Referral is needed to examine for underlying secondary causes, such as systemic amyloidosis. There are reports of complete resolution with radiation therapy, but this treatment modality has not gained mainstream acceptance (37). Surgical intervention is usually undertaken to address specific symptoms and can improve vocal deficits. Recurrence is quite common (38).

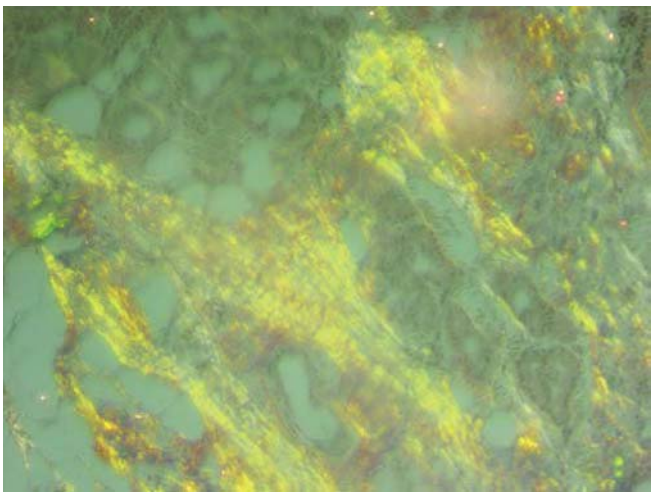


Figure 67.4 Amyloidosis after Congo red staining: note apple-green birefringence with polarimetric filtered microscopy.

Relapsing Polychondritis

Relapsing polychondritis is characterized by intermittent recurrent episodes and inflammation of cartilaginous structures. While the ears and nose are most commonly affected, the larynx can also become involved. Early studies demonstrate 14% of patients have laryngeal involvement at presentation but that up to half of patients eventually develop airway symptoms (39). Radiographic studies, such as magnetic resonance imaging (MRI) and computed tomography (CT) can identify cartilaginous changes. Patients may present to the otolaryngologist with ear, nasal, and/or airway complaints such as exertional dyspnea or stridor. Purulent chondritis of the laryngeal framework has been described as a sequela of superimposed infection (40). Medical management is paramount as maintenance includes low dose corticosteroids and/or methotrexate. Dapsone has also shown to be beneficial (41). Surgical intervention may be indicated to secure the airway with tracheotomy. A small case series of patients underwent airway reconstruction to provide more long-term airway stability (42).

Systemic Lupus Erythematous

Like rheumatoid arthritis, systemic lupus erythematous (SLE) has a predilection for females. Its effects are not usually limited to the larynx as roughly two-thirds of patients never experience laryngeal symptoms. Patients can present with a wide variety of laryngopharyngeal complaints, which include dysphonia and dyspnea. A study including 12 patients with SLE found that 11 had laryngeal abnormalities (43). Physical signs ranging from edema or ulceration to vocal fold paralysis can be seen on examination (44). However, a direct causal relationship between SLE and the above laryngeal pathology has yet to be demonstrated.

Pemphigus and Pemphigoid

Pemphigus and pemphigoid are related autoimmune conditions differentiated by the target of their autoantibodies. While both conditions lead to a robust inflammatory reaction that can possibly lead to epithelial injury, pemphigus autoantibodies are directed against intraepithelial targets while pemphigoid autoantibodies target subepithelial antigens. Immunofluorescence of tissue biopsy is used to identify the characteristic autoantibodies for definitive diagnosis.

Patients may present with signs of disease within the nasal cavity or the larynx. The prevalence of laryngeal involvement seems to differ between the diseases for unknown reasons. One study demonstrated that 21 of 53 (40%) patients with head and neck manifestations of

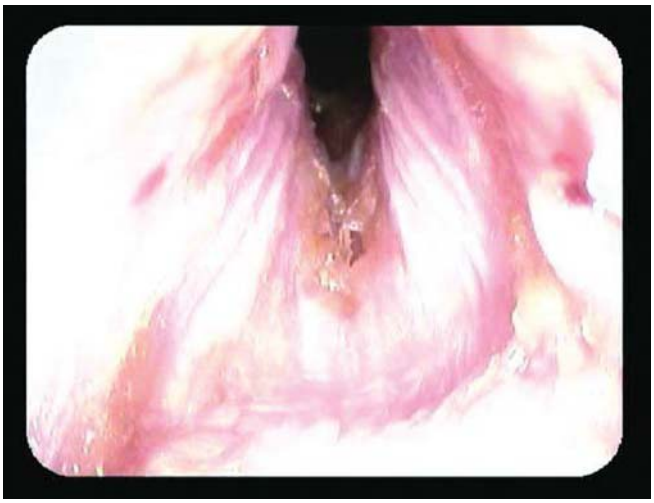


Figure 67.5 Laryngeal pemphigus in typical supraglottic location.

pemphigus had laryngeal involvement (45). However, a separate study of pemphigoid patients demonstrated that 10 of 38 (26%) patients with head and neck symptoms had laryngeal involvement (46). Other studies have demonstrated relatively similar prevalence in pemphigus (47). Both pemphigus and pemphigoid appear to have a predilection for supraglottic mucosa (Fig. 67.5). High-dose corticosteroids are utilized to control active disease and are decreased for maintenance therapy. Other immunomodulators, such as azathioprine, cyclophosphamide, and cyclosporine, have also been utilized for medical management. Surgical intervention is limited to diagnostic biopsy and/or airway intervention, such as tracheotomy or less invasive airway surgery (dilation) to provide a stable airway.

Sarcoidosis

Sarcoidosis is an autoimmune condition defined pathologically by noncaseating granulomas. Patients most commonly affected are young adult African American women. Laryngeal involvement is seen in 3% to 5% of cases and usually affects the supraglottis (Fig. 67.6) (48). Laryngeal complaints from sarcoidosis, such as nonproductive cough and dyspnea, may be difficult to differentiate from the pulmonary manifestations of the disease. Diagnosis of sarcoidosis relies on multiple modalities as there are usually multiple organ systems involved. The establishment of laryngeal sarcoidosis relies on laryngoscopic evaluation, with hallmark exam findings of submucosal infiltration in the infraglottic, paraglottic space, and the supraglottis. Involvement of the epiglottis leads to a distortion and thickening and has been commonly referred to as a turban epiglottis. Sarcoidosis remains an elusive diagnosis; however, biopsy of lesions classically reveals noncaseating granulomas.

Treatment mainly relies on corticosteroids, but other immunomodulators, such as azathioprine, have also been administered with good treatment success (49). Surgical intervention is limited to diagnostic biopsy, excision of symptomatic lesions, or management of obstructive airway lesions.

External Beam Radiation

As the role of external beam radiation has increased for the treatment of head and neck malignancies, many of these patients later present with laryngopharyngeal complaints, such as dysphonia, dysphagia, and globus sensation post-treatment. Electron beam radiation induces gradual, dose-dependent fibrotic changes to include muscle atrophy and fibrosis in the larynx as well as desiccation of mucosa (Fig. 67.7). Fibrosis within the lamina propria can be appreciated as decreased mucosal pliability on stroboscopy. Patients will exhibit atrophy that is disproportionate to their expected age-related vocal fold volume loss. Vocal fold hypervascularity is a common finding due to prior vasculitis incurred during radiation therapy. Improvement in voice is commonly reported following laryngeal radiation for early laryngeal cancer, but voice outcomes associated with late radiation fibrosis of the vocal folds remains

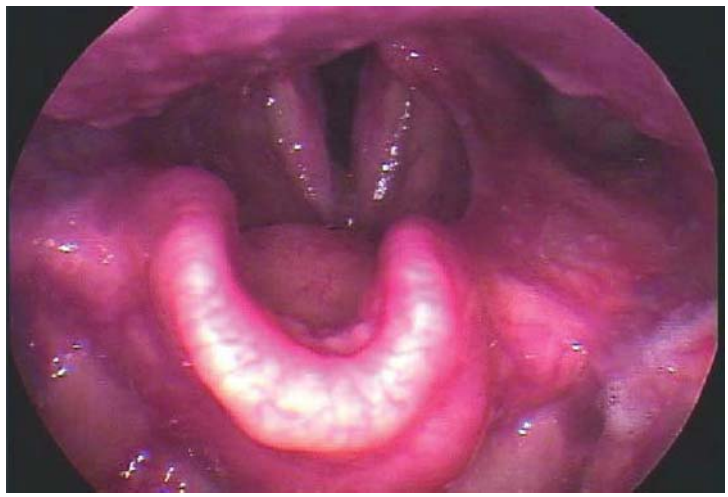


Figure 67.6 Sarcoidosis in typical supraglottic location.



Figure 67.7 Radiation effects on the larynx: note global erythema, slight atrophy of muscular anatomy, and limited light reflex indicating decreased secretory function of the mucosa.

uncertain (50,51). A prior report of postradiation vocal quality suggests that vocal fold stripping or excisional biopsy rather than limited biopsy for initial diagnosis and continued tobacco smoking after treatment are significantly associated with an increased risk of perceived worse voice quality after treatment (52).

As radiation oncologists develop more sophisticated techniques to avoid collateral damage to uninvolved structures, the extent of radiation changes may decrease.

BENIGN NEOPLASIA OF THE LARYNX

When one excludes nonneoplastic vocal fold lesions, such as vocal fold polyps, nodules, and cysts (see Chapter 68), benign tumors of the larynx are varied and quite rare. Diagnosis relies on thorough history with appropriate examination and imaging.

Hamartoma

Hamartomas are rare, benign lesions that can present as congenital malformations or lesions later in life. They are generally loosely organized neoplasms with multiple types of tissue, all of which are native to the affected subsite of the larynx. Hamartomas can be incidentally identified or cause significant airway symptoms, especially in a young child. Presentation and symptomatology are related to the location of the neoplasm, and hamartomas have been mostly commonly identified in the supraglottis and subglottis (53,54). Excisional biopsy is both diagnostic and curative if resection is complete (55).

Chondroma

Chondromas are benign tumors consisting of cartilaginous cells. They are slow-growing lesions that do not metastasize, and they generally present as a smooth, submucosal lesion. Laryngeal chondromas may be difficult to differentiate from low-grade chondrosarcomas and clinically follow a similar course. While the bulk of these tumors present within the posterior cricoid cartilage, lesions have been found within other subsites of the larynx as well as the hyoid bone (56,57). Patients may be relatively asymptomatic, but lesions can cause airway obstruction or external neck masses (56). CT is generally the preferred imaging modality to define the extent of the lesion (58). Surgical excision is the treatment of choice for chondromas. Surgery has been traditionally performed via open procedures involving laryngofissure, but, more recently, endoscopic ablation techniques have been shown to be successful (59). Comparative efficacy between open and endoscopic surgical excision is unknown.

Rhabdomyoma

Rhabdomyomas of the larynx are benign tumors comprising striated muscle. Laryngeal involvement is the most common location for rhabdomyomas of the head and neck (60). These tumors present in variable locations within the larynx and have been documented to involve both intrinsic and extrinsic laryngeal musculature (61,62). Diagnosis with biopsy or magnetic resonance is indicated, and complete resection is curative.

Respiratory Papillomatosis

Though primarily seen in the pediatric population, adult-onset recurrent respiratory papillomatosis (RRP) is not an uncommon presentation. For further information regarding juvenile onset RRP, please refer to Chapter 94.

Caused by human papillomavirus (HPV) subtypes 6 and 11, RRP occurs most commonly at the level of the vocal folds. The virus can be transmitted vertically or by sexual transmission. RRP can present anywhere within the upper aerodigestive tract from the nasal vestibule to the bronchioles with a predilection for areas of transition from pseudostratified columnar to stratified squamous epithelium.

Lesions can be relatively small, noticeable only because of resultant dysphonia from decreased vocal fold mucosal wave propagation, dysphonia related to mass-effect that impairs glottal closure, or variable degrees of airway obstruction (Figs. 67.8 and 67.9). Though benign, they do have significant morbidity and have the potential for malignant transformation (63,64). A recent study including 54 adults demonstrated that dysplasia was identified in 50% of patients, and dysplasia was diagnosed on biopsy specimens at an average of 16.2 months from initial diagnosis. Of the initial 54 patients, 3 progressed to carcinoma *in situ* while 1 patient progressed to squamous cell carcinoma (64). Use of inhaled corticosteroids, increasing number of procedures, distal spread of disease, and previous exposure to cidofovir have been implicated as risk factors for dysplastic reaction (65). In addition, history of



Figure 67.8 Adult RRP occluding anterior glottis, limiting phonation.

radiation therapy, cigarette smoking, and systemic immunosuppression have been implicated in malignant transformation (66).

The verrucous papillomatous growth of the lesions are pathognomonic. Though multiple treatment modalities are available, conservative removal of disease is the first-line treatment. If cold instrumentation is to be utilized, careful attention must be dedicated to only removing the papilloma and leaving the superficial lamina propria undisturbed. Ablation with CO_2 or potassium titanyl phosphate (KTP) lasers has also been shown to be a successful treatment modality for both initial and subsequent treatments (67). A great benefit of fiber-based laser treatment is that it can be performed in an awake patient using a channeled endoscope through which the fiber can be advanced. Awake procedures decrease use of operative resources and eliminate the need and dangers of general anesthetic. Regardless of the surgical technique utilized, the physician must avoid deepithelialized surfaces in juxtaposition to avoid anterior glottic webbing and/or posterior glottic stenosis.



Figure 67.9 Adult RRP nearly occluding entire glottis.

While surgical removal of lesions remains the first-line treatment for RRP, other adjuvant therapies have been developed. Cidofovir is an antiviral shown to decrease disease burden in both intralesional injection and inhaled forms (68,69). Both treatment modalities have been shown safe, but hepatotoxicity has been identified with the injected form. Interferon-alpha and indole-3-carbinol (an extract found in cruciferous vegetables) have both been used to control disease propagation (70).

The United States Food and Drug Administration (FDA) approved Gardasil, a vaccination against HPV subtypes 6, 11, 16, and 18, in June of 2006 as a means of potentially preventing cervical cancer. While cervical cancer is mainly caused by HPV subtypes 16 and 18, the vaccination against subtypes 6 and 11, could drastically affect the prevalence and presentation of RRP. Currently, there is no definitive association between vaccination and disease modulation, thus vaccination is not presently indicated in patients with prior exposure (71).

Hemangioma

Laryngeal hemangiomas are more prevalent in the pediatric population, and this is presented in Chapter 104. In contrast to pediatric hemangiomas, which usually present in the subglottis, adult laryngeal hemangiomas present in the supraglottis (Fig. 67.10) (72). Hemangiomas are usually asymptomatic but can cause airway obstructive symptoms (73). As these are incredibly rare tumors, no standardized treatment exists. A conservative approach emphasizing medical management with either corticosteroids or radiation therapy was historically advocated. Though successful in the pediatric population, laser ablation was initially avoided in adults for concern that the vasculature would exceed CO_2 laser coagulation capacity. However, a report of four laryngeal hemangiomas ablated without incident calls that initial theory into question (74). Propanolol has also been successful in treating laryngeal hemangiomas in children, but there are no reports of its use in the adult population (75).

Benign Salivary Neoplasia

Pleomorphic adenoma, a benign salivary neoplasm, may arise within the larynx. Scattered case reports identify fewer than 20 instances within the literature. More than half of the cases appeared in the supraglottis, and patients most commonly present with dysphonia. Surgical resection was reported as curative, though follow-up was limited (76).

Fibroma

Laryngeal fibromas are exceedingly rare with fewer than a dozen cases reported. Histologic examination demonstrates abundant extracellular matrix with interspersed

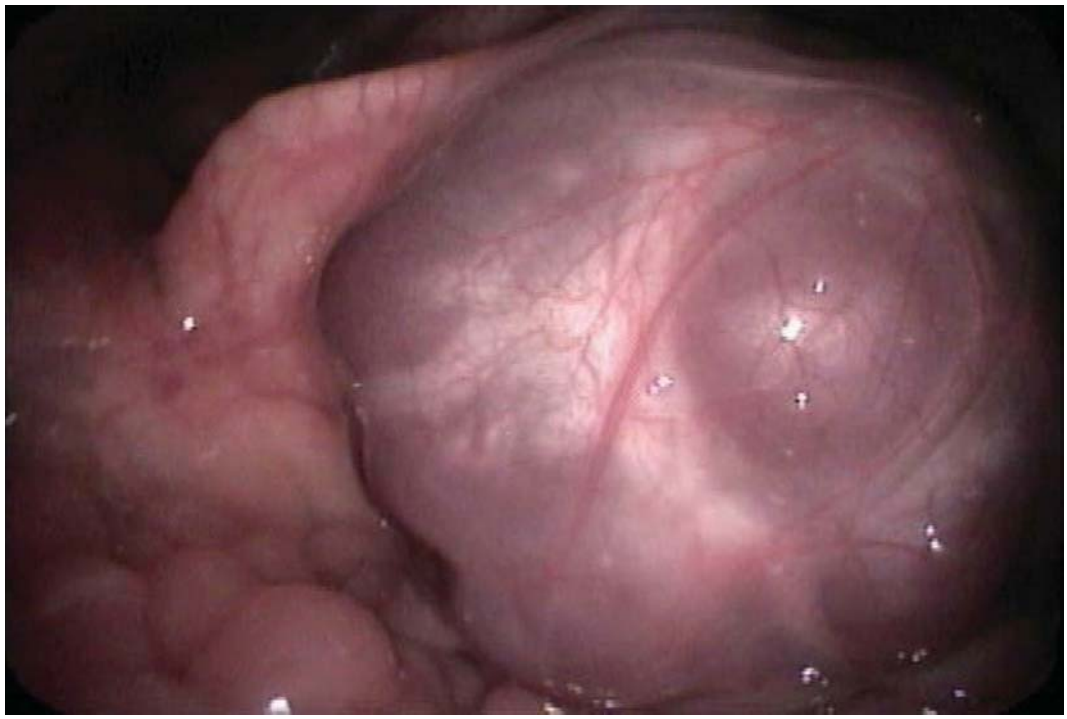


Figure 67.10 Adult supraglottic hemangioma. Cobblestone-appearing lingual tonsils are visible at the inferior aspect of this image. The epiglottis is completely obscured by this hemangioma.

paucicellular areas, and the extracellular matrix tends to be composed of "cytologically bland spindle cells." The reported cases all appear to be isolated lesions that presented with dysphonia and cough (77). Radiographic imaging (CT and MRI) can delineate the full extent of the lesion in planning for surgical resection. Excision with margins is advocated to minimize chance of recurrence (78).

Schwannoma

Schwannomas arise from nerve sheath fibers and account for less than 1% of all laryngeal tumors. The endoscopic appearance may be mistaken for a laryngocele and commonly appear as smooth submucosal mass within the pyriform sinus or aryepiglottic space (79). Patients may present with globus sensation, dysphagia, dysphonia, and if large, airway obstruction (80). Imaging with CT and/or MRI help to plan surgical resection. Histopathologic examination demonstrates the classic Antoni A and Antoni B areas seen with other schwannomas. The associated nerve was not identified in the available case reports. Some patients have postoperative dysphonia and vocal fold paresis, possibly implying recurrent laryngeal involvement (79).

Granular Cell Tumor

Granular cell tumors can occur anywhere within the body but are often seen within the head and neck (81). The larynx, however, is a rare location for these neoplasms. They are neural in derivation and, within the larynx, tend to grow slowly and isolate within the vocal folds themselves. Presenting symptoms include hoarseness, stridor, dysphagia, and cough. Biopsy must be completed to evaluate for malignant neoplasm as there is an association with pseudo-epitheliomatous hyperplasia, which can mimic squamous cell carcinoma. Serologic staining of biopsy specimens will yield positive results for S-100, neuron-specific enolase, vimentin, and CD 68 (81). Complete resection with microlaryngeal phonosurgical instruments and principles can yield cure with good vocal outcome.

LARYNGOCELES AND SACCULAR CYSTS

While laryngoceles and saccular cysts are not neoplasms, they present as benign appearing masses in the larynx. The laryngeal saccule is a mucous gland containing appendage that lies between the false vocal fold and the thyroid cartilage. It is an out pouching of the normal laryngeal ventricle and extends as a blind-ended sac posterolateral to the edge of the laryngeal surface of the epiglottis. The function of the saccule is unknown although it has been theorized that it may represent a vestigial air sac. Both laryngoceles and saccular cysts involve expansion of the saccule to form a mass. Laryngoceles by definition must have air contained within their lumen, while saccular cysts are strictly fluid-filled masses.

Laryngoceles contain air due to patent communication with the laryngeal lumen. Further classification of laryngoceles depends on their location. They can be defined as

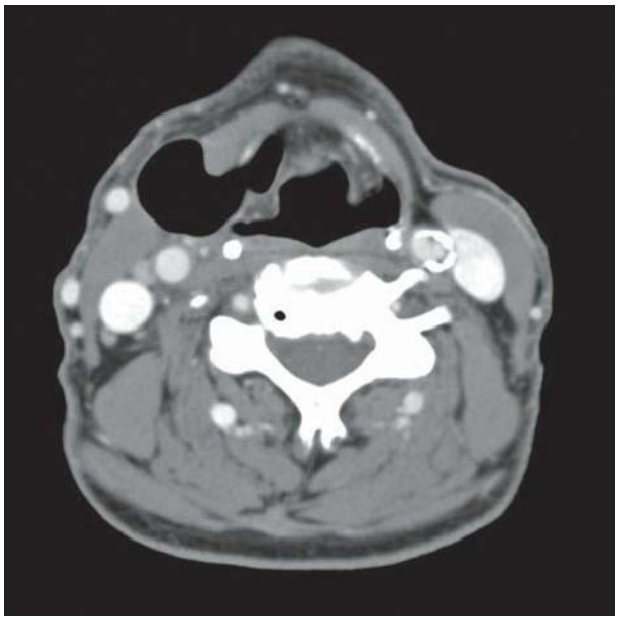


Figure 67.11 Combined laryngocele. Axial CT showing air-filled dilation of the saccule extending through the thyrohyoid membrane into the neck.

internal, external, or combined. Internal laryngoceles are strictly confined within the thyroid cartilage, external laryngoceles lie exclusively outside the cartilaginous laryngeal framework, and combined laryngoceles span both the inside and outside of the thyroid cartilage (82,83) (Fig. 67.11).

Saccular cysts are also classified according to their location; anterior and lateral. Anterior saccular cysts appear as rounded fluid-filled masses emanating from the anterior portion of the ventricle and extend medially into the lumen of the larynx (Fig. 67.12). They lie superior to the glottal level at or near the anterior commissure, and interfere with phonation or airway depending on their size. Lateral saccular cysts expand within the paraglottic space and appear similar to internal laryngoceles as a submucosal fullness in the ventricular fold.

Although the etiology of saccular masses is unclear, they result from abnormal dilation of the saccule. It has been suggested that those who routinely develop high transglottic pressures (glass blowers, trumpet players) are at a higher risk of developing laryngoceles. It is thought that saccular cysts arise secondary to obstruction of the saccular orifice as they have been found in patients with laryngeal carcinoma or following an upper respiratory tract infection (84). Congenital saccular cysts can occur in infants and present as a weak cry, stridor, or cyanosis (83).

Patients with laryngoceles and saccular cysts report symptoms consistent with a laryngeal mass: dysphonia, stridor, chronic cough, a neck mass, and occasionally dysphagia. Severity of symptoms depends on the size and location of the lesion. Small or nonobstructing lesions may be asymptomatic. The diagnosis is most commonly made by physical examination including transnasal or transoral laryngeal imaging and neck exam. In the case of



Figure 67.12 Anterior saccular cyst. Fluid-filled mass arising from the saccule and protruding into the laryngeal lumen.

anterior saccular cysts, a mass can be seen emanating from the vestibule to the laryngeal lumen while lateral saccular cysts and laryngoceles present as a submucosal mass in the false vocal fold. External and combined laryngoceles can present as a neck mass that enlarges with valsalva. Both laryngoceles and saccular cysts can become acutely infected to form a laryngopyocele or an infected saccular cyst. Super-infection can lead to rapid expansion and acute presentation with worsening symptoms, fever, and occasionally, airway obstruction.

Fine-cut CT is a useful adjunctive tool diagnostically. The presence of air within the lesion differentiates laryngoceles from saccular cysts. The location and extent of the lesion can be accurately assessed with a fine-cut CT scan. Endoscopic excision of these lesions is the mainstay of treatment and the recurrence rate is very low with long-term follow up (84).

SUMMARY

The larynx can be subject to infectious agents, inflammatory conditions, and neoplasia. The initial management of the patient must be to ensure a stable, secure airway. Once the airway is ensured, a thorough history and physical examination, followed by detailed laryngeal endoscopy

and directed biopsy, can usually narrow the differential diagnosis and guide the physician to appropriate diagnostic testing. Treatment should address the patient's symptoms and ideally ensure both airway stability and future vocal performance.

HIGHLIGHTS

- Multiple infections, inflammatory, and benign processes can affect the larynx. Each has its own unique presentation and treatment considerations.
- Infectious laryngitis is most commonly viral in etiology, and should be initially treated with voice rest and supportive measures in most cases. Bacterial, fungal, and mycobacterial infection is considerably more rare.
- Inflammatory and infiltrative processes of the larynx can occur from Wegener granulomatosis (typically subglottic involvement), sarcoidosis (typically supraglottic involvement), amyloidosis, and autoimmune processes (such as rheumatoid arthritis, SLE, and pemphigus/pemphigoid)
- The most common benign neoplasm of the larynx is laryngeal papillomatosis. Laryngeal chondromas, hamartomas, schwannomas, fibromas, pleomorphic adenomas, and granular cell tumors are far more rare.

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Benign Vocal Fold Lesions and Phonomicrosurgery

68

John W. Ingle *Clark A. Rosen*

Benign vocal fold lesions are a common cause of dysphonia. Their diagnosis and subsequent care can be a complex and important quality-of-life issue to individuals who suffer from this set of disorders. The ability to communicate without dysphonia is important to the population at large for both occupational and social reasons. A growing percentage of the occupations in the world are voice and communication dependent as opposed to labor dependent; thus, it is vital to have the ability to use the voice throughout the day in a clear, efficient manner without voice loss or without causing undue negative attention because of dysphonia (1).

The overriding treatment principle for caring for patients with benign vocal fold lesions is the assessment and improvement of the patient's functional status regarding an ability to communicate with the voice. Many ways exist to improve the functional status of the voice, including treatment of associated medical conditions, voice therapy (see Chapter 71), and surgery. This chapter is designed to discuss a variety of benign vocal fold lesions that commonly cause dysphonia from the categories of epithelial lesions, lamina propria pathology, and vascular pathology. A large portion of benign vocal fold lesions and subsequent dysphonia arise from lesions of the lamina propria due to presumed greater sensitivity to trauma associated with inflammation, coughing, voice misuse, and/or voice overuse. Over the last several decades, a specialized form of laryngeal microsurgery—phonomicrosurgery—has evolved. The principles and concepts of this type of surgery are presented below.

BENIGN EPITHELIAL LESIONS OF THE VOCAL FOLD

Epithelial abnormalities of the vocal folds are caused by infectious processes (fungal), keratosis of the epithelium, papillomatous growth of the epithelium, or malignant degeneration of the epithelium. Infections, papillomatosis, and cancers of the epithelium of the vocal fold are covered in other chapters of this book (Chapters 66, 67, 94, and 123). Nonmalignant epithelial abnormalities can be grouped under the category of keratosis. Keratosis includes both white (leukoplakia) and red (erythroplakia) lesions of the vocal folds. The terms "leukoplakia" and "erythroplakia" are descriptive only and have no prognostic or diagnostic value. The primary concern of keratotic lesions of the vocal folds is the potential for these lesions to transform from a benign process to a malignant process. The clear etiologic factors for the formation of these lesions and potential for their subsequent transformation is not clear. Irritation from tobacco smoke has been implicated. In addition, vocal misuse and overuse and irritation from refluxed gastric contents (laryngopharyngeal reflux disease) have also been scrutinized and associated with the development of keratotic lesions of the vocal folds.

The diagnosis and treatment of keratotic lesions include a careful diagnostic evaluation including microlaryngoscopy with high-power magnification and excisional biopsy to rule out a malignant process. This is done best using the principles and approaches of phonomicrosurgery, specifically microflap surgery, to remove the keratotic lesion of the vocal fold in a controlled, conservative, subepithelial, and oriented fashion (see below). After a definitive diagnosis has been made, management includes removal of the most common etiologic agents, tobacco smoke exposure, laryngopharyngeal reflux disease, and vocal abuse (see Chapters 21, 66, and 71).

Vocal misuse and overuse can be related to the patient's phonatory pattern, environment, and overall demands. In addition, a theory of excessive vocal fold collision and impact forces created to attempt to compensate for glottal insufficiency leading to keratosis is held by some. The glottal insufficiency can be caused by vocal fold atrophy, paralysis, paresis, or scarring. Until the underlying glottal

insufficiency is addressed with an augmentation procedure (medialization laryngoplasty or vocal fold injection augmentation), the keratotic activity will persist and recur following excision. Often the glottal insufficiency is not recognized and it results in recurrent keratosis following surgical excision. This theory has never been validated but should be considered in the most recalcitrant cases of keratosis.

Close observation and photo documentation of keratotic lesions are essential for long-term care and treatment of patients with this disease. Once infectious and malignant processes have been ruled out, patients can be observed in the office with serial examinations and especially helped with the aid of photo documentation to monitor for any specific change in the nature of the keratotic lesion(s). If the patient does not have significant functional limitation from the keratosis and the lesion is stable, repeated surgical removal is not indicated. Any discrete change in the nature, size, or location of the keratosis should prompt a surgical excision of the keratotic lesion(s) for pathologic review (2).

BENIGN LESIONS OF THE VOCAL FOLD LAMINA PROPRIA

Midmembranous Vocal Fold Lesions

The lamina propria of the vocal fold is a key component to vocal fold vibration and, thus, voice quality depends on the elastic properties of the lamina propria. The lamina propria is frequently injured by direct trauma, such as surgery, radiation therapy, or repeated collisional impact associated with phonation (vocal abuse). Most benign, midmembranous vocal fold lesions caused by trauma occur from repeated injury to the vocal fold lamina propria. Most of these lesions occur in the subepithelial space but also can be found near the vocal ligament. These lesions, which typically occur in the midmembranous vocal fold, are often bilateral. This region of the vocal fold has been termed "the striking zone," because of the theoretical concept of maximal vocal fold collision or impact forces resulting in their formation (3).

Benign, midvocal fold lesions cannot be defined by morphology and stroboscopy alone. Great difficulty in discussion and management of these lesions stems from the lack of accepted nomenclature for defining the lesions. This has resulted in great confusion and lack of clarity regarding etiology, diagnosis, and treatment. Without being able to clearly define distinct lesions within the larger group of benign vocal fold lesions of the lamina propria, it has been impossible to assess treatment methods and efficacy. To this end, a recent move has been made to implement a rigorous and clearly defined vocal fold lesion nomenclature paradigm (4). This classification scheme defines nine distinct benign midvocal fold lesions: (a) vocal fold nodules; (b) vocal fold polyp; (c) vocal fold cyst-subepithelial; (d) vocal fold cyst-ligament; (e) fibrous mass-subepithelial; (f) fibrous mass-ligament; (g) reactive vocal fold lesion; (h) nonspecific vocal fold lesion; and (i) pseudocyst. Outlined below is a brief description of each of these vocal fold lesions based on their morphologic appearance, stroboscopic pattern, response to voice therapy, and intraoperative findings. Please refer to Figures 68.1 to 68.12 for some examples of these lesions.

1. **Vocal fold nodules** are always bilateral and fairly symmetric. Their stroboscopic pattern shows normal or minimal reduction of the mucosal wave activity during stroboscopy. These lesions reduce in size or disappear in response to behavioral modification of voice use (voice therapy). Note any lesions that do not improve with behavioral modification are not vocal fold nodules. Refer to Figure 68.1 for an example of vocal fold nodules.
2. **Vocal fold polyps** can be unilateral or bilateral lesions and are typically exophytic lesions that are often clear in appearance or associated with a vocal fold hemorrhage and heme colored (hemorrhagic polyp). These lesions have minimal reduction of the mucosal wave vibratory activity on stroboscopy and typically do not change in size in response to voice therapy. Intraoperatively, these lesions are composed of gelatinous unorganized material in the subepithelial space. Refer to Figures 68.2 and 68.3 for examples of vocal fold polyps.
3. **Vocal fold cysts** can be unilateral or bilateral and located either near the ligament or in the subepithelial space. Practically, the subepithelial space is defined as the region immediately underneath the vocal fold epithelium. When the vocal fold pathology (cyst, polyp, or fibrous mass) is adherent to the undersurface of the microflap as it is elevated, it is located in the subepithelial space. When the pathology is located "deep" to the microflap following cordotomy, the pathology (cyst or fibrous mass) is classified as a ligamentous lesion. A vocal fold cyst does not respond to voice therapy and,

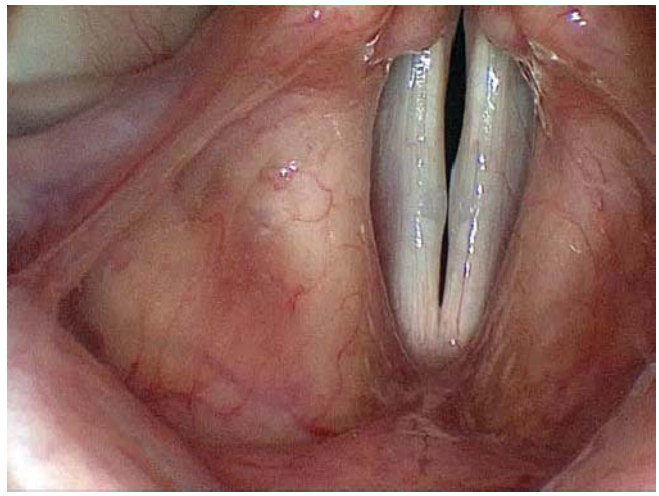


Figure 68.1 Vocal fold nodules.

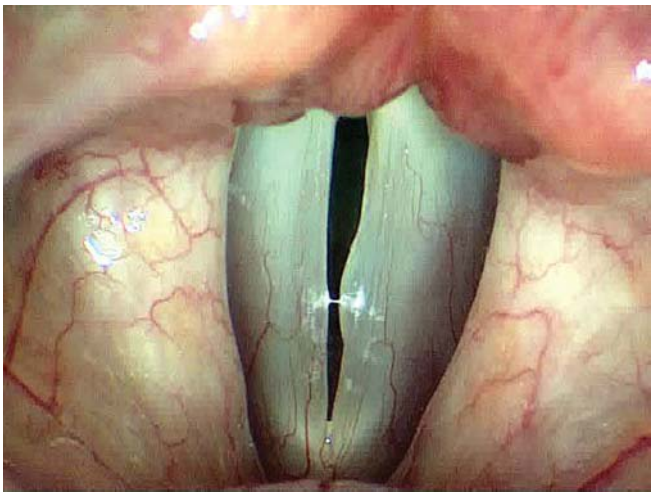


Figure 68.2 Vocal fold polyp.

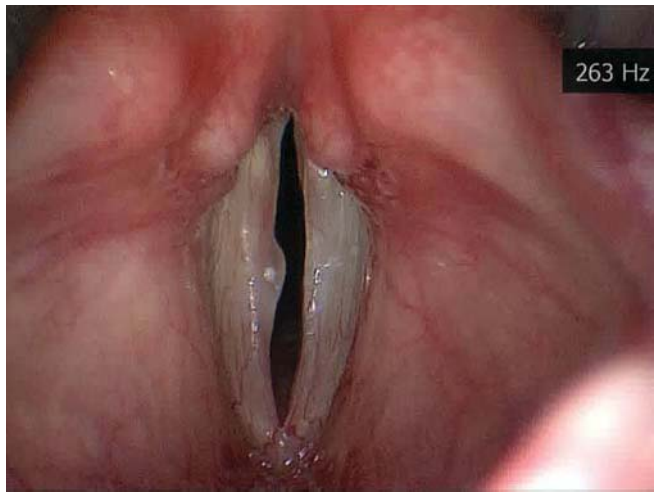


Figure 68.4 Vocal fold cyst-subepithelial.

depending on the location (subepithelial or ligament) and size, the stroboscopy pattern is either minimally impaired or significantly impaired (usually ligamentous). The intraoperative finding for a vocal fold cyst is the presence of a lesion with a distinct capsule in either of the above-described locations. Refer to Figures 68.4 to 68.6 for examples of vocal fold cysts.

4. **Fibrous mass of the vocal fold** is a lesion that can be unilateral or bilateral and can be located in the subepithelial or ligamentous area. These lesions do not respond to voice therapy and often induce a significant impairment in the mucosal wave activity during stroboscopy. Intraoperatively, the lesion is seen as a fibrous gray, unorganized, unencapsulated lesion in the midmembranous vocal fold in either the subepithelial or ligamentous region. Refer to Figures 68.7 to 68.9. These lesions often have thin extensions of the "fibrous material," extending anteriorly or posteriorly toward the anterior commissure or vocal process, respectively.

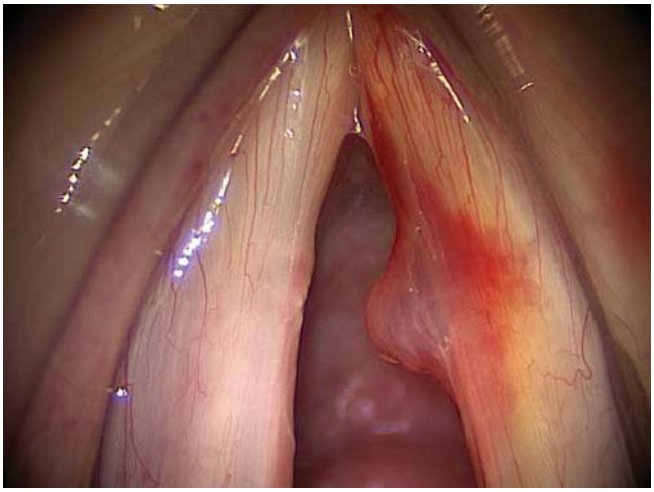


Figure 68.3 Vocal fold polyp (with associated hemorrhage).

5. **Reactive Vocal Fold Lesion**
   A reactive vocal fold lesion has good vibratory characteristics seen on stroboscopy and always occurs in response to a contralateral lesion (vocal fold polyp, vocal fold fibrous mass, vocal fold cyst). Commonly, the reactive lesion has an indentation where the contralateral lesion has created a concavity on the free edge of the lesion due to repeated trauma during vocal fold vibration. This appearance of the two lesions interdigitating with each other during vocal fold closure and vibration is often called a "cup and saucer" deformity. This lesion often will reduce in size with behavioral therapy. Refer to Figure 68.10 for an example of a left true vocal fold reactive lesion associated with a right true vocal fold polyp.
6. **Nonspecific vocal fold lesion**
   Nonspecific vocal fold lesion can be unilateral or bilateral, and is denoted by either subepithelial or ligamentous pathology that is not responsive to nonsurgical interventions (voice rest, medical therapy of comorbidities, and voice therapy) but does not impair function sufficiently to necessitate phonomicrosurgical removal. Thus, when a lesion is classified as a nonspecific vocal fold lesion, the clinician immediately knows that the patient has persistent vocal fold pathology in the face of significant functional improvement and a high functioning level after maximal medical therapy (nonsurgical). Refer to Figure 68.11 to see the vocal folds of a patient who met the clinical criteria for bilateral nonspecific vocal fold lesions.
7. **Pseudocyst**
   Pseudoscyt is a superficial subepithelial pathology that, by definition, corresponds to glottal incompetence most often associated with vocal fold scar but can also be associated with a vocal fold paresis or paralysis. The clinical nature of this lesion includes a very superficial, almost "water blister" appearance of the lesion, with a very thin epithelial covering to the

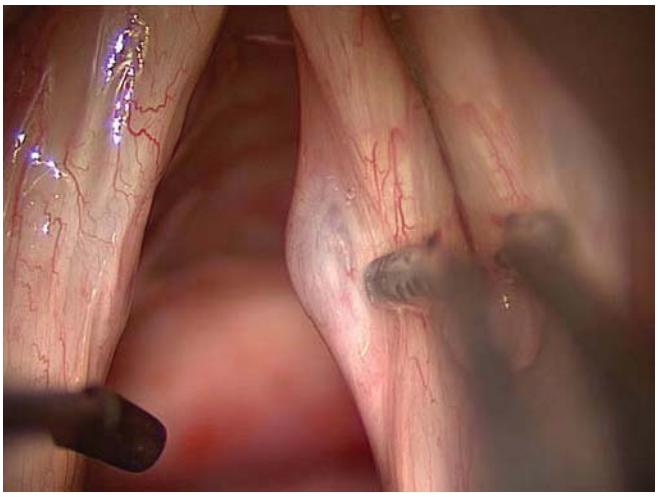


Figure 68.5 Vocal fold cyst-ligament.



Figure 68.7 Fibrous mass-subepithelial and bilateral.

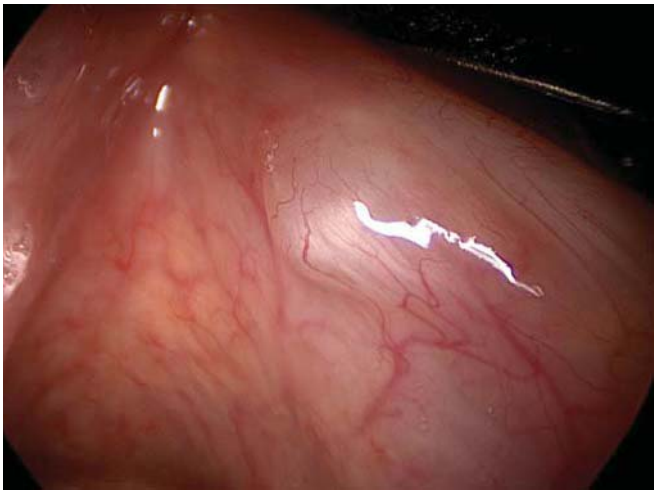


Figure 68.6 Vocal fold cyst-ligament (30-degree telescopic view of same lesion as Fig. 68.5).

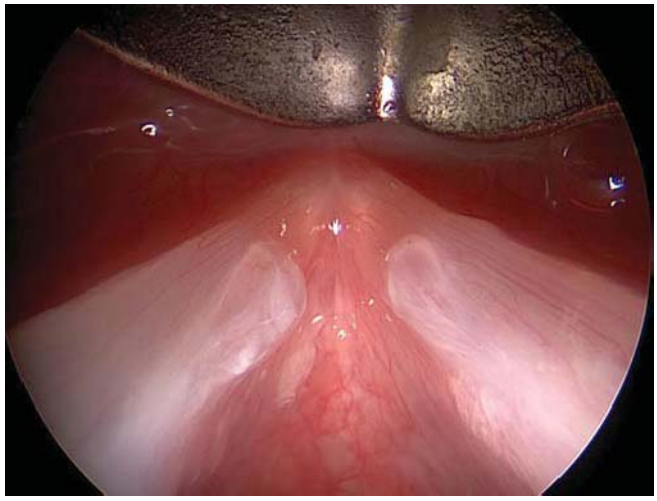


Figure 68.8 Fibrous mass-subepithelial and bilateral (70-degree telescopic view of same lesions as Fig. 68.7).

lesion without any evidence of encapsulation nor negative impact to the mucosal wave of the affected vocal fold. If this lesion is removed surgically without the glottal incompetence being addressed, it has a high likelihood of recidivism. Refer to Figure 68.12 to see an example of a left true vocal fold pseudocyst with associated right true vocal fold scar.

The definitive diagnosis of most midmembranous benign lesions of the lamina propria requires evaluation following resolution of any acute inflammatory processes, stroboscopy, voice therapy treatment, and possibly intraoperative findings. The treatment approach for these lesions is fairly standardized, given that most patients should receive nonsurgical treatment for these lesions, which consists of medical therapy for comorbid medical conditions (e.g., allergies, reflux) and voice therapy (see Chapter 71). At the initial evaluation session and after maximal nonsurgical medical therapy, assessment of the patient should include

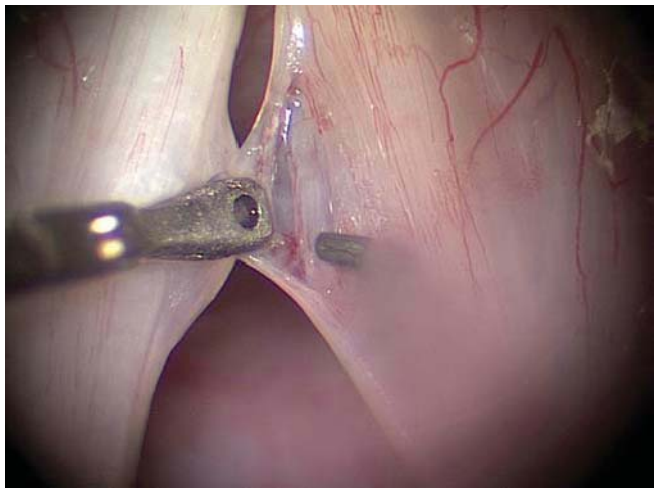


Figure 68.9 Microflap excision of the fibrous mass-subepithelial, seen in Figures 68.7 and 68.8.



Figure 68.10 Reactive vocal fold lesion of left true vocal fold.

functional measures and stroboscopy (see Chapter 65). The decision to proceed with surgery, which is highly individualized, should be based on the patient's voice quality, functional needs, and demands following maximal nonsurgical treatment modalities. After conservative nonsurgical therapy has been implemented, the patient should be asked "can you do what you need to do with your voice at the present time?" If the patient still has significant functional limitations with the voice, then a discussion regarding surgical treatment of the vocal fold lesion(s) is reasonable.

Another advantage of the above-described vocal fold nomenclature system is that these lesions have different prognostic implications and can be helpful in counseling the patient regarding expected clinical course and treatment outcome. In general, patients with subepithelial pathology have a greater likelihood of excellent vocal fold recovery than do patients with disease within the ligament and, similarly, patients with vocal fold nodules, reactive lesion, and vocal fold polyp have a better prognosis for a high degree of vocal recovery after treatment than do those with a vocal fold cyst and fibrous mass (5).

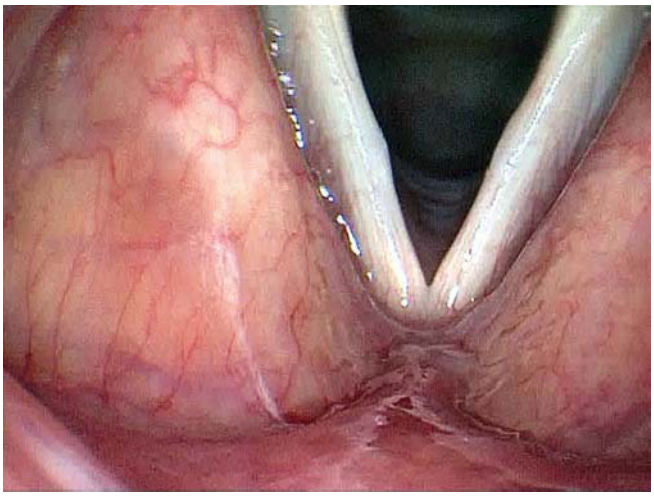


Figure 68.11 Nonspecific vocal fold lesion, bilateral.

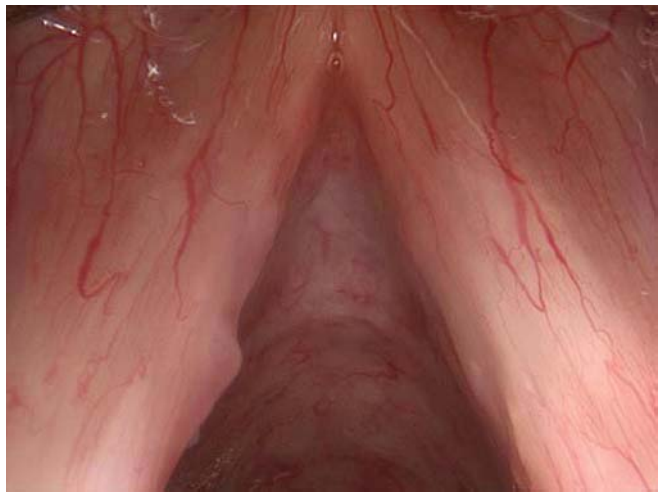


Figure 68.12 Pseudocyst of the left true vocal fold and associated right vocal fold scar defect.

Vocal Fold Scar and Sulcus Vocalis

Vocal fold scar and sulcus vocalis are abnormalities of the lamina propria of the vocal fold that result in poor vocal fold vibratory function (loss of viscoelasticity) and often glottal insufficiency. The former is a hallmark of vocal fold scar and sulcus vocalis, and the latter is dependent on the nature of the vocal fold pathology. For reasons that are unclear, some patients with vocal fold scar develop a "deposition" form of the vocal fold pathology where the normal lamina propria of the vocal fold is substantively taken over (replaced) by thick, fibrous scar tissue that can match the normal size of the lamina propria or can even slightly expand the size of the vocal fold as the vocal fold epithelium becomes adherent to the vocal ligament. The theory behind this form of vocal fold scar involves repeated hemorrhage into the vocal fold, resulting in serial deposition of scar tissue, which eventually replaces and even expands the lamina propria. Other patients with vocal fold scar and all patients with sulcus vocalis have an opposite effect: the lamina propria is reduced or lost during the formation of the disease process without any subsequent replacement at all. This results in a loss of vibratory function and a change in the size and dimension of the vocal fold. These pathologic occurrences cause glottal insufficiency. Limited research has looked at the etiology of vocal fold scar and sulcus vocalis. Clinical reports, however, indicate that most of the patients with these disorders have a history of repeated vocal abuse (phonotrauma). Refer to Figures 68.13 and 68.14 to view the vocal folds of a patient with bilateral sulcus vocalis. There is also a belief that sulcus vocalis can occur as a congenital deformity. These patients have an abnormal sounding cry and abnormal phonation from birth forward and, typically, have a very severe form of sulcus vocalis. The varying degrees and types of deformation that sulcus vocalis can present have been described as either a type I, type II, or type III sulcus vocalis deformity (6).



Figure 68.13 Sulcus vocalis, bilateral.

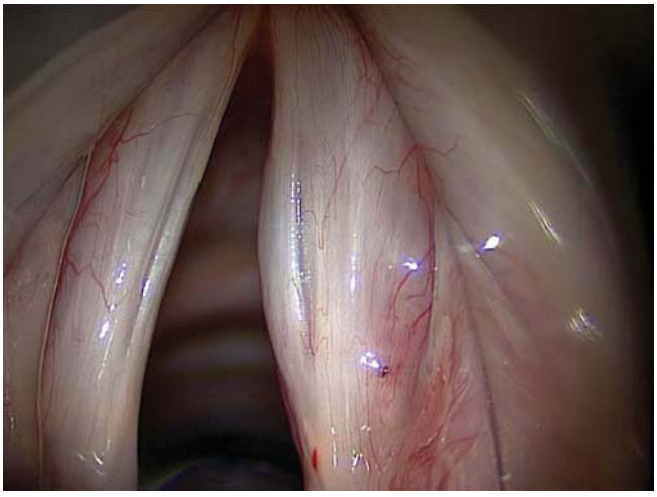


Figure 68.14 Sulcus vocalis, bilateral. (After right deep true vocal fold injection augmentation with Radiesse Voice Gel.)

Treatment for vocal fold scar and sulcus vocalis can be successful, depending on the patient's motivation, voice demands, and quality of available voice therapy and surgeries. Surgical treatment is directed at addressing a stiffened and volumetric-deficient lamina propria (7). As in the treatment of all benign voice disorders, nonsurgical treatment for vocal fold scar and sulcus vocalis should be implemented first. This involves treatment of comorbid medical problems, voice therapy, and sometimes singing voice therapy. Following these treatment options, if significant functional limitations are still present, the patient may be a candidate for surgical treatment for vocal fold scar or sulcus vocalis. The surgical approaches for this disorder are focused at the specific functional limitation (voice quality vs. volume or vocal fatigue) and the dominant pathophysiologic problem. For patients with problems of vocal fatigue and volume and correlated significant problems with glottal insufficiency, a vocal fold augmentation procedure (vocal fold injection or medialization laryngoplasty, refer to Fig. 68.14) is helpful as a first and possibly sole therapy. For patients with vocal fold scar or sulcus vocalis and severe dysphonia without any problems of glottal incompetence, surgical procedures that address the vibratory or elastic characteristics of the lamina propria are indicated. These procedures include direct implantation of fat into the vocal fold via a microflap approach or Gray mini-thyrotomy, collagen injection into the lamina propria, or the mucosal slicing technique of Pontes (8–10). Direct implantation of fat into the lamina propria for vocal fold scar and sulcus vocalis is a technically demanding and difficult surgery. When successful, however, the fat graft material provides excellent vibratory characteristic to the injured vocal fold. Superficial vocal fold injection of collagen-based materials is presently limited by technical difficulty in depositing the material in the area of scar or sulcus vocalis and currently available collagen-based materials (11). In the future, different materials that more appropriately match the native extracellular matrix proteins may be available to improve this treatment approach.

The mucosal slicing technique of Pontes involves an attempt to reorganize the lines of stress throughout the severely scarred and damaged vocal fold lamina propria by making multiple, parallel mucosal slices of varying lengths. This technique has not been widely utilized. It is also reported that recovery from this surgery is prolonged, and patients should be advised that a 9- to 12-month time period is required for voice improvement.

Miscellaneous Vocal Fold Lesions

Rheumatologic Lesions of the Vocal Folds

Rheumatologic lesions of the vocal folds involve an inflammatory and fibrotic process occurring within the vocal fold, associated with various rheumatologic disorders such as rheumatoid arthritis. These lesions, which occur deep within the lamina propria, typically around the vocal ligament, cause severe dysphonia because of the vocal fold stiffness, changed size, and the infiltrative nature of the lesion(s). These lesions should be differentiated from the typical benign midmembranous vocal fold lesions, such as vocal fold polyp, cyst, and fibrous mass. Refer to Figure 68.15 for an example of bilateral midmembranous rheumatologic lesions. Patients may present with a rheumatologic lesion of the vocal fold without prior diagnosis of their rheumatologic condition. Thus, it is important that patients have a rheumatologic evaluation and treatment before surgical excision of the vocal fold lesions when a rheumatologic condition is suspected (see Chapter 67).

Conditions including Wegner granulomatosis, amyloidosis, sarcoidosis, and rheumatoid arthritis can exhibit manifestations in the larynx. Wegner granulomatosis is classically known for its predisposition to the subglottis, but patients can present with dysphonia before obstructive symptoms. Primary amyloidosis of the respiratory tract most commonly involves the larynx and presents as a submucosal mass. Sarcoidosis can present as epiglottic noncaseating granulomas, which rarely need surgical

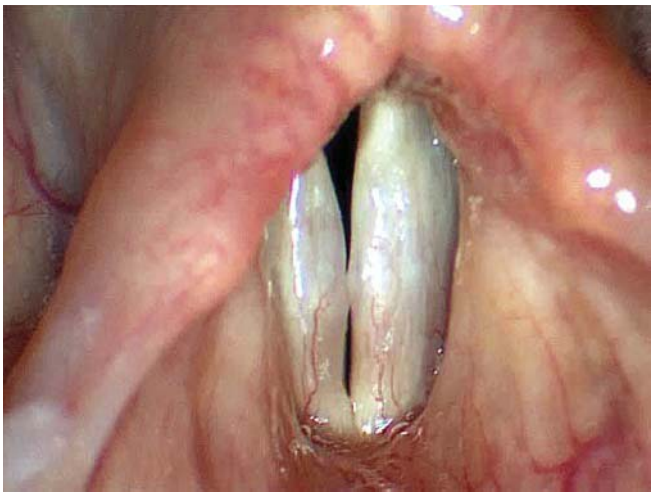


Figure 68.15 Rheumatologic lesions of the bilateral true vocal folds.



Figure 68.16 Vocal process granuloma.

intervention as they often exhibit spontaneous remission. The presence of cricoarytenoid joint rheumatoid arthritis does not show any relation to age, disease duration, or severity of disease. Furthermore, patients with cricoarytenoid rheumatoid arthritis (RA) can present with acute and intermittent symptoms, which can make the diagnosis difficult (See Chapter 67). Methotrexate, when used for rheumatologic disease, may promote rheumatologic deposits within the vocal folds, given that they have a propensity to cause rheumatologic nodule formation in other parts of the body. Collaboration with the patient's rheumatologist is essential to provide optimal care for this condition. Voice and surgical therapy should start after the patient has been maximally treated for the rheumatologic condition.

Vocal Fold Granuloma

The term vocal fold granuloma (also known as vocal fold contact ulcer) is a misnomer, given that this condition is an inflammatory mass originating from chronic inflammation and irritation of the perichondrium of the arytenoid cartilage. It is not a granulomatous disease as defined by histopathology, such as sarcoidosis or tuberculosis. Vocal fold granulomas typically occur near or at the vocal process of the arytenoid cartilage and can be subdivided into two groups: intubation related and not intubation related. The former, which occurs following endotracheal intubation, is characterized by rapid resolution of the lesion once all the offending agents are removed or eliminated (e.g., endotracheal intubation, laryngopharyngeal reflux [LPR], and vocal abuse or chronic cough). Patients with an intubation-related vocal fold granuloma, typically, can be treated conservatively, and over several months their lesions will resolve spontaneously. Patients with a granuloma that is not intubation related are typically more difficult to treat. These patients require a detailed evaluation from a glottal competence, laryngeal reflux, and vocal behavior perspective because these conditions are the most common etiologic agents for a vocal fold granuloma that is not intubation related. Refer to Figure 68.16 for an example of a chronic left vocal process granuloma that was not related to intubation. Surgery should be reserved until all associated comorbid medical conditions (allergy and laryngopharyngeal reflux disease) and appropriate voice use issues have been addressed unless a concern of malignancy exists. A delayed approach to surgical removal is wise given the high degree of recidivism with these lesions following surgery. When surgery is performed for vocal fold granulomas, the surgeon must remember that any additional irritation to the underlying arytenoid perichondrium will likely result in a recurrent vocal fold granuloma. Thus, vocal fold granuloma should be removed, using an approach that involves minimal trauma to the underlying perichondrium of the arytenoid cartilage (see "Phonomicrosurgery of the Vocal Folds" below). An alternative to surgical excision of vocal fold granuloma after all nonsurgical treatment modalities (voice therapy, LPR treatment, etc.) have been addressed is the use of botulinum toxin A (btxA) injection to the thyroarytenoid–lateral cricoarytenoid muscle complex (12). The btxA injection is thought to reduce the vocal fold closing force and thus allowing the vocal fold granuloma site to heal. This approach has not been thoroughly studied, causes prolonged breathy dysphonia during the treatment period, and in many cases does not address the underlying etiologic cause of the vocal fold granuloma.

A different type of vocal fold granuloma is a membranous vocal fold granuloma, which differs from granulomas classically present on the vocal process of the arytenoid. Membranous vocal fold granulomas occur after microlaryngeal surgery and typically arise at the surgical site in the early postoperative course. All patients with membranous vocal fold granulomas should be treated with a proton pump inhibitor and the condition usually resolves spontaneously under this management. Surgical excision is of little benefit and in most cases can accelerate the formation of additional granulation tissue (13).

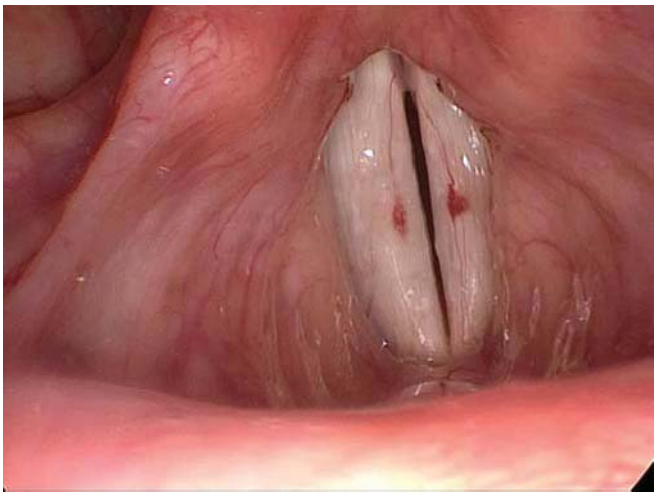


Figure 68.17 Vascular lesions of the bilateral true vocal folds.

Vascular Lesions of the Vocal Folds

Abnormal vascular lesions of the vocal folds are subepithelial blood vessels that have been termed "vascular ectasias" or "venous lakes" of the vocal fold (3). These lesions, which are characterized as having a transverse course within the vocal fold (perpendicular to the longitudinal axis of the vocal fold), are often associated with vocal fold lesions and past or present phonotrauma. It is not clear if these vascular lesions occur because of the vocal fold lesions or vice versa. Most patients with vascular ectasias of the vocal fold do not require surgical treatment unless they have a history of documented vocal fold hemorrhage or that the lesion is located along the striking edge of the vocal fold and the clinician has a high-index suspicion that this lesion is extremely susceptible to vocal fold hemorrhage. Surgical treatment of these lesions should be done with great precision and with cold steel excision or pulsed angiolytic laser ablation (3,14). The role of angiolytic lasers in the management of vocal fold vascular lesions has recently become more prominent. Both pulsed potassium-titanylphosphate (KTP) and pulse dye lasers (PDL) have been found to be both efficacious and relatively safe in singers (14). Vessel rupture may be less frequent with pulsed KTP versus PDL (14). The chromophore for these lasers is hemoglobin rather than water, as with CO_2 lasers, resulting in more precise delivery of laser energy to the abnormal blood vessel and thus, less thermal injury risk. Refer to Figure 68.17 for an example of interesting bilateral vascular lesions of the true vocal folds.

Reinke Edema

Reinke edema of the vocal folds is a poorly understood chronic condition involving the development of a gelatinous, inflammatory exudate within the subepithelial space of the vocal fold, unilateral or bilateral. This condition is most commonly associated with the triad of laryngopharyngeal reflux disease, vocal abuse, and tobacco abuse. Not all patients with Reinke edema must have all three etiologic factors present, but typically patients will have two of these three when Reinke edema is present. Reinke edema causes increased mass of the vocal folds, which results in a lowering of the voice pitch and a decrease in the phonatory efficiency and stability of the voice, resulting in frequent voice breaks, and harshness and raspiness of the voice (see Chapter 65). Treatment of Reinke edema should first and foremost involve treatment of the underlying causative factors (reflux, phonotrauma, and tobacco abuse). After these conditions have been addressed, patients can be treated with a combined approach of voice therapy and surgery. The success rate of surgical treatment of Reinke edema is usually favorable, especially when redundant mucosa is carefully excised (15). Recurrence or lack of perceptual voice improvement can be problematic in some patients. Elimination of the causative factors for Reinke edema has a significant impact upon the long-term prognosis after surgery (16). The amount and timing of voice therapy in relationship to surgery is controversial and should be done on a case-by-case basis. Refer to Figures 68.18 and 68.19 for an example of a Reinke edema of the true vocal folds.

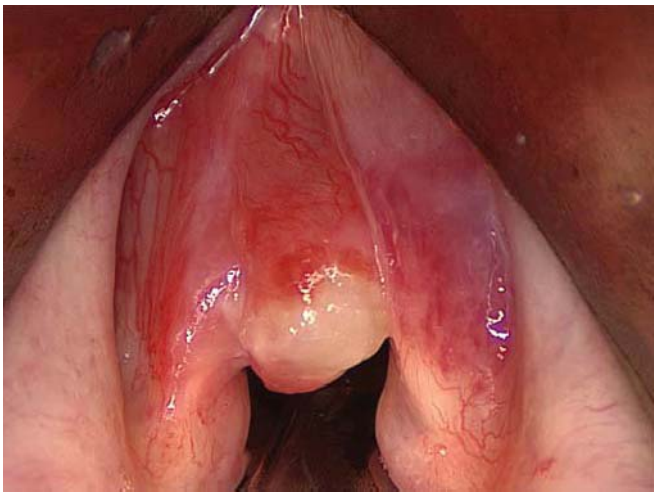


Figure 68.18 Reinke edema of the bilateral true vocal folds, left greater than left.

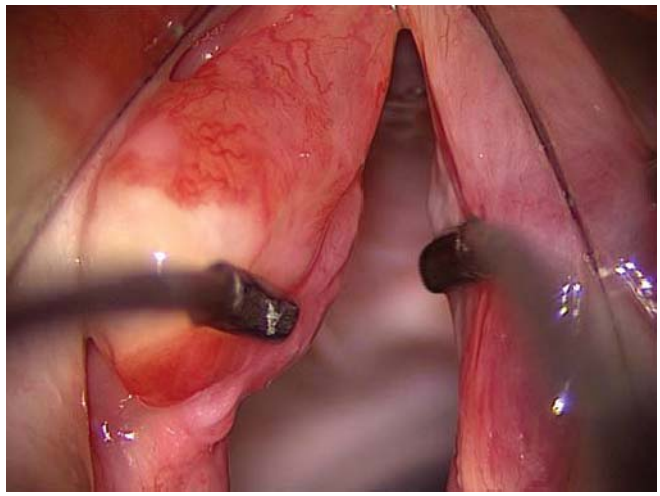


Figure 68.19 Displacement of left true vocal fold Reinke edema from Figure 68.18.

PHONOMICROSURGERY OF THE VOCAL FOLDS

Overview

Phonomicrosurgery encompasses a variety of operations that have the primary goal of improving voice quality. These are elective operations that involve precision microsurgical removal of benign vocal fold pathology, most often from the subepithelial space of the vocal fold. The surgical procedures and principals are based on vocal fold physiology, specifically Hirano cover-body theory of the vocal fold vibration (see Chapter 58). Given the importance of the interaction between the epithelium and the superficial area of the lamina propria (cover) and the underlying deep layer of the lamina propria and muscle (body), phonomicrosurgery was born and has evolved to minimally disrupt the normal microarchitecture of the vocal fold while removing dysphonia-inducing pathology. The overarching goal is to limit dissection to as superficial plane as possible and to maximally preserve epithelial and lamina propria. The latter tenet is important to facilitate primary wound healing versus secondary wound healing. This is thought to allow maximal functional recovery (vocal fold mucosal vibration) following surgery.

Prephonomicrosurgery Considerations

Phonomicrosurgery is an elective surgery and, thus, pressure should not be placed on the patient to decide to proceed with surgery. The risks and benefits of the surgery should be detailed to the patient and, most importantly, a realistic and thorough evaluation of the patient's present vocal functional limitations and abilities (speech and singing) should be reviewed. Often, this review process should be done over several weeks and involve the patient, otolaryngologist, family members, speech–language pathologist, and possibly a singing voice specialist. When all nonsurgical treatment modalities have been exhausted and significant vocal functional limitations exist, it is appropriate to proceed with phonomicrosurgery.

Important preoperative measures before phonomicrosurgery include avoiding (a) nonsteroidal anti-inflammatory medications or other anticoagulation medications and (b) significant vocal abuse and misuse immediately before surgery. Preoperative voice therapy (one to two sessions) is extremely important in preparation for phonomicrosurgery for a variety of reasons: (a) psychological preparation for surgery and postoperative voice rest, (b) to modify and improve improper speaking technique, and (c) to lay the foundation for postoperative voice therapy, from both a psychological and a behavioral perspective. Preoperative voice therapy stresses to the patient the importance of changing inappropriate vocal techniques and use patterns in the postoperative period, thus reducing the chances of vocal fold pathology recidivism.

Before phonomicrosurgery, patients must realize that they will be on absolute voice rest and reduced voice use for a variable period of time (from 3 to 14 days) and that they must adjust their voice demands to comply with the surgeon's restrictions regarding voice use.

Preoperative consent for phonomicrosurgery should involve the risks of general anesthesia and injury to the temporomandibular joint (TMJ), dentition, and lingual nerve. The latter has been shown to be temporary, lasting an average of 2 weeks to a maximum of 1 month (17). A discussion regarding postoperative voice quality following phonomicrosurgery should be taken seriously and done by the surgeon before the phonomicrosurgical procedure. It should involve the small but real risk of either no improvement of voice quality (1% to 2% incidence) or a reduction in vocal function or voice quality (1% to 2% incidence).

All patients should undergo preoperative stroboscopy. Before phonomicrosurgery, the surgeon should review the patient's most recent stroboscopy. Preferably, this review is done the day of surgery or 1 to 2 days before the surgery. The optimal situation would be to have the preoperative stroboscopy examination available for review in the operating room immediately before (as well as during) the procedure. This allows the surgeon to correlate stroboscopic findings with surgical findings and make important decisions on pathology location, incision placement, and dissection and excision degree.

Equipment for Phonomicrosurgery

Specialized laryngoscopes are required for phonomicrosurgery. In general, the larger the laryngoscope, the better for phonomicrosurgery, which allows improved exposure and access to the surgical site(s). Multiple large and specialized laryngoscopes exist and a wide variety of laryngoscopes are necessary to manage all types of phonomicrosurgical lesions and procedures. It is important to have specialized laryngoscopes for special laryngoscopy needs.

Key microlaryngoscopy instruments used for phonomicrosurgery involve specialized blunt microelevators, cup forceps, scissors, curved alligators, and small suctions (3, 5, and 7 French). Phonomicrosurgery cannot be done properly and safely without these specialized instruments. In addition, a specialized set of instruments have been developed for microflap retraction. These are called triangular or Bouchayer forceps. The microelevators should be blunt and have several different angles and sizes to allow the surgeon to work in various angles in different positions within the vocal fold, specifically, dissecting the vocal fold lesion off the overlying microflap. A microsurgical knife (sickle or diamond shaped) should be always available for phonomicrosurgery. This knife tends to get dull very quickly and, thus, this knife should be replaced with every case or at least on a very frequent basis. A dull knife can result in tearing of the mucosa and can significantly limit the efficacy of phonomicrosurgery. Several small special cup forceps have been developed to facilitate several specific situations that are encountered in phonomicrosurgery. One of these cup forceps is a round, 1-mm diameter, angled-up cup forceps. This forceps has a sharp cutting

edge but a limited cutting surface, only the most distal 180 degrees of the forceps cup.

Suspension of the laryngoscope is a basic aspect of phonomicrosurgery. Two basic designs for placing the laryngoscope into a fixed and stable position exist. These are categorized as a gallows suspension device and a rotation or fulcrum device. The gallows suspension laryngoscope is advantageous and favorable, given that its more appropriate upward vector of pull of the laryngoscope can provide optimal exposure of the endolarynx with minimal risk of dental injury, especially to the maxillary teeth (18). This device is not the one most commonly used because of traditional and historical use of rotational/fulcrum devices (Lewy suspension).

Long Hopkins rod telescopes with various visualization angulations are an essential component to phonomicrosurgery. Rarely is the surgery performed using these telescopes, but they do provide the surgeon with multiple angles of visualization for varied perspective of the vocal folds and its related pathology. The 30- and 70-degree telescopes, which are approximately 4 to 5 mm in diameter and 30 cm long, should be used immediately before phonomicrosurgical incision; they are often used during phonomicrosurgery as well as at the end of the surgery to ensure that all appropriate pathology has been removed. These angled telescopes are readily available in most operating rooms, given they are used regularly for cystoscopy.

The microscope used for phonomicrosurgery should be of the highest quality and provide the surgeon with a stable method to view the endolarynx. This microscope should be the same microscope that is used for precision otologic procedures (e.g., stapes surgery and other middle ear operations). Furthermore, the microscope should be compatible with a CO_2 laser micromanipulator attachment. Typical focal length of the lens used on the surgical microscope for phonomicrosurgery is 400 mm. This allows an adequate space between the proximal end of the laryngoscope and the microscope for placement and use of hand instruments for phonomicrosurgery. Another important feature of the surgical microscope is an articulated eye piece; this allows for optimal surgeon ergonomics, which is important for lengthy phonomicrosurgery cases as well as for the long-term health of the phonomicrosurgeon (19).

Lasers have a limited role in phonomicrosurgical procedures. The CO_2 laser with the micromanipulator has also been used to incise vocal fold tissue. No distinctive advantages for the use of this laser exist for this application, and the risks of thermal injury and costs of the instrument outweigh any potential benefits. Most phonomicrosurgery can and should be done with "cold steel" instrumentation. The CO_2 laser allows an "instrument free" approach to surgery of the vocal folds and in a small crowded surgical space, this can be an advantage. However, for most phonomicrosurgical situations, this is not a key problem and thus the CO_2 laser is rarely indicated for this reason alone. Angiolytic lasers including pulsed KTP and PDL have been used for laryngeal surgery, but the indication and validation of this new technology for most phonomicrosurgical procedures, except for papilloma disease, has not been determined.

PHONOMICROSURGERY PROCEDURES, TECHNIQUES, AND METHODS

A working relationship based on mutual respect, communication, and teamwork with your anesthesia colleague(s) is essential for successful phonomicrosurgery. Phonomicrosurgery involves general anesthesia; complete muscle relaxation should be implemented following the induction of general anesthesia and the muscle paralysis continuously monitored throughout the surgery. Preoperatively, anesthesia should administer intravenously (IV) steroids and glycopyrrolate (unless contraindicated). Endotracheal tube placement is extremely important, given that misplaced or traumatic placement can cause injury to the vocal folds and may result in cancellation of surgery. Endotracheal tube placement should be done to minimize the risk of trauma to the vocal folds (i.e., under completely controlled conditions, no stylet if possible, etc.). Furthermore, the otolaryngologist should be present during the intubation to monitor the situation and be available to assist with placement if required. In a similar fashion, controlled extubation at the end of phonomicrosurgery is another important aspect of the necessary teamwork between the anesthesia team and the phonomicrosurgeon.

The ventilation options for phonomicrosurgery are endotracheal intubation, jet ventilation, or apneic methods. Most phonomicrosurgery is best performed using endotracheal intubation with a small (5.0 or 5.5) specialized endotracheal tube. This provides both a still operating field and complete control of the airway. Sometimes, the endotracheal tube can obstruct the surgical site and may need to be repositioned or completely removed. Jet ventilation for phonomicrosurgery, which should be done only on an as-needed basis, is best done with a midtracheal jet ventilation catheter (Hunsaker tube, Medtronic Xomed Co., Jacksonville, FL). Tracheal jet ventilation is preferred to supraglottic jet ventilation because it provides the surgeon with less vibration and desiccation of the vocal fold tissues during phonomicrosurgery. These suggestions result in a still operating site and less risk of vocal fold desiccation.

Phonomicrosurgery patients are placed in a supine position on the operating room table. The optimal head and neck position for exposure of the endolarynx with the laryngoscope is having the neck flexed on the body and the head extended on the neck (20). A shoulder roll, which places the patient in a suboptimal position for optimal laryngoscope placement, should not be used. Neck flexion can be achieved by using an articulated head on the operating room table with the head extension on the neck being done by the surgeon, and then secured with the suspension device. Dental and alveolar ridge protection before insertion of the laryngoscope is important.

The optimal position of the laryngoscope within the endolarynx is determined by the vocal fold pathology

and pending surgical procedure. In general, however, the laryngoscope should be positioned immediately above the vocal fold pathology, specifically, resulting in retraction of the false vocal fold tissues. Take care to avoid contacting the superior surface of the vocal fold, given that this will significantly alter the anatomic orientation and nature of the vocal fold and often distort the vocal fold pathology.

Any Gallows suspension device used should be positioned to provide upward and slightly forward (caudal) suspension of the laryngoscope in the endolarynx. This special angulation of the laryngoscope will provide optimal laryngoscopic visualization and minimal adjacent tissue injury or damage. For a rotation or fulcrum laryngoscope device holder, it is of utmost importance to remember to provide special care and attention to the maxillary teeth as the laryngoscope holder is put into place. This is especially important given that as the fulcrum holder is adjusted, each degree of upward rotation at the distal tip of the laryngoscope results in an equal amount of downward pressure at the proximal aspect of the laryngoscope on the maxillary alveolar ridge.

A Velcro strap or silk tape can be applied to the external neck (in the area of the cricoid or trachea) in a downward and slightly cephalad vector to improve the endolaryngeal exposure on an as-needed basis. The surgeon checks the improved view through the laryngoscope while applying this external counter pressure. A small amount of gauze or a foam pad can be positioned between the tape or strap and the neck skin to prevent any injury to the overlying skin of the larynx and care should be taken to avoid placing pressure on the carotid arteries.

Using the 0-, 30-, 70-, and, as needed, 120-degree telescopes to visualize the endolarynx in a "three-dimensional" fashion is of great value. This is done after the laryngoscope is suspended. This allows for unique visualization of the vocal fold pathology, photo documentation, and surgical planning. Specifically, decisions are often made about where the optimal location is for an incision when evaluating the vocal fold pathology, especially with the 30- and 70-degree angled telescopes.

After placement and suspension of the laryngoscope and telescopic examination, the surgical microscope is brought into position and attention should be drawn to the position of the laryngoscope in relation to the microscope and the surgeon. A microscope with an articulated eyepiece is essential. Optimal hand control of instrumentation during phonomicrosurgery occurs when the forearms can be supported with a stable device, such as an operating room chair with arm supports in the region of the elbows, forearms, or wrists. The wrists are the best location for precise control and, thus, some type of surgical support should be identified (an ophthalmology or plastic surgery operating room chair with arm supports) that will allow the most steady and stable hand and wrist motions. After proper ergonomic planning, the surgeon should not experience any strain or tension in the shoulders or arms (19). The utility of trendelenburg or reverse trendelenburg adjustments should also be considered when optimizing ergonomics.

Binocular vision at high-powered magnification (the microscope's highest level of magnification) must be maintained during all aspects of the procedure. This will require minor but important adjustments to the position of the microscope and laryngoscope to ensure that the viewing access of the microscope is coaxial with the longitudinal aspect of the laryngoscope. This is an extremely important component to phonomicrosurgery and should not be overlooked. The novice phonomicrosurgeon will initially struggle with this task, but patience and practice will ensure success.

The microflap approach to submucosal pathology is a key aspect to most phonomicrosurgery operations. The key principles of the microflap approach to submucosal pathology include (a) making an incision through the epithelium at the closest possible location to the submucosal pathology; (b) minimal disrupting of the surrounding tissue to the vocal fold pathology; and (c) staying in as superficial a plane as possible. After the vocal fold pathology is palpated and an incision is planned, hemostatic measures should be implemented. The topical application of 1/10,000 epinephrine on a cottonoid can be used to achieve improved hemostatis. Consideration should be given for the utility of a subepithelial injection. An injectable solution of 1/10,000 epinephrine is used with a laryngeal injector to infiltrate Reinke space surrounding the vocal fold lesion. The subepithelial infiltration technique can result in elevation of the mass, increased epithelial tension, and less traumatic dissection from the superficial lamina propria and underlying vocal ligament. After the implementation of hemostasis, an incision is then made with a sharp knife. The incision for the microflap should be over or immediately lateral to the vocal fold pathology (Fig. 68.20), which results in minimal disruption of normal vocal fold mucosa. It is important to note that the tip

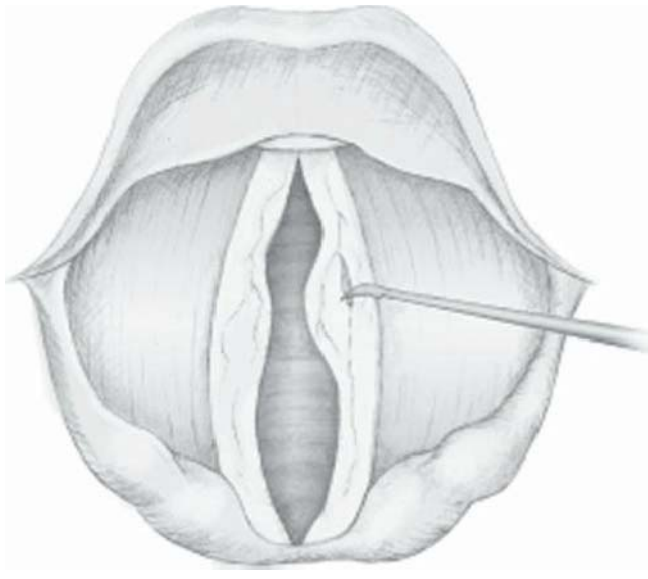


Figure 68.20 Incision immediately lateral to submucosal pathology for microflap approach for removal of the vocal fold lesion.

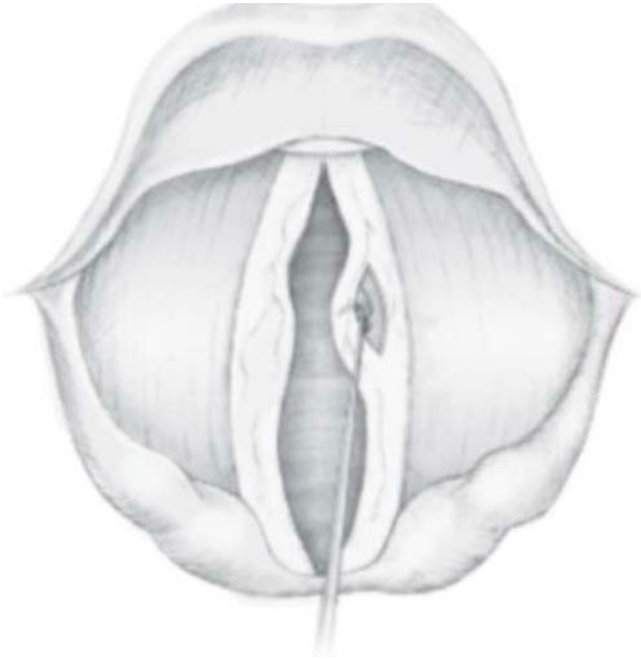


Figure 68.21 Microflap elevation.

of the knife should be used to penetrate the epithelium and then the surgeon must take great care to stay as superficial as possible while the incision is completed. After the incision has been made, the vocal fold pathology may be palpated and directly visualized through the incision. A small curved elevator can be used to start the elevation of the microflap in a plane between the vocal fold pathology and the overlying epithelium (Figs. 68.21 and 68.22). This plane is the single hardest activity of phonomicrosurgery and should be done with great patience and caution. It is often easiest to initiate and develop this plane anterior and posterior to the vocal fold lesion. Once a plane is developed anteriorly and posteriorly to the lesion, then careful submucosal dissection with a small, fine, blunt elevator, (curved or angled) completes the elevation and creation of the microflap (Fig. 68.23). In some instances the microcurved scissors need to be used to release fibrous bands in adherent areas of the submucosal pathology off the overlying microflap or, similarly, when the submucosal pathology is adherent to the deeper aspects of the vocal fold in the area of the vocal ligament (Figs. 68.24 and 68.25). Take great care not to tear or fenestrate the microflap as it is tediously and carefully elevated off the submucosal pathology. Often, various angulated or curved elevators are required to perform this aspect of the procedure. Most benign vocal fold submucosal pathology is located in the immediate subepithelial plane and, to a varying degree, is often adherent to the overlying microflap. This is the case in approximately 75% of cases (4). However, situations occur in which the pathology is not adherent to the microflap and located deeper within the vocal fold (in the area of the vocal fold ligament). This is especially true for vocal fold cysts and fibrous mass pathology. When these pathologies are encountered,

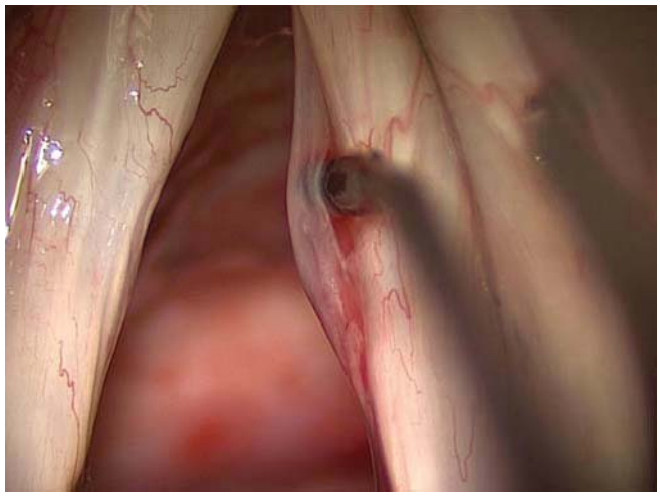


Figure 68.22 Careful elevation of the microflap overlying the vocal fold cyst-ligament. Same cyst also seen in Figures 68.5 and 68.6.

the surgeon will notice that the microflap elevation is easily accomplished. Subsequently, during the second aspect of the dissection, in which a plane between the vocal fold pathology and the vocal ligament is created, the dissection can be found to be quite difficult (Fig. 68.25). When this is the case, take great care to use either a blunt dissection technique or microscissors to release the adhering bands from the vocal fold ligament to the pathology, always erring on the side of the pathology (in a superficial fashion). After the superficial and deep planes around the submucosal pathology have been elevated, some additional connections may remain within the vocal fold anteriorly and posteriorly. These bands can be released with blunt dissection or microcurved scissors (Figs. 68.24 and 68.25). This

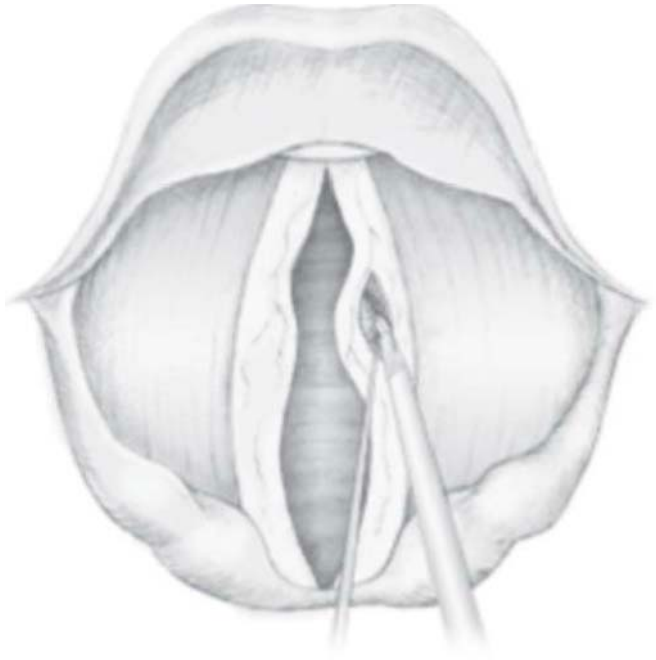


Figure 68.23 Removal of submucosal pathology via microflap.

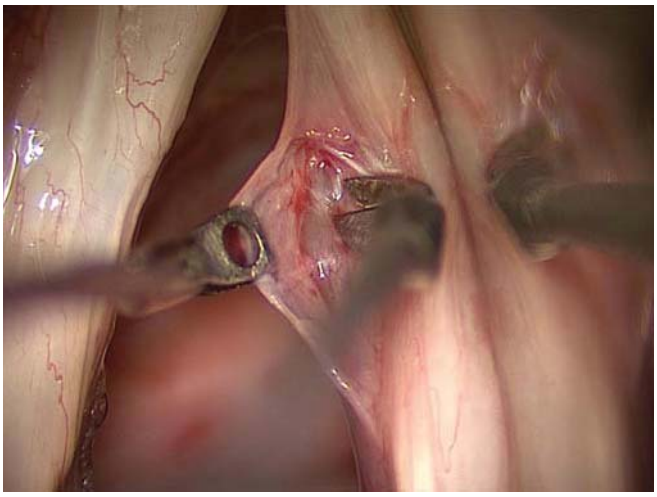


Figure 68.24 Release of fibrous bands over the vocal fold cyst-ligament with microcurved scissors.

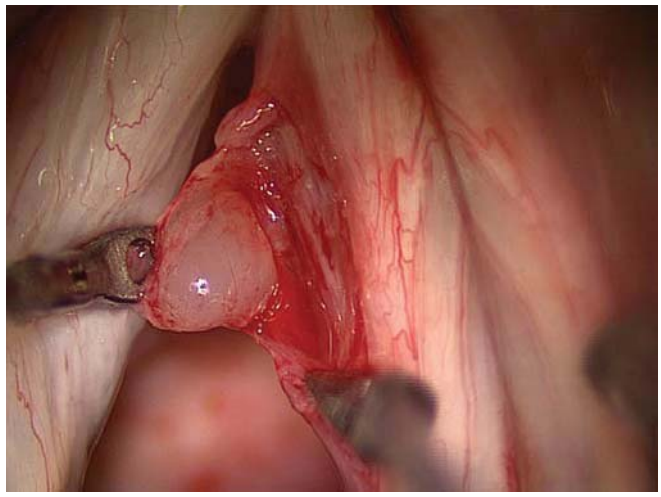


Figure 68.26 Vocal fold cyst-ligament undergoing final release with microcurved scissors.

allows the submucosal pathology to be removed and sent for pathologic examination (Fig. 68.26). It is then important to carefully examine the surgical site to look for remnants of the lesion (Fig. 68.27). The microflap is then redraped. (Figs. 68.28 and 68.29). After the microflap has been redraped, palpate the free edge of the vocal fold to determine if any residual submucosal pathology remains that requires further attention.

The free edge of the vocal fold should be straight after the pathology is removed; if not, further inquiry into either the undersurface of the microflap or the deeper aspect of the vocal fold is required. If any residual pathologic tissues (e.g., fibrous material or scar) remain, remove this tissue in a conservative and reasonable fashion. This material can be removed with a microelevator or microcup forceps. Extreme care is required at this juncture of the surgery because too aggressive removal of this material can result in significant scar formation as well as a permanent deformity of the free edge of the vocal fold. At the completion of the vocal fold lesion(s) excision, the free edge of each vocal fold should be completely straight without exophytic mucosal tags and without a divot along the vocal cord free edge at the surgical sites (Figs. 68.28 and 68.29).

Almost all phonomicrosurgical procedures are followed by some period of voice rest. This period can range from 2 days to 14 days, depending on the specific nature of the surgery, compliance of the patient, and the surgeon's philosophy and previous experience. In addition to voice rest, the patient should be encouraged to stay well hydrated, and to continue empiric treatment with a proton pump inhibitor and gastroesophageal reflux disease behavior modification to minimize the possibility of an acid reflux event(s) during the postoperative period.

At the end of the prescribed strict voice rest period, postoperative stroboscopy should be performed to evaluate the recovery and healing process of the vocal fold. Recovery is

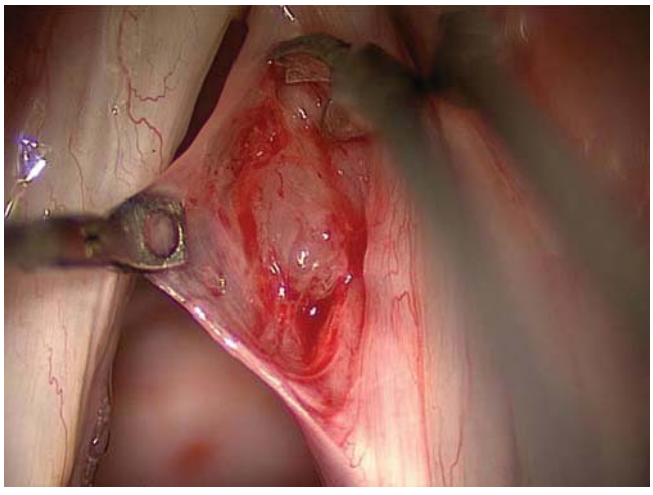


Figure 68.25 Difficult dissection of vocal fold cyst with adherent bands to the vocal ligament.

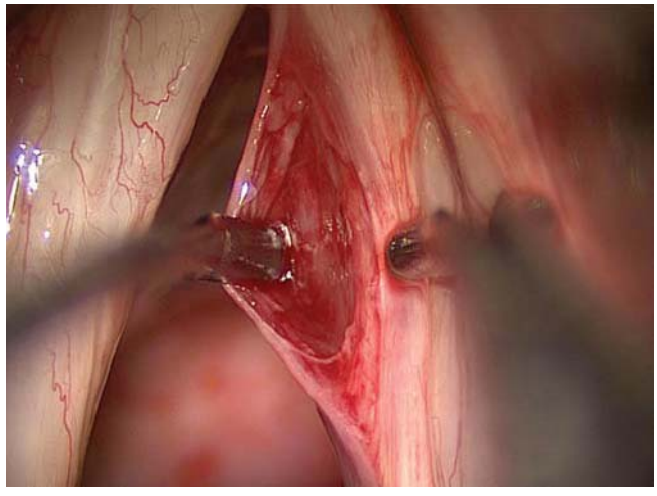


Figure 68.27 Inspection of the microflap and vocal ligament after phonomicrosurgical excision of a vocal fold cyst-ligamentous.

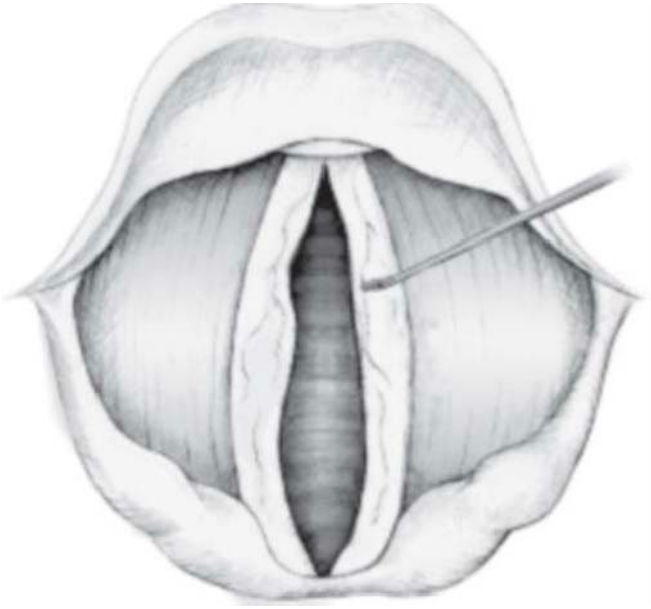


Figure 68.28 Redraping of microflap following submucosal pathology removal.

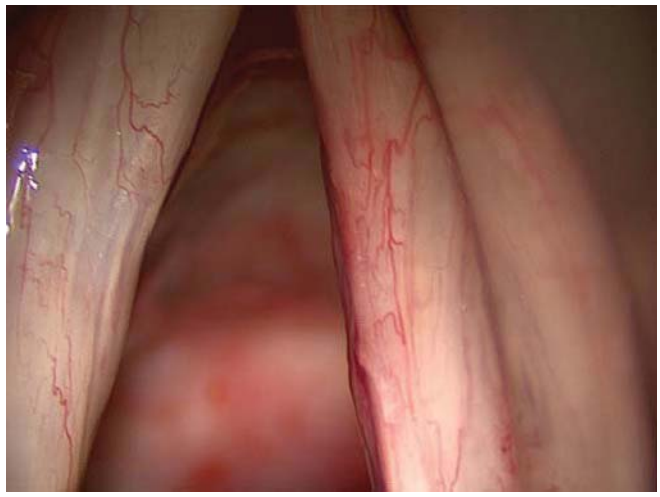


Figure 68.29 Microflap redraped after phonomicrosurgical excision of a vocal fold cyst-ligament.

demonstrated by the return of mucosal pliability. The timing of mucosal wave return can vary among patients and with the type and depth of a vocal lesion. Stroboscopy can help to identify an aberrant healing process such as significant postoperative scar formation. With the identification of adequate epithelial coverage, the patient can be transitioned to light voice use, which is usually defined as speaking using a breathy, "airy" type of voice for 5 to 10 minutes per hour. Light voice use is often used for an additional 7 to 10 days after the period of strict voice rest. Rarely does an indication exist for postoperative antibiotics or a prolonged steroid course after phonomicrosurgery. Some surgeons may use IV or intramuscular steroids perioperatively to minimize postoperative edema.

It is important to utilize a speech–language pathologist to assist the patient in transitioning from complete voice rest to light voice use to ensure that the patient is using the optimal postoperative voice technique to facilitate healing and prevent injury during this important time period. Postoperative voice therapy can then be initiated to optimize the rehabilitation following surgery.

COMPLICATIONS

Complications from phonomicrosurgery include failure of the microflap to appropriately redrape and adhere to the vocal fold. When this occurs, epithelial ingrowths underneath the microflap occur and surgical excision of the microflap is mandated. This is a rare complication. Excessive edema and even necrosis can occur to the microflap; this typically occurs when the microflap is overly traumatized or injured during the surgical procedure. Often, when this occurs, the vocal fold will heal adequately on its own with appropriate time and care. Also unusual, but important to recognize, is postoperative granuloma formation of the membranous vocal fold at the surgical site (13). This lesion differs from the well-known vocal process or "contact" granuloma. A membranous granuloma should be suspected when a lesion appears early in the postoperative course and should not be mistaken for a recurrence of the lesion. The membranous granuloma often responds to several weeks of proton pump inhibitor and rarely needs repeat surgical excision. Consideration and counseling should be given in patients with TMJ syndromes, who may experience increased symptoms after phonomicrosurgery. Lingual nerve injuries (e.g., numbness of the tongue and a change in taste sensation) occur in approximately 10% to 20% of patients following phonomicrosurgery. These symptoms are usually transitory and, thus, the patient should be informed that these postoperative changes will resolve on their own within the first month following surgery (17).

The outcomes after phonomicrosurgery can vary depending on patient selection, postoperative care, adherence to voice rest, management of comorbid disease such as LPR, and changes in damaging voice habits. Many otolaryngologists hesitate to operate on singers and performing artists due to concerns of poor postoperative outcomes. However, nearly all singers and performing artists with poor voice function secondary to persistent lesions of the superficial lamina propria have all shown improvement in subjective and objective measures in a study of 185 artists (21). Large multicenter studies are necessary to further establish the outcomes of phonomicrosurgery in a wider variety of individuals. Standardized measures such as the voice-related quality of life, voice handicap index-10, and computerized voice analysis should be routinely implemented to evaluate outcomes in individuals as well as larger groups of patients (22,23). Further understanding of vocal fold wound healing and the factors that maintain normal lamina propria may yield tangible therapies to modulate healing and maximize outcomes.

HIGHLIGHTS

- The most common benign vocal fold lesions involve subepithelial masses (e.g., vocal nodules, fibrous mass of the vocal fold, and vocal fold cysts). Differentiation of these lesions involves stroboscopy, longitudinal evaluation of the lesion(s), and sometimes intraoperative findings.
- Vocal fold scar and sulcus vocalis are entities that involve a significant derangement of the lamina propria of the vocal fold without focal accumulation of a mass type lesion. These pathologies typically involve severe dysphonia, which is caused by poor mucosal vibratory characteristics and glottal insufficiency.
- Phonomicrosurgery is an elective, precise surgery aimed to improve vocal function based on vocal fold physiology principles.
- Phonomicrosurgery, which requires use of small, delicate surgical instrumentation, is done with maximal control via high-power microlaryngoscopy for optimal results.
- Conservative removal of submucosal pathology with preservation of overlying normal epithelium allows healing by primary intention and optimal voice quality following phonomicrosurgery.
- Microflap approach to submucosal pathology of the vocal fold is an essential component of most phonomicrosurgical procedures and is a challenging surgical task that requires patience, appropriate instrumentation, and surgical skill and experience.
  - Preoperative stroboscopy is essential for evaluation and operative planning. Postoperative stroboscopy should be routinely used after the period of voice rest has been completed to monitor for the return of a normal mucosal wave.
- Preoperative and postoperative voice therapy is essential to prepare patients for postoperative voice rest and to improve poor voice habits that may play a role in the pathology of the benign lesion.

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69 Treatment of Vocal Fold Paralysis

VyVy N. Young *C. Blake Simpson*

Vocal fold paralysis (VFP) can have a profound impact on a patient's quality of life. Bilateral vocal fold paralysis (BVFP) is life threatening because of airway compromise, and occasionally, unilateral vocal fold paralysis (UVFP) is potentially life threatening, if poor airway protection leads to aspiration pneumonia. In the case of UVFP in a professional voice user, severe dysphonia or aphonia can lead to loss of income or unemployment. For these reasons, prompt and sometimes aggressive treatment of VFP is frequently indicated. The surgical armamentarium available to treat UVFP and BVFP continues to expand, and otolaryngologists should be aware of the myriad treatment options available to the patient. This chapter outlines the many changes that have occurred in the diagnosis and treatment of VFP during the past few years, highlighting the armamentarium that is available to the treating otolaryngologist.

For the purpose of clarity, this chapter deals primarily with adult VFP and is divided into two distinct topics: UVFP and BVFP.

UNILATERAL VOCAL FOLD PARALYSIS

Etiology

The etiology of UVFP involves dysfunction of either the brainstem nuclei, the vagus nerve, or the recurrent laryngeal nerve (RLN) supplying the involved side of the larynx (Fig. 69.1). Corticobulbar fibers from the cerebral cortex descend through the internal capsule and synapse on the motor neurons in the nucleus ambiguus. The nucleus ambiguus is the area within the brainstem (medulla) from which arise the fibers that will contribute to the vagus nerve. Lower motor neurons leave the nucleus ambiguus and travel laterally, exiting the medulla between the olive and the pyramid as a series of eight to ten rootlets. These rootlets coalesce into a single nerve root, known as the vagus nerve, which then exits the skull base via the jugular foramen. The vagus nerve descends in the carotid sheath, giving off three major branches: the pharyngeal branch, the superior laryngeal nerve, and the RLN. The SLN supplies sensation to the glottic and supraglottic larynx, as well as motor input to the cricothyroid (CT) muscle, which controls vocal fold lengthening and pitch. The RLN arises from the vagus nerve in the upper chest and loops under the aortic arch (left) or subclavian artery (right) and ascends back into the neck, traveling in the tracheoesophageal groove. The nerve enters the larynx posteriorly, adjacent to the CT joint. The RLN innervates the ipsilateral posterior cricoarytenoid (PCA), interarytenoid (IA) (an unpaired muscle), lateral cricoarytenoid (LCA), and thyroarytenoid (TA) muscles. Thus, the RLN supplies all of the intrinsic laryngeal muscles with the exception of the CT muscle. Ipsilateral RLN transection results in near-complete vocal fold immobility. (The ipsilateral CT muscle does not contribute to vocal fold adduction or abduction). It is important to remember, however, that the IA muscle is unpaired, and contralateral RLN input to the IA can lead to some adduction of the vocal fold on the paralyzed side (Fig. 69.2) (1).

The causes of unilateral VFP are myriad, but can be broken down into categories to highlight the relevant pathophysiology (2). These are shown in (Table 69.1).

In the past, nonlaryngeal malignancy was generally cited as the most common cause of UVFP, while iatrogenic nerve injury likely represented the most common cause for otolaryngologic referral. Recently, a large retrospective study over 20 years demonstrated a reversal of this trend, such that iatrogenic surgical trauma has now become the most common etiology for unilateral vocal fold immobility (3).

Traditionally, thyroidectomy was often thought to account for most of these iatrogenic cases. However, more recent data have shown that nonthyroid surgeries such as carotid endarterectomies and anterior cervical spine

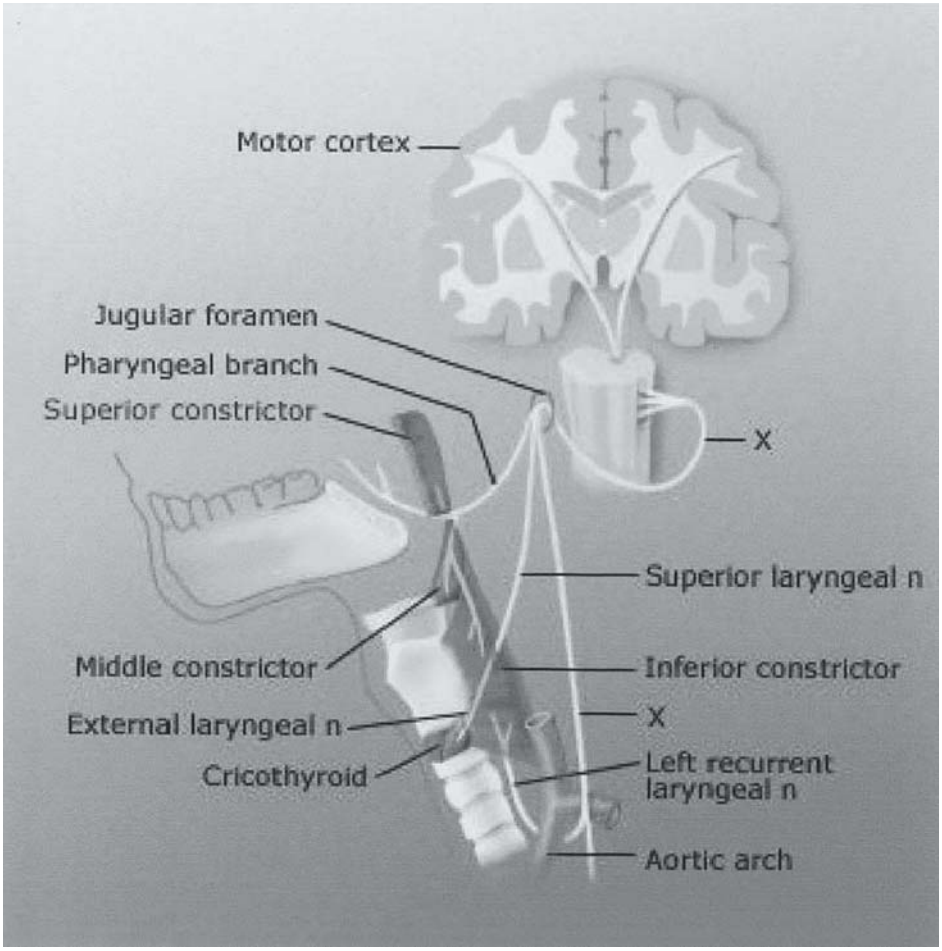


Figure 69.1 Illustration of the neural pathway for the nerves controlling laryngeal function, beginning in the central nervous system (CNS), and terminating with the RLN in the endolarynx. From Academy of Otolaryngology-Head and Neck Surgery: Patient of the Month Program, Volume 31, Number 7. Simpson CB: Breathy dysphonia. Hamilton, Ontario: BC Decker Inc., 2002, with permission.

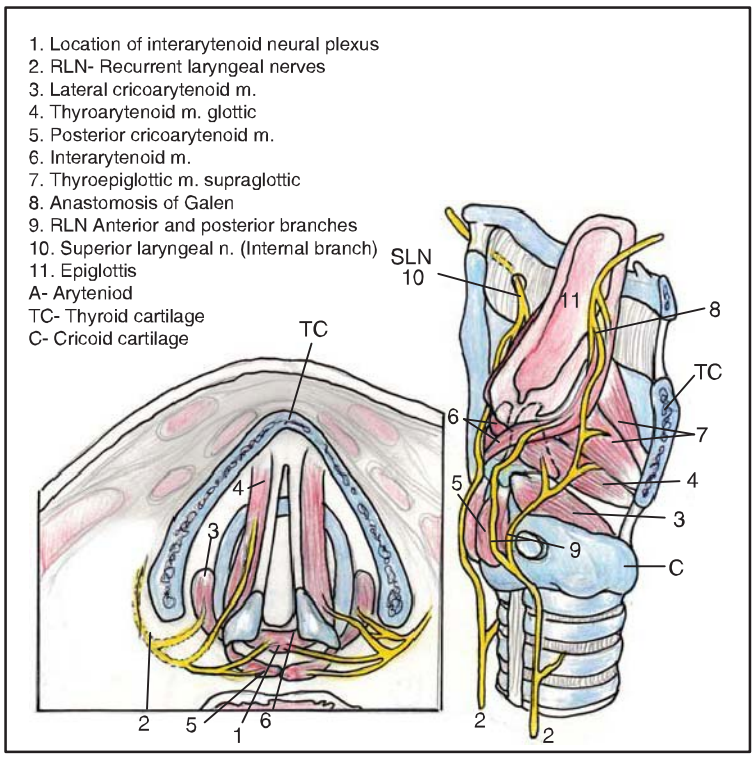


Figure 69.2 Intrinsic laryngeal musculature and innervation schematic. Note the bilateral innervation of the IA muscle by the RLN. From Rosen CA, Simpson CB. *Operative techniques in laryngology*. New York, NY: Springer, 2008, with permission.

TABLE 69.1 UNILATERAL VOCAL FOLD IMMOBILITY: CAUSES

Cause	Percentage
Iatrogenic (surgical trauma)	
Nonthyroid	30.6
Thyroid	15.7
Malignancy	
Lung	6.6
Nonlung	6.9
Idiopathic	17.6
Neurologic	7.9
Intubation	4.4
Nonsurgical trauma	2.2
Aortic/cardiac	0.6
Other	12.6

Adapted from Rosenthal LHS, Benninger MS, Deeb RH. Vocal fold immobility: a longitudinal analysis of etiology over 20 years. *Laryngoscope* 2007;117:1864–1870, with permission.

surgery are the causative etiology approximately twice as often as thyroidectomy, 31% versus 16% of all causes, respectively (3). Merati et al. (4) also reported a 47.6% rate of iatrogenic injury in 84 patients with acute vocal fold motion impairment, including 27.5% following cervical spine procedures and 15% after thyroidectomy. While iatrogenic VFP caused by anterior cervical spine surgery is clearly on the rise, it is unclear whether this increase is caused by a change in surgical technique or by a rise in the overall number of these surgeries being performed. The overall incidence of this complication has previously been reported to be around 1% but more recent studies have found a higher rate (11%) of early persistent RLN palsy (5). Netterville et al. (6) has noted that the complication is almost exclusively right-sided and is probably caused by a stretch injury of the RLN by the Cloward retractor. The shorter, more oblique course of the right RLN seems to predispose it to injury (6). Other common iatrogenic surgical causes of UVFP include esophagectomy, thymectomy, neck dissection, mediastinoscopy, and cardiothoracic surgery, including aortic surgery, coronary artery bypass grafting, and pulmonary lobar resection (2,7,8). Endotracheal intubation (9), prolonged nasogastric tube placement, and even esophageal stethoscope placement have been implicated as occasional causes of VFP (Table 69.2).

Nonlaryngeal malignancies are another common cause of unilateral VFP. The most common scenario involves bronchiogenic carcinoma of the lung associated with a left RLN paralysis. The cause in these cases is usually mediastinal spread of the malignancy into the aortopulmonary window. These paralyses rarely resolve spontaneously, and deserve early intervention. Other nonlaryngeal malignancies include thyroid, esophageal, and skull base (i.e., paraganglioma) tumors. Because of the common association of nonlaryngeal malignancies with VFP, it is imperative that all unexplained VFP cases be evaluated by means of an appropriate imaging study that looks at the full course of the cervicothoracic vagus and RLN (1).

The neurologic event most commonly associated with unilateral VFP is stroke, usually of the brainstem. In these patients, however, other neurologic symptoms (e.g., paraplegia) or additional cranial nerve (CN) involvement are the rule, and isolated unilateral VFP in this setting is highly unlikely (1). Many of these patients have severe dysphagia and aspiration caused by ipsilateral laryngopharyngeal sensory and motor deficits. Such patients can be challenging to treat, and may fail to improve despite adequate medialization surgery of the paralyzed vocal fold.

Uncommon neurologic causes of VFP include Arnold-Chiari malformation, amyotrophic lateral sclerosis (ALS), Guillain-Barré syndrome, Eaton-Lambert syndrome,

TABLE 69.2 SURGICAL OR IATROGENIC CAUSES OF VFP

Surgery or Procedure	Mechanism of Nerve Injury or Relevant Anatomy
Anterior cervical spine	Retraction; stretch injury of RLN (right more common) (6)
Esophagectomy	RLN injury in tracheoesophageal groove
Carotid endarterectomy	Vagal injury during dissection
Mediastinoscopy	RLN injury, usually left
Coronary artery bypass grafting	1. Retraction or direct injury to vagus or RLN during internal mammary artery harvest for grafting (8) 2. Hypothermic nerve injury from ice cardioplegia (7)
Pulmonary resection	Usually left upper lobe or RLN injury
Endotracheal intubation	Possible pressure neuropraxia from compression of anterior rami of RLN caused by a high-riding endotracheal cuff in the subglottis (9)

RLN, recurrent laryngeal nerve.

Parkinson disease, Shy-Drager syndrome, progressive bulbar palsy, myasthenia gravis, multiple sclerosis, and postpolio syndrome. Almost all of these disorders will have other obvious signs of progressive neurologic disease in addition to unilateral VFP and, in many cases, the neurologic condition has already been diagnosed before the patient presents with voice complaints. Most of these progressive neurologic conditions present with much more complicated (yet often subtle) findings on head and neck examination, such as a bowed vocal fold or vocal fold atrophy (Parkinson, ALS, postpolio syndrome), unexplained vocal fatigue with subtle reduced vocal fold mobility (myasthenia gravis in particular), vocal spasms (ALS), tongue fasciculations (ALS), and dysarthria (ALS, bulbar palsy). It is important to obtain a neurology consultation when a progressive neurologic disease is suspected.

Idiopathic and miscellaneous causes of unilateral VFP are also seen frequently. A few case reports suggest that "idiopathic" UVFP may be caused by herpes simplex infection (HSV1) of the vagus nerve or its branches. The injury is presumed to be an inflammatory neuropathy, similar to the cranial neuritis observed with Bell palsy (10). Although this theory is widely regarded as true, little scientific data have been published to demonstrate that HSV neuritis is the causative agent in "idiopathic" UVFP. In addition, no studies exist that evaluate the benefit of corticosteroids or antiviral medications in the treatment of this condition. Limited data are available to document the natural history of this "idiopathic" UVFP, although Blau and Kapadia (11) reported spontaneous recovery in approximately 50%. Dworkin and Treadway (12) also described spontaneous recovery in 25% of patients with more than 3-month follow-up. It is apparent that additional study is needed to evaluate the cause and treatment of "idiopathic" UVFP. Lastly, it is important to remember that idiopathic UVFP is a diagnosis of exclusion, once a detailed history and appropriate imaging studies fail to demonstrate a cause.

Rarely, medications can cause VFP. The most notorious substances are the Vinca alkaloids (vincristine and vinblastine), which are known to cause neurotoxicity. The VFP in this case is dose related and usually resolves over a 4- to 6-week period after stopping or adjusting the dose of the medication. Both unilateral and bilateral VFP have been reported (13). Cisplatinum, also a potential source of neurotoxicity, has been implicated as a cause of reversible bilateral VFP (14,15).

Systemic diseases can (also rarely) cause vocal fold immobility, because of either paralysis or joint fixation. Such diseases include gout, sarcoidosis, tuberculosis, rheumatoid arthritis, and hypothyroidism (only in cases of myxedema) (16). Again, these systemic diseases would be expected to have myriad symptoms in addition to unilateral vocal fold immobility, and these conditions should *not* be suspected in cases of isolated VFP.

In the case of endotracheal intubation leading to unilateral vocal fold mobility, it is important to rule out the possibility of arytenoid cartilage dislocation or subluxation as the true cause of an immobile vocal fold. This is best done with laryngeal electromyography (LEMG) (see below and also Chapter 70.) Other traumatic causes of VFP include blunt or penetrating injuries to the neck.

History

Vocal Quality and Swallowing

The evaluation of UVFP begins with a thorough history and physical examination. The symptoms of UVFP are well known to all otolaryngologists. These symptoms are related to glottic insufficiency resulting from some degree of lateral displacement of the paralyzed vocal fold. The primary symptom of UVFP is dysphonia, or hoarseness. The voice can vary from simple vocal fatigue in mild or well-compensated cases, to almost complete aphonia in severe cases. Much of the quality of the voice is determined by the muscular tone and position of the affected vocal fold and each patient's unique glottal compensatory strategy during phonation. An atrophic and poorly compensated VFP typically presents with a breathy, weak voice caused by air escape. The voice may also have a "watery" or "wet" quality to it if secretions are retained in the pyriform sinus, as is typical in high vagal injuries. With time, most patients eventually progress to a stronger but not normal voice using various compensatory strategies. Supraglottic hyperfunctional strategies are common. These patients constrict the supraglottic tract either laterally, apposing the false folds, or in an anterior posterior dimension, apposing the epiglottis to the arytenoids or the arytenoid cartilage to the contralateral false fold. This hyperfunctional muscular contraction leads to a characteristic rough, pitch-locked, low-frequency voice. This voice can sound similar to that of a patient with primary muscular tension dysphonia, and the diagnosis of VFP may not be suspected (17). "Unloading" of the voice, as described later in this chapter, is used to help analyze these patients. In contrast, other patients may develop an unnaturally high-pitched voice that is breathy in quality. This has been referred to as a "paralytic falsetto," and is characterized by a mean increase in fundamental frequency 85 Hz above "natural" pitch. This condition is thought to be caused by compensatory contraction of the ipsilateral CT muscle, which remains innervated in isolated RLN paralysis (18).

Swallowing difficulties are often encountered, specifically aspiration of liquids, along with a weak and ineffective cough. Some dysphagia for solids may also be present, especially in brainstem or high vagal injuries, because of the concomitant denervation of the pharyngeal constrictors. Risk of aspiration is heightened in these instances as well, because of the loss of ipsilateral laryngeal sensation from SLN involvement.

Vocal Inventory

It is important to obtain a vocal inventory of the patient's voice responsibilities (both work related and social). Vocal professionals rely on a serviceable voice for their livelihood, and these patients should be questioned regarding their upcoming work schedule to help determine the urgency of early surgical intervention (19). Most professional voice users will opt for temporizing vocal augmentation (e.g., Gelfoam, carboxymethylcellulose, and hyaluronic acid) so that they can return to work as soon as possible. Standardized patient-based voice handicap instruments are useful during the initial assessment and for documenting treatment progress (see Chapter 65).

Airway

A patient with UVFP can occasionally complain of being "short of breath"; however, careful history will show that the patient is not experiencing airway obstruction, as seen with BVFP. These patients are actually reporting a breathlessness that principally occurs during conversation and is caused by inefficient laryngeal closure. Poor glottal closure impairs the capacity to project the voice because of a "leaky" valve. Many patients increase respiratory effort and laryngeal muscle activity in an attempt to achieve glottal closure and produce a louder voice. These compensatory behaviors are mostly ineffective, placing undue strain on the paralaryngeal musculature, and resulting in vocal fatigue. This leaky laryngeal valve obviously requires increased respiratory drive to function, further contributing to the breathless feeling many patients report. In addition, exertional activity that requires lifting, pushing, and pulling can be difficult for patients with UVFP, because of the lack of an effective valsalva mechanism.

Physical Examination

General

Examination of the neck for adenopathy and thyroid masses should be performed. CN X neural compression and infiltration by a neck or thyroid neoplastic process can lead to VFP in advanced cases. Palatal movement when phonating /a/ should be observed. Palatal paralysis in combination with ipsilateral VFP may indicate a "high" vagal lesion. In the case of palatal paralysis, the palate retracts toward the uninvolved "good" side (e.g., in a left vagal paralysis, the palate retracts to the right). A complete cranial nerve examination should evaluate for other involved nerves, especially CN XI and XII because of the close proximity these have to CN X at the skull base. Involvement of these adjacent cranial nerves warrants a thorough radiographic evaluation of the base of the skull.

Laryngeal

The appropriate evaluation for VFP starts with the recognition of unilateral vocal fold immobility on examination. Indirect (mirror) laryngoscopy and rigid 70 or 90 degrees laryngoscopy are helpful, but do not replace flexible laryngoscopy. Flexible laryngoscopy is the only method to view vocal fold mobility in its natural state. Tongue protrusion, and the immobility produced by grasping it with a piece of gauze during indirect and rigid office laryngoscopy, changes the biomechanics of the larynx and can affect laryngeal examination findings. It is important to obtain an unencumbered, extended viewing period of the vocal folds during a variety of tasks. The best way to obtain this is flexible laryngoscopy.

When evaluating for suspected UVF paralysis or paresis, it is useful to ask the patient to perform an "ee-sniff" maneuver, where the patient alternates between phonating an "e" vowel and sniffing vigorously. This causes the vocal folds alternately to adduct and abduct maximally and is an excellent way to judge the degree of paresis or paralysis. Any *ab*duction of the affected vocal fold indicates incomplete paralysis (paresis), which generally has a better prognosis than total paralysis. It is important not to falsely attribute a small amount of *ad*duction of the affected vocal fold as representing evidence of partial innervation. RLN sectioning leads to paralysis of the ipsilateral TA, PCA, and LCA, but not the IA. The IA is a midline muscle, and has dual innervation from both RLN; therefore, some residual adduction may be present in complete unilateral VFP, because of innervation from the contralateral RLN.

A paralyzed vocal fold can be in a variety of positions, including lateral (cadaveric), median, paramedian, and intermediate (Fig. 69.3). It was once thought that the position of the paralyzed vocal fold had some topognostic



Figure 69.3 Laryngoscopic view of right VFP, during phonation. Note the lateralized position of the right vocal fold, and the glottal gap along the entire length of the vocal folds. Typically, the glottal gap is maximal at the posterior aspect of the vocal fold, as is seen in this patient. From Academy of Otolaryngology- Head and Neck Surgery: Patient of the Month Program, Volume 31, Number 7. Simpson CB: Breathy dysphonia. Hamilton, Ontario: BC Decker Inc., 2002, with permission.

significance (e.g., that lateral vocal fold position indicated complete CN X paralysis caused by RLN and SLN involvement). This theory was later disproved by Woodson (20). The final position of the vocal fold after nerve injury seems to be caused entirely by the degree of reinnervation and synkinesis present, and nothing else.

Some clinicians focus on the position of the arytenoid when evaluating vocal fold immobility. In most cases, it is much more fruitful to focus on the vocal fold movement itself, rather than on the arytenoid cartilage position, in determining vocal fold immobility. In some cases of vocal fold immobility, however, an overhanging arytenoid cartilage obscures the observation of the underlying vocal fold, making it impossible to ignore its position. This overhanging, anteriorly displaced arytenoid cartilage is sometimes mistaken for an arytenoid cartilage dislocation (Fig. 69.4). Electromyography (EMG) data from patients with an immobile vocal fold accompanied by an "overhanging" arytenoid cartilage, however, will almost always show complete denervation or poor reinnervation of the TA muscle (21). Therefore, in nontraumatic cases, anterior displacement or an overhanging, sagging arytenoid cartilage should *not* raise the suspicion for arytenoid dislocation.

The actual incidence of arytenoid cartilage subluxation and dislocation is a source of much debate. Many investigators believe it is an exceedingly rare clinical entity, and is almost exclusively caused by external trauma associated with motor vehicle crashes and penetrating injuries. Some laryngologists feel that intubation-related cricoarytenoid (CA) cartilage dislocation is virtually nonexistent, owing to the extremely strong supporting CA ligaments (Netterville, personal communication). A few small case reports, however, have demonstrated endotracheal intubation-associated arytenoid cartilage dislocations. A study by Sataloff et al. (22) has described 26 CA dislocations and subluxations over a 9-year period; however, only six cases in the series were EMG-confirmed cases of intubation-associated arytenoid cartilage dislocation.

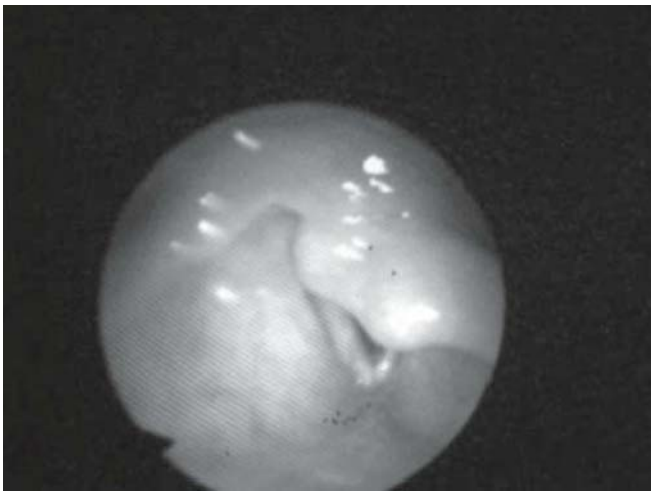


Figure 69.4 Laryngoscopic view of a patient with left vocal fold immobility and an overhanging arytenoid. LEMG confirmed that the immobility was caused by a neuropathic process, not CA joint dislocation or subluxation.

Clues that can raise the suspicion of an arytenoid cartilage dislocation when evaluating unilateral vocal fold immobility include the following:

1. Arytenoid cartilage edema
2. Difference in vocal fold level. Generally, an anterior arytenoid cartilage dislocation would result in a lower vertical position of the vocal process on the affected side. Note that vocal fold height differences are also commonly seen with VFP.
3. Absence of a "jostle sign," which is a brief lateral movement of the arytenoid cartilage on the immobile side during glottic closure caused by contact from the mobile arytenoid.

Because none of the above is pathognomonic for arytenoid cartilage dislocation, a high degree of suspicion and further diagnostic testing (such as LEMG or CA joint palpation) are needed to confirm this entity.

In some patients with UVFP, compensatory supraglottic contractions (i.e., "plica ventricularis") obscure vocal fold movement. In these cases, "unloading" of the voice is a useful technique to eliminate this unwanted effect. This may be achieved with humming or with prolonged phonation of "who." This technique is invaluable in many cases of compensated, long-standing VFP and glottic incompetence that have been misdiagnosed as "muscle tension dysphonia" or "plica ventricularis" (Fig. 69.5A and B).

Videostroboscopy is a helpful part of the workup of vocal fold movement abnormalities. Videostroboscopy may show incomplete closure or a large glottal gap in uncompensated VFP and, in these cases, useful information from the strobe examination may be limited if vibration of the vocal folds cannot be initiated. In many cases of VFP, however, the paralyzed vocal fold shows increased amplitude of vibration because of the atrophic, "floppy" nature of the denervated vocalis muscle. In cases of mild or moderate vocal fold *paresis*, the increased amplitude seen on stroboscopy may be the only sign of vocal fold weakness (Fig. 69.6) (23).

Other potentially useful information obtained via stroboscopy concerns vocal fold height differences and the status of vocal process contact during phonation. These parameters help determine the need for arytenoid cartilage adduction, when evaluating patients for laryngeal framework surgery.

A simple test to evaluate the degree of glottic incompetence is to measure the patient's maximal phonation time (MPT). This is done by simply instructing the patient to take a deep breath and to phonate an "ee" vowel for as long as possible. Normal MPT for a healthy adult is approximately 25 seconds. In cases of VFP, the MPT typically is reduced to 10 seconds or less. Shorter MPT values indicate more severe glottic incompetence, worse voice,

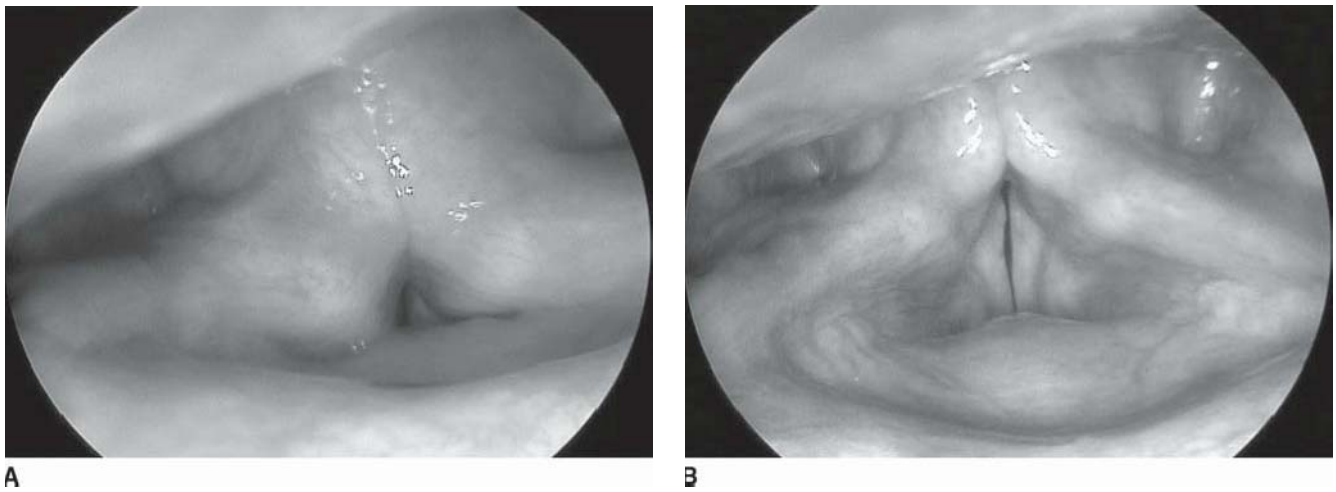


Figure 69.5 **A:** Laryngoscopic view of a patient with left VFP and compensatory supraglottic muscular constriction during phonation. Vocal fold movement and glottal closure are difficult to evaluate. **B:** Laryngoscopic view of the same patient after "unloading" (removing the supraglottic compensatory activity). The vocal folds can now be clearly seen, and a small glottal gap is noted caused by right VFP with an atrophic or "bowed" vocal fold.

and increased vocal fatigue. MPT values of 5 or less indicate severe, uncompensated VFP that may need arytenoid adduction (AA) in addition to medialization laryngoplasty (ML) (24). Poor pulmonary reserve from asthma or chronic obstructive pulmonary disease can reduce MPT significantly, so results need to be taken in context of the patient's pulmonary status and effort levels. MPT should be expected to improve (i.e., increase) after successful medialization surgery for VFP. The main limitation of MPT is the inability to distinguish between upper and lower airway sources of dysfunction. A clinically more useful indicator of glottic incompetence is the S:Z ratio. In the presence of glottic insufficiency, duration of /z/ phonation is significantly decreased but the duration of /s/ phonation remains unchanged. This phenomenon results in an increased S:Z ratio (greater than 1.4) in these patients as compared to normal controls (1.0) (25).

Lastly, it should be noted that "unilateral vocal fold immobility" is a physical finding, and not a diagnosis; the cause of the immobility must be determined. In most cases of unilateral vocal fold immobility, paralysis is indeed the underlying cause and the evaluation should reflect this accordingly. Other causes of unilateral vocal fold immobility may include CA joint arthritis (rheumatoid arthritis, gout); CA joint effusion, subluxation, or dislocation (external trauma or traumatic endotracheal intubation); or neoplastic infiltration ("occult" squamous cell carcinoma in the ventricle or paraglottic space with invasion of the RLN). In general, the history will suggest whether CA joint derangements are the culprit, and careful flexible laryngoscopy combined with computed tomography (CT) scan will reveal neoplastic infiltration as the cause of vocal fold immobility. In cases where one cannot confidently exclude the CA joint involvement or neoplasm in cases of unilateral vocal fold immobility, LEMG and a laryngoscopy (either in the office or in the operating room [OR]) with palpation for passive mobility of the vocal folds is warranted (see Chapter 73) (26).

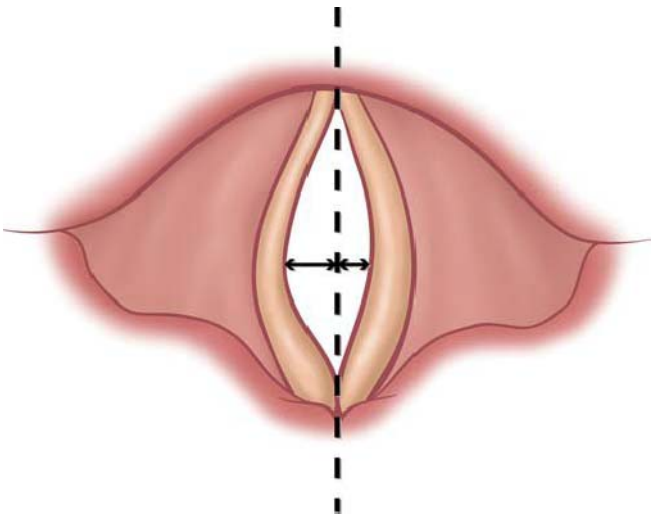


Figure 69.6 Illustration of laryngovideostroboscopy during phonation. The vocal folds are in the open phase at maximal amplitude. Note the increased amplitude (excursion of the vocal fold laterally from the midline) of the left vocal fold compared with the right. This is consistent with an atrophic, paretic left vocal fold. From Rosen CA, Simpson CB. *Operative techniques in laryngology*. New York, NY: Springer, 2008, with permission.

Workup

Serology

There is little yield from ordering screening laboratory tests such as chemistry panel, complete blood count, urinalysis,

Venereal Disease Research Laboratory, or fluorescent treponemal antibody absorption test, thyroid function tests, autoimmune panels, or erythrocyte sedimentation rate. Terris et al. (27) studied 84 patients with UVFP in which serologic studies had 0% yield in determining the cause. If additional elements of the history and physical examination point toward a systemic process as the cause of UVFP, directed serology tests may be indicated. In general, however, a "shotgun" approach to the workup of uncomplicated UVFP is unnecessary and wasteful.

Imaging Studies

As screening tools, barium swallow and thyroid scans have virtually no yield in determining the cause of VFP and are not advocated in the diagnostic workup (28). In contrast, a modified barium swallow or functional endoscopic evaluation of swallowing to evaluate swallowing and aspiration risk (29) is frequently helpful in managing cases of dysphagia in the workup of VFP.

In cases where a clear-cut temporal relation exists between surgical iatrogenic trauma and VFP, no additional radiologic workup is necessary. In cases where no cause can be found for the VFP, imaging studies are essential. Some disagreement exists to what constitutes an "adequate" radiologic assessment for unexplained VFP. Most investigators agree that a CT scan (with contrast) or magnetic resonance imaging (MRI) encompassing the base of the skull through the upper chest is adequate. The radiologist should be informed that the entire course of the vagus down to the take-off point of the RLN in the thoracic cavity needs to be included in the study. Benninger et al. (1) have argued that CT or MRI of the neck combined with chest radiography constitutes an adequate workup. They noted that 100% of pulmonary or mediastinal malignancies associated with VFP were detected on routine chest radiography, and that imaging of the chest by CT was unnecessary. Others disagree with this approach. Glazer et al. (28) demonstrated that of 18 metastatic mediastinal masses seen on CT, only 5 were visualized on routine chest radiographic study. Koufman et al. (30) advocate the addition of MRI of the brainstem in cases of obvious "high vagal" lesion (palatal paralysis + VFP), because this is a difficult area to image and small lesions can be missed.

The utility of imaging studies in the setting of vocal fold paresis is less well defined, as the presence of partial vocal fold motion is considered by many to be indicative of a lower likelihood of a radiographically identifiable compressive lesion of the RLN. These authors do not routinely perform radiologic evaluation of patients with vocal fold paresis.

Laryngeal Electromyography

LEMG has an increasingly crucial role in the workup of unilateral vocal fold immobility. The findings of LEMG are important in determining prognosis, differentiating UVFP and CA joint pathology, diagnosing suspected vocal fold paresis, and directing treatment decision making (31–36).

Useful information from LEMG is obtained between *1 and 6 months* after the onset of VFP. Evaluation outside of these parameters can render the information misleading (too early), or of limited usefulness (too late) (37). Munin et al. (37) have shown that serial LEMG provide better prognostic information in the determination of UVFP recovery.

Qualitative LEMG has been a long-time tool in the evaluation of VFP. More recent reports describe *quantitative* aspects of LEMG that provide additional information regarding prognosis (38,39). The term "spontaneous activity" refers to fibrillation potentials (spontaneous discharges during rest). This finding is consistent with active nerve denervation (Fig. 69.7B). "Recruitment" is the finding of increase in the number and rate of motor unit discharges as contraction is increased (as the patient increases the loudness of the vocalization); this can be reduced or absent with nerve injury. Normal motor unit potentials (MUP) are biphasic or triphasic, whereas polyphasic MUP indicate early reinnervation (Fig. 69.7C). Clear-cut cases of normal (class I) and grossly abnormal (class V) give good prognostic information. Statham et al. (38) have recently demonstrated that motor unit recruitment can be quantitatively measured within the TA muscle complex by a "turns analysis," evaluating the number of "turns," or peaks of the measured MUP signal. Their report evaluated both control and UVFP patients and revealed that a mean decrease in turns below 400 at maximal effort is reflective of a neurogenic lesion (Fig. 69.8).

Additionally, synkinesis reflects a misdirected reinnervation following RLN injury and/or reinnervation from nonnative nerves and is demonstrated by MUP in the TA muscle complex during vocal fold abduction tasks (such as a sniff) (Fig. 69.9A and B). The presence of synkinesis has been shown to be a poor prognostic indicator (34). Smith et al. (39) demonstrated that use of *quantitative* LEMG improves the ability to predict return of vocal fold motion, with 100% positive and 89.5% negative predictive values in their study utilizing this technique. Clearly, LEMG in general, and quantitative LEMG specifically, represent a clinically useful tool in the management of patients with VFP.

Treatment

The treatment of unilateral VFP (40) can be broken into three management strategies:

1. Observation for 6 to 12 months, reserving treatment for patients with continued symptoms
2. Referral to speech pathology for voice strengthening or swallow therapy, as indicated

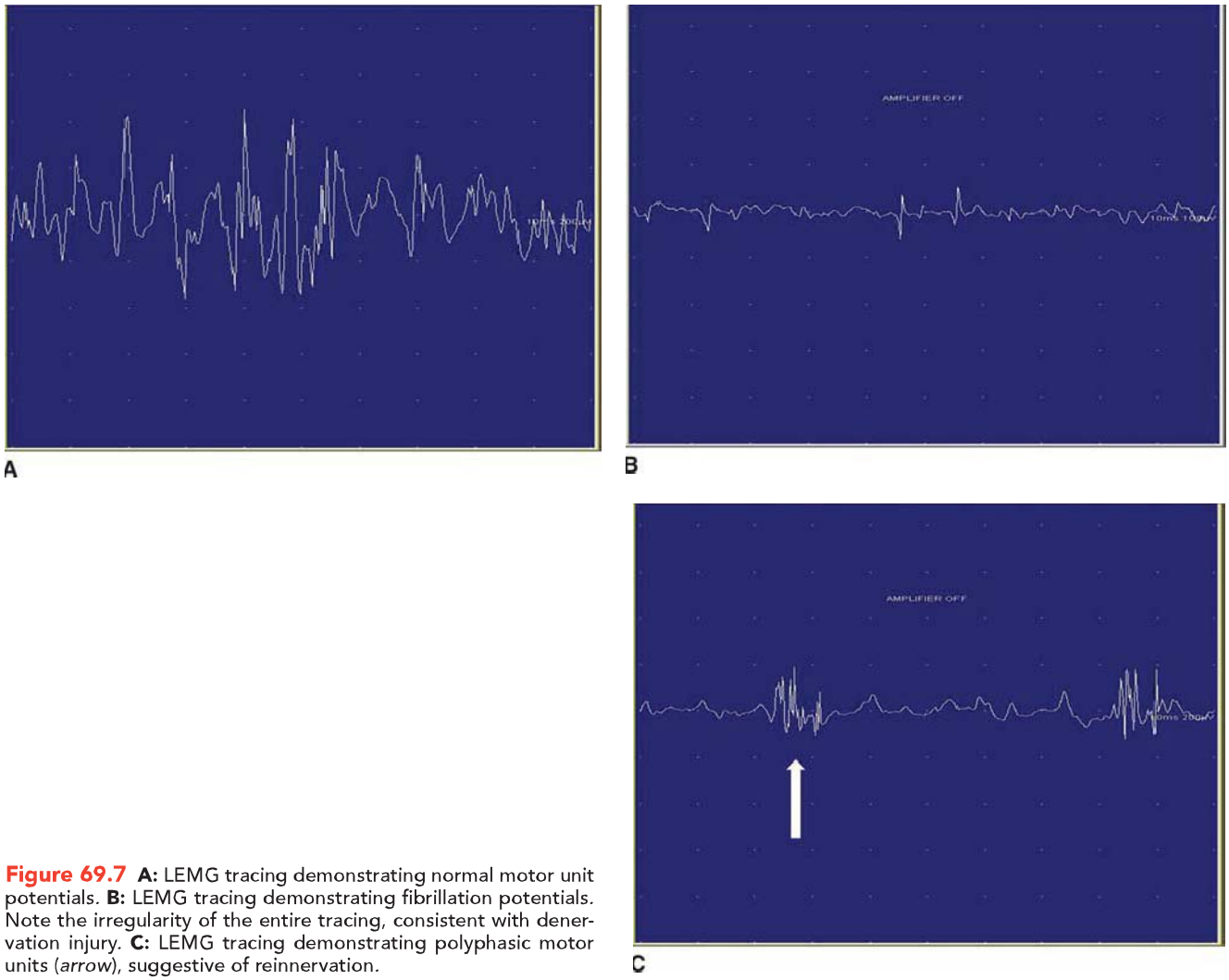


Figure 69.7 **A:** LEMG tracing demonstrating normal motor unit potentials. **B:** LEMG tracing demonstrating fibrillation potentials. Note the irregularity of the entire tracing, consistent with denervation injury. **C:** LEMG tracing demonstrating polyphasic motor units (*arrow*), suggestive of reinnervation.

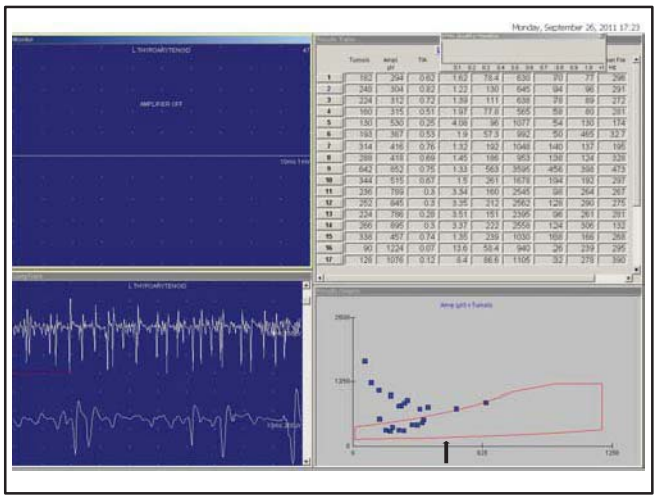


Figure 69.8 LEMG tracing depicting a graphic representation of number of "turns." Note that the majority of measurements fall below 400 (*arrow*), a finding pathognomonic for neurogenic injury.

3. Early surgical intervention:
   a. Temporary: injection augmentation of the vocal fold with temporary "filler" substance
   b. Permanent: ML (with or without AA) or injection augmentation of the vocal fold with durable substance.

Obviously, these treatment strategies can overlap or can be used simultaneously, but a management plan should be developed and followed as soon as all of the important diagnostic information is gathered. Several factors should be considered when determining the best course of action and treatment must be individualized for each patient, as shown in Table 69.3. A *treatment* algorithm is not advocated by the authors, as each patient's expectations and vocal needs are unique.

Classical teaching for the treatment of VFP advocates a watchful waiting period of 9 to 12 months before surgical intervention is considered. This management strategy was

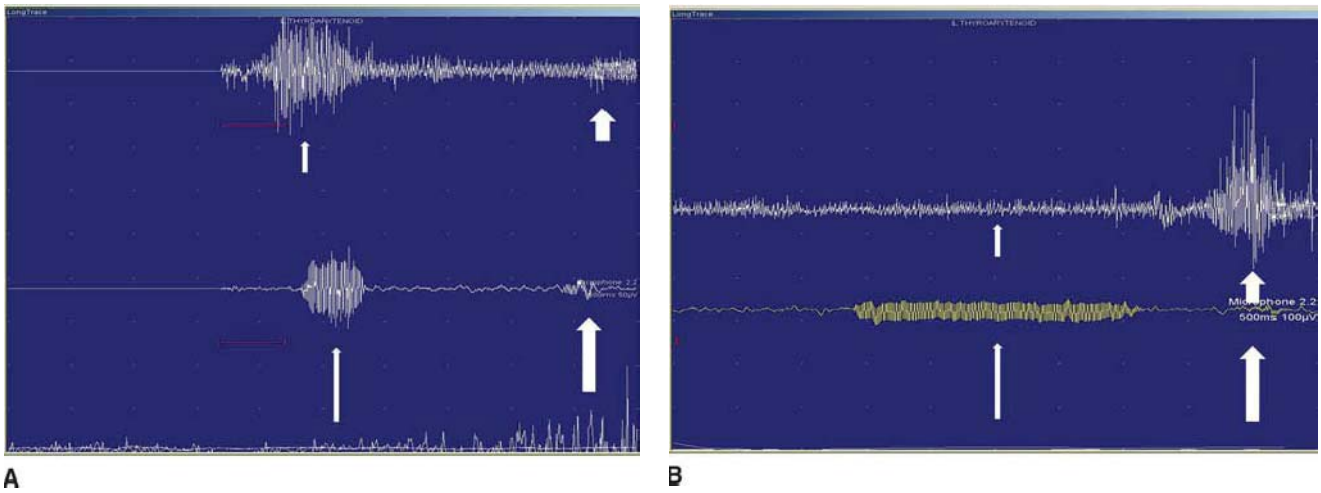


Figure 69.9 LEMG tracing demonstrating normal **(A)** and abnormal **(B)** tests for synkinesis. **A:** Activity is observed (*short narrow arrow*) in the TA/LCA muscle during phonation (*long narrow arrow*) but *not* (*short wide arrow*) during vocal fold abduction as demonstration by sniff (*long wide arrow*). **B:** In this tracing, no activity is observed (*short narrow arrow*) during phonation (*long narrow arrow*), consistent with neuropathic RLN injury. However, synkinesis is present as shown by the presence of electrical activity (*short wide arrow*) during sniff (*long wide arrow*).

TABLE 69.3 PATIENT FACTORS AFFECTING TREATMENT STRATEGY FOR VOCAL FOLD PARALYSIS

Patient Factor	Influence on Treatment (Early Surgical Intervention vs. Observation)
Presence of clinical aspiration	Favors early surgical intervention
Nature of nerve injury (transection, stretch, or unknown)	Nerve cut: favors early treatment[a]
	Nerve intact or stretch injury: favors conservative treatment (observation vs. temporizing injection laryngoplasty)
Vocal demands of patient	Nonvocal professional or limited voice use: favors observation
	Vocal professional—favors early surgical treatment
Medical comorbidity	Minimal comorbidity: all options open
	Significant comorbidity: favors local anesthetic (office-based injections vs. ML in OR)
LEMG findings	Good prognosis: favors observation or temporary injection
	Poor prognosis: favors early ML[a] or permanent injection

[a]In general, it is recommended that 2 to 3 months pass after nerve transection or injury before permanent surgery is performed to allow for muscular atrophy of the vocal fold to occur, to lessen the need for revision surgery months later.
LEMG, laryngeal electromyography; ML, medialization laryngoplasty; OR, operating room.

developed in the 1970s, when the only viable treatment option for VFP was injection augmentation with Teflon. As Teflon injection is irreversible and sometimes associated with an unfavorable vocal outcome, early surgical intervention was ill-advised during this era. Modern laryngoplastic techniques, along with an arsenal of injectable substances, have made early surgical intervention an excellent option in the treatment of VFP. Presently, 6 to 9 months following the onset of UVFP is a reasonable interval before proceeding with permanent treatment.

The decision to proceed with permanent intervention should be made on an individual, case-by-case basis and may be influenced by various considerations. The presence of unfavorable findings on serially performed LEMG (especially when performed in a quantitative manner) reflects a considerably decreased likelihood of spontaneous return of vocal fold motion. In this circumstance, awaiting the conclusion of a full 6- to 9-month observation period may be unnecessary, and it may be practical to proceed with permanent surgical treatment even as early as 4 to 5 months after onset of VFP. The nature of the VFP is also an important issue. A patient who has undergone known resection of the RLN (such as in an oncologic procedure) may be appropriate for earlier permanent intervention, particularly if unfavorable LEMG findings are found. Finally, patient factors (such as symptomatology, geographic distance, and patient preferences, age, vocal demands, and comorbidities) should also be taken into account.

The most appropriate time to pursue surgical intervention may vary considerably on an individual basis. The

authors advocate careful consideration of all pertinent factors when determining the most appropriate time to pursue both early as well as permanent surgical intervention.

Determining the Need for Early Intervention

Early surgical intervention is indicated for patients with clear-cut aspiration caused by VFP. Evidence of severe denervation injury (class V) on LEMG can also lead to early surgical intervention. Clinical experience has shown that RLN paralysis caused by pulmonary carcinoma or iatrogenic thoracic surgery injury (especially repair of aortic aneurysm) rarely recovers, and patients are counseled to consider early permanent intervention in these cases. Patients with VFP and high-level vocal demands (e.g., sales persons, clergy, teachers, attorneys) often have difficulty continuing their work-related duties. In these cases, it may be necessary to intervene early (less than 6 months) to get the patient back on the job. Temporary surgical procedures (e.g., injection augmentation of the vocal fold with temporary materials) should be considered in this population. More recent reports also suggest that early temporary injection medialization may decrease the need for permanent intervention by encouraging the vocal fold to maintain a more medialized position (41,42). Additional clinical study is needed to investigate this concept further.

The medical health of the patient should be considered. Patients with significant cardiopulmonary and other medical comorbidity may not be candidates for a general anesthetic (i.e., for microlaryngoscopy with vocal fold injection augmentation), yet may be perfectly suitable for ML or injection augmentation performed under local anesthesia. In most cases, the patient should be counseled regarding the different treatment options, including the advantages and disadvantages of the three main strategies of treatment. In this way, the patient can actively participate in the decision-making process (40). When LEMG is available, it can serve as a crucial guide to the patient and surgeon regarding (a) treatment or observation and (b) temporary versus permanent treatment (37).

Surgical Treatment

Injection Augmentation

Injection augmentation with temporary materials is an excellent means of temporizing the patient's voice for weeks to months while awaiting return of function. General characteristics of the current materials available for augmentation are listed in Table 69.4. Specific information regarding preparation of the injectables, as well as injection techniques, is contained in the references. The reader is encouraged to consult these references before using the materials for injection augmentation. Additional information is also available in Chapter 73.

Several points are worth highlighting. Gelfoam as an injected material (43) is too short-acting to justify a trip to the OR, and is rarely employed. Bovine collagen injectables (44) (Zyplast, McGhan Pharmaceuticals, Santa Barbara, CA) reliably lasted 4 to 6 months and were a good temporizing substance but were recently discontinued and are no longer available. Cymetra, or micronized AlloDerm (LifeCell Corporation, Branchburg, NJ), does not require skin testing, is immediately available for injection with a moderate degree of preparation, and lasts between 2 and 4 months. The length of effect is somewhat variable and unpredictable. Sodium carboxymethylcellulose (Radiesse Voice Gel, Merz Aesthetics Inc., San Mateo, CA) was introduced in 2005, is United Stated Food and Drug Administration (FDA) approved, lasts between

TABLE 69.4 LARYNGEAL INJECTABLES

Material	Length of Effect	Advantages	Disadvantages
Gelfoam	4–6 wk	Long track record	1. Short duration 2. Must use 18 g
Cymetra (Micronized AlloDerm)	2–4 mo	No allergy testing	1. More prep time 2. Expensive 3. Unpredictable
Fat	2 yr+ (Possibly permanent)	Autologous Forgiving	1. Time/morbidity from harvest 2. Unpredictable
Teflon	Forever	Long lasting	1. Granuloma 2. VF stiffness
Radiesse (calcium hydroxylapatite)	18 mo	1. 24 g needle 2. Long lasting	Risk of VF stiffness with superficial injection
Radiesse Voice Gel (carboxymethylcellulose)	1–3 mo	1. 24 g needle 2. Temporary/trial VFI	
Restylane (hyaluronic acid)	2–4 mo	1. 25 g needle (office) 2. Temporary/trial VFI	Few data

2 and 3 months, and has excellent safety and efficacy rates (45,46).

Calcium hydroxylapatite (Radiesse, Merz Aesthetics Inc., San Mateo, CA) was developed as a longer-lasting alternative for augmentation (47). Initially believed to last up to 2 to 5 years, more recent studies have demonstrated excellent long-term results but with an average duration of only 18 months (48–50). Hyaluronic acid (Restylane, Medicis Aesthetics Inc., Scottsdale, AZ) has potential implications for use both in vocal fold augmentation as well as in treatment of vocal fold scar but requires further study (51,52). The disadvantages of Teflon are well known (53), and most otolaryngologists have abandoned the use of this substance except in rare instances. Autologous fat (54) continues to be a relatively unpredictable substance, with some patients having complete resorption of the fat in 2 months, whereas others show persistence of the fat for years. Fat has been frequently described as a "forgiving" substance, in that less-than-perfect injection placement can still result in good voice results. Lipoinjection requires overinjection by a significant degree (sometimes as much as 100%) to correct for the expected resorption of fat in the first 4 to 6 weeks (55).

The injected material is typically delivered through a Bruening syringe (Storz Medical AG, Kreuzlingen, Switzerland), orotracheal injector (Medtronic Xomed, Jacksonville, FL), or transoral needle (Merz Aesthetics, San Mateo, CA), depending on the substance injected and the needle gauge required. Injections should be placed in the "deep" portion of the vocal fold to avoid disruption of the superficial layer of the lamina propria. The intended injection location is the medial aspect of the TA muscle (vocalis), at the midmembranous and posterior vocal fold (Fig. 69.10). Injection into the ligament has been advocated by some authors, but Courey (56) has shown that the limitations in the size of the needle gauge used make vocal ligament injection virtually impossible. Care should be taken not to inject superficially into Reinke space, because this can result in permanent loss of vibratory function.

Injection laryngoplasty can be performed under local anesthetic in clinic with flexible or rigid telescopic guidance, using either transcutaneous or peroral approach (Fig. 69.11A, B, and C). The advantages of this approach to injections include patient convenience and improved voice feedback in gauging the amount of injection needed. Alternatively, injection laryngoplasty via direct laryngoscopy can be performed under general anesthetic, with either telescopic or microscopic guidance. The advantages of the latter are improved precision and patient comfort (especially for patients with an active gag reflex). Disadvantages include lack of vocal feedback to gauge the injection. Ultimately, the technique used and material selected for injection laryngoplasty depends on the surgeon's experience and comfort level (57).

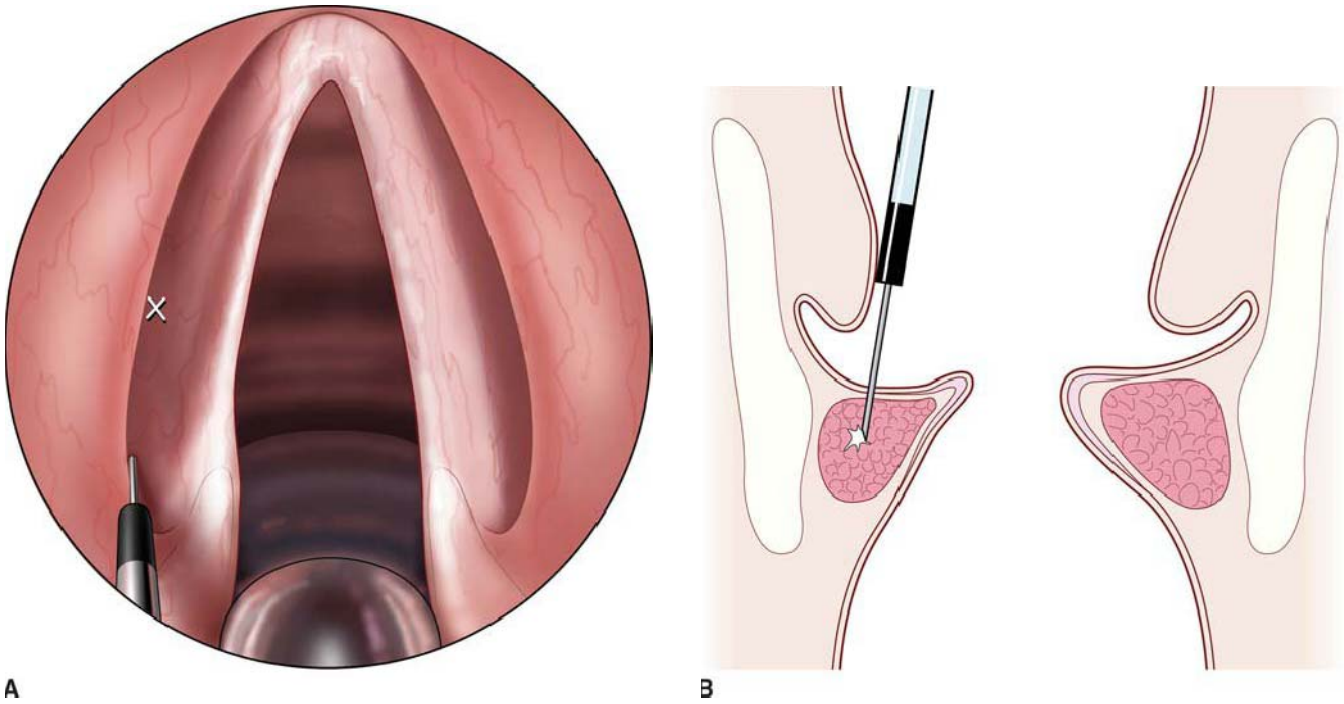


Figure 69.10 **A:** Illustration of an injection augmentation of the left vocal fold under direct laryngoscopy. "*X*" marks the injection site seen on direct visualization, at the posterior aspect of the vocal fold, lateral to the vocal process. **B:** The depth of injection into the TA muscle is depicted on coronal section. The needle tip should be deep into the vocal fold, and not superficially in Reinke space. From Rosen CA, Simpson CB. *Operative techniques in laryngology.* New York, NY: Springer, 2008, with permission.



Figure 69.11 Fiberoptic laryngoscopy view from a right vocal fold injection augmentation. **A:** Preinjection. **B:** Initial injection. **C:** Postinjection. From Rosen CA et al. Advances in office-based diagnosis and treatment in laryngology. *Laryngoscope* 2009;119:S185–214, with permission.

Framework Surgery for UVFP: Medialization Laryngoplasty (ML) and Arytenoid Adduction (AA)

Laryngeal framework surgery including ML (specifically type I Isshiki thyroplasty) and AA are currently considered standard treatment for long-term treatment of unilateral VFP. Isshiki perfected the technique of thyroplasty in the early 1970s, but it was Koufman who popularized the technique in the United States and advocated the use of hand-carved silicone elastomer (Silastic) implants instead of cartilage.

The technique of ML represented a considerable departure from the traditional management of VFP. The operation is reversible (unlike Teflon injection laryngoplasty, the primary treatment for VFP in the 1970s and early 1980s), and fine-tuning of the voice result can be achieved, because the procedure is performed under local anesthesia. Multiple medialization materials have been developed and currently include Gore-Tex strips (Gore Medical, Inc., Newark, DE), the preformed silicone Montgomery system (Boston Medical Products, Inc., Westborough, MA), silastic Netterville PhonoForm block (Medtronic ENT, Inc., Jacksonville, FL), hydroxyapatite VoCoM systems (Gyrus ACMI, Inc., Bartlett, TN), and titanium Kurz implant (Heinz Kurz, Dusslingen, Germany). A recent preliminary study also evaluated an adjustable silicone balloon implant in excised canine larynges (58).

The optimal choice of medialization implant material has long been debated. However, there are few studies that directly compare medialization implants (59–61). All of these studies are limited by early postoperative assessments without long-term follow-up and do not clearly identify a superior long-term option. Future prospective studies with extended follow-up are needed to determine what differences, if any, exist in the long-term results following implantation of these various materials.

No one implant material is superior to another in performing ML. It is mostly a matter of surgeon preference. In past years, use of a custom-carved Silastic block as described by Netterville et al. (62,63) was a preferred technique by many surgeons. Proponents of this technique praised its precise medialization and superior voice results. With the introduction of other, less time-intensive materials, the use of custom-carved Silastic block has significantly decreased. Currently, the choice of implant material is mostly based on surgeon preference but appears to more often involve the use of Gore-Tex strips or prefabricated implants (64). The reader is encouraged to review appropriate references for more detailed descriptions of ML (62,63,65,66).

Most patients having ML have good to excellent voicing intraoperatively, but develop varying degrees of postoperative dysphonia as a result of paraglottic edema or submucosal hemorrhage. Within hours, a good postoperative voice will become rough and breathy. The patient should be warned of this before the surgery. In the past, all patients were kept for 23-hour observation, because of concern for airway edema. However, ML is increasingly performed as a same-day surgery, although additional caution is advised in cases of bilateral ML. In a survey of 860 otolaryngologists performing nearly 24,000 ML procedures, the rate of airway-related complications were low, including prolonged observation (greater than 24 hours) in 2%, intubation in 0.1%, and tracheostomy in 0.07% of cases (64). To decrease the risk of airway compromise secondary to edema, preoperative intravenous dexamethasone is given (10 mg), followed by two additional (8 mg) doses at 8 and 16 hours postoperatively. The period of postoperative dysphonia is variable, but can last between 2 and 6 weeks (62). Rare cases can persist up to 3 months. Voice conservation is advocated; total voice rest is unnecessary.

Both Silastic and Gore-Tex implants are reversible (67,68), if revision surgery is necessary at a later date. A thin, fibrous capsule forms around the implant, and this must be incised and released at the medial aspect to allow for medialization without tethering. Neither Gore-Tex nor Silastic implants are overly problematic in revision surgery, as long as a single strip of Gore-Tex is used (as opposed to multiple small strips), and the implant is not inadvertently placed too deep (in the substance of the TA muscle), which seems to lead to excessive fibrosis and tethering of the implant.

Patients who have had successful ML, with or without AA, often express concerns about the safety of having endotracheal intubation for surgical procedures in the future. A waiting period of 6 months post-ML (if the proposed surgery is elective) is advised. The anesthesiologist should place a 6.0 endotracheal tube (or smaller) to avoid inducing laryngeal edema from a slightly constricted glottic aperture. The risk of perioperative airway complications in this population remains low (less than 7%) but is not negligible. All health care personnel (surgeon, anesthesia, and nursing) involved in the perioperative care of these patients should be aware of this particular risk (69).

ML is an operation designed to augment or medialize the vocal fold in three dimensions: anterior-posterior, medial-lateral, and superior-inferior. During ML, the surgeon should be aware of these three dimensions and have the ability to control the implant shape in each of these dimensions. ML is an operation that has a simple premise (implant placement for vocal fold medialization) but nuances are present, which can significantly impact the success of the surgery. In general, the surgeon must avoid

placement of the implant too anterior (strained voice quality) or too superior. These are the most common mistakes made in ML surgery (70). Other revisions typically include placement of a larger implant (which may be required due to perioperative vocal fold edema obscuring accurate visualization at the time of the primary surgery) although replacement with a smaller implant or repositioning of the current implant are sometimes needed (64). Experience with ML surgery (greater than 10 and a frequency of 2 or more per year) has been shown to decrease the likelihood of postoperative complications (including lack of voice improvement) (70). Nevertheless, ML has a high success rate, with revision rates around 5% to 6% (64,70).

AA is an important adjunct in selected cases of VFP. This operation involves placement of a suture from the muscular process of the arytenoid to an anterior location on the thyroid cartilage. This simulates the action of LCA contraction. The physiologic effects of AA are not completely understood, and some debate continues. General consensus exists concerning the following basic premises (71):

Arytenoid adduction:

- Lowers the position of the vocal process
- Medializes and stabilizes the vocal process
- Rotates the arytenoid cartilage.

In patients with VFP who have a lack of vocal process contact during phonation (large posterior gap) and those with vocal folds at different levels, AA should be considered in addition to ML. Videostroboscopy often provides valuable information about vocal process contact and vocal fold height and, therefore, is useful preoperatively in assessing whether a patient needs an AA. MPT of less than 5 seconds has also been identified as a predictor of the need for AA in cases of VFP (24). The technique of AA was originally described by Isshiki, and excellent illustrations of the technique have been published by Netterville et al. (72).

Laryngeal Reinnervation

Various procedures attempting to reinnervate the larynx have been proposed. These include direct end-to-end anastomosis of the RLN, hypoglossal-to-RLN anastamosis, ansa cervicalis-to-RLN anastamosis, neuromuscular pedicle, free nerve grafting, and nerve implantation procedures. Much controversy has surrounded the utility of these procedures. In most reports, the main postoperative benefit seen was improved vocalis muscle tone, rather than purposeful vocal fold motion. More recent reports have also described LEMG findings of increased recruitment suggestive of reinnervation (73–76). In a recent multicenter randomized trial, Paniello et al. (77) directly compared ML and laryngeal reinnervation and found no difference between these procedures.

Other Therapies

Preliminary studies in a small number of animal and human subjects have shown early promise in the use of nimodipine in the treatment of acute VFP. Nimodipine may facilitate growth of the regenerating nerve via an effect on its calcium channels (78–82). Clinical trials are needed to investigate this modality further.

BILATERAL VOCAL FOLD PARALYSIS

Bilateral vocal fold immobility (BVFI) can be caused by either BVFP or posterior glottic stenosis (PGS) with or without CA joint fixation. It is important to distinguish clinically between these two entities to successfully manage BVFI.

Etiology

The etiology of BVFP is listed in Table 69.5. In most cases, BVFP is caused by iatrogenic surgical injury (55.5% to 82.8%), and most of these cases occur during thyroid surgery (3,4,83). Malignancy (esophageal or bronchogenic), neurologic, traumatic, and idiopathic causes account for the remainder of cases. In contrast to the data listed for BVFP, BVFI does not have one dominant cause (2) (*see Table 69.5*), probably because this group of patients represents a more heterogeneous population of both paralysis *and* stenosis cases.

It is clear that most patients with BVFP present a simple diagnostic picture that points to iatrogenic surgical injury involving both RLN; in these cases, little diagnostic workup

TABLE 69.5 ETIOLOGY OF BVFP AND BILATERAL VOCAL FOLD IMMOBILITY (BVFI)

Etiology	Percentage
BVFP[a]	
Iatrogenic (surgical trauma)	55.5
Thyroid surgery	48.6
Nonthyroid surgery	6.9
Malignancy (lung/nonlung)	9.7
Intubation	9.7
Idiopathic	8.3
Neurologic	6.9
Trauma	1.4
Other	8.4
BVFI[b]	
Iatrogenic	25.7
Malignancy	17
Neurologic	12.8
Intubation	15.4
Idiopathic	12.8
External trauma	11.1
Rheumatoid arthritis or inflammatory disease	3.4
Radiation therapy	1.7
TOTAL	100

[a]Adapted from (3) Rosenthal LHS, Benninger MS, Deeb RH. Vocal fold immobility: a longitudinal analysis of etiology over 20 years. *Laryngoscope* 2007;117:1864–1870, with permission.
[b]Adapted from Benninger MS, Gillen JB, Altman JS. Changing etiology of vocal fold immobility. *Laryngoscope* 1998;108:1346–1349, with permission.

is necessary. In some uncommon circumstances, the finding of BVFP may represent an acute unilateral VFP in the presence of a previously undiagnosed preexisting paralysis of the contralateral vocal fold, such as may occur in completion thyroidectomy procedures. These so-called "staged" BVFP can be identified by electromyographic findings and may be preventable with appropriate preoperative evaluation, including laryngoscopy. The noniatrogenic presentations of BVFP, however, often require an extensive and detailed workup to reveal the cause. So-called "idiopathic" causes of BVFP are rare, in contrast to UVFP. In addition, a substantial number of rare neurologic conditions can present with BVFP, and an extensive differential diagnostic list (Table 69.6) should be used as a guide in the workup of "unexplained" BVFP (84,85). Often, a neurology consult is needed to sort out complex presentations of BVFP.

TABLE 69.6 NONSURGICAL CAUSES OF BILATERAL VOCAL FOLD PARALYSIS

I. Neurologic
  a. Transient ischemic attacks or stroke
  b. CNS neoplasms
  c. CNS infections and Creutzfeldt-Jacob disease
  d. Arnold-Chiari malformation
  e. Idiopathic congenital bilateral vocal fold paralysis
  f. Hydrocephalus
  g. Meningomyelocele
  h. Syringomyelia
  i. Traumatic brain injury
  j. Myoclonus
  k. Parkinson-plus syndromes
    i. Multiple-system atrophy
    ii. Shy-Drager
    iii. Progressive supranuclear palsy
  l. Myasthenia gravis
  m. Spinocerebellar ataxia
  n. Charcot-Marie-Tooth
  o. Poliomyelitis and post-polio syndrome
  p. Multiple sclerosis
  q. ALS
  r. Guillain-Barré syndrome
  s. Myopathy
  t. Pseudotetanus (spasmophilia, hyperventilation)
II. Malignancy
  a. Bronchogenic cancer
  b. Esophageal cancer
  c. Thyroid cancer
III. Endocrine or metabolic
  a. Diabetes mellitus
  b. Hypokalemia or hypocalcemia
IV. Medication
  a. Vincristine therapy
  b. I-131 treatment
V. Other
  a. Endotracheal intubation
  b. Nasogastric tube syndrome
  c. Radiation therapy

Adapted from Dray TG, Robinson LR, Hillel AD. Idiopathic bilateral vocal fold weakness. *Laryngoscope* 1999;109:995–1002, with permission.

Clinical Presentation and Evaluation

The clinical presentation of BVFP is considerably different from that observed in patients who present with UVFP. The chief presenting complaint in BVFP is typically shortness of breath or stridor, often accompanied with a normal voice. The vocal folds typically drift to the midline soon after neural injury (although this can be delayed for days or weeks in some cases). This leads to a narrow 1- to 3-mm slit-like glottic inlet, which results in airway compromise (Fig. 69.12). The degree of airway compromise, which is highly variable, can range from mild stridor associated only with exertion to life-threatening airway obstruction. Voice quality can be relatively good because of the close proximity of the immobile vocal folds. It is not uncommon, however, for patients to demonstrate a monotone voice and a speech pattern characterized by short, hurried phrases followed by stridorous, inspiratory interruptions.

Clinical History

The most important part of the history when evaluating a patient with BVFP is the surgical history. Specifically, one must inquire whether the patient had any neck, chest, or neurosurgical procedures before the onset of the current condition. In general, most patients with BVFI have a straightforward history that suggests an iatrogenic cause, because the onset of breathing difficulty is temporally related to a surgical procedure that puts both RLN at risk. This is seen most commonly with thyroidectomy. In most cases, the patient develops stridor immediately on extubation or several hours after the procedure, and a prompt evaluation by an otolaryngologist reveals the typical findings of BVFI. It is important for the otolaryngologist to specifically inquire about the integrity of the nerves directly with the surgeon (if acting as a consultant): specifically, whether the nerves were identified and preserved, never identified, or a known nerve transection occurred. This information is not often very revealing, but may help determine the immediate course of action in some cases.

In cases where no clear-cut and immediate surgically induced (neck or chest) RLN trauma exists, three primary

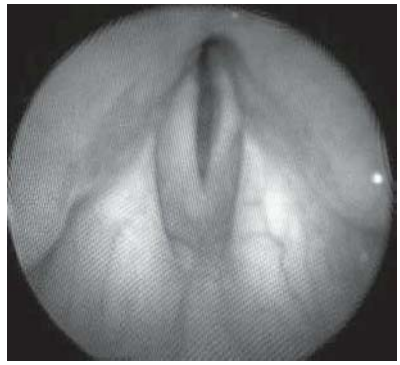


Figure 69.12 Fiberoptic laryngoscopy of the larynx in a patient with BVFP. Both vocal folds are immobile and located near the midline, resulting in airway obstruction.

questions help to sort out the direction of subsequent workup (85):

1. History of rheumatoid arthritis
2. History of blunt or penetrating neck trauma
3. Endotracheal intubation in non-neck or -chest cases, especially if a history of prolonged ventilatory dependence exists

If any of the above questions are positive, a high likelihood exists that CA fixation or PGS is the cause of the bilateral immobility, not paralysis. This necessitates a different diagnostic algorithm than that used for bilateral paralysis. On the other hand, if the answer to all three questions above is negative, then BVFP is almost certainly present, and represents a manifestation of a progressive neurologic, congenital, endocrine, metabolic, toxic, neoplastic, or inflammatory condition. These conditions are listed in Table 69.6. As can be observed, this is an extensive and exhaustive list of causes that make up a small fraction of an already rare condition, BVFP.

Because of the rarity of noniatrogenic BVFP, it is best to keep a differential diagnostic list handy for review when this scenario presents itself. Frequently, the admitting or treating physicians in these difficult cases (internal medicine, neurology) are *not* aware that BVFP can be a manifestation of the conditions listed in Table 69.6. For this reason, the otolaryngology consultant can provide valuable information to the team both by identifying the presence of BVFP and by providing a differential diagnostic list to the consulting physicians.

Physical Examination

The physical examination should consist of a complete head and neck examination (84) as well as neurologic assessment and cranial nerve examination. The most important part of the physical examination in patients presenting with BVFI, however, is a systematic and detailed flexible laryngoscopic examination.

Workup

Serology

No justification is seen for ordering routine screening laboratory serum tests in the workup of unexplained BVFI. A directed battery of tests can be used at the discretion of the medical or neurology team, based on suspected causes. In the rare case of pediatric congenital BVFP associated with other congenital abnormalities, chromosomal analysis should be performed along with evaluation by a geneticist (86).

Imaging

In unexplained cases of adult BVFI, imaging studies (generally MRI) can be ordered to evaluate for base of skull, brainstem, neck, or mediastinal pathology. In the pediatric population with BVFI, MRI is particularly valuable because 40% of cases are neurologic in origin. The common causes of BVFI in children are related to hydrocephalus and Arnold-Chiari malformation (87).

Neurology and Internal Medicine Workup

As stated, noniatrogenic cases of BVFP are rare, but an otherwise unexplained finding of BVFP in a patient should raise suspicions that an underlying global disease process is present. A thorough workup by the patient's medical team (with neurology consultation) is imperative in these rare cases.

Laryngeal Electromyography

LEMG is an important component of the evaluation for BVFI. Hillel et al. (84) advocate testing of not only both TA and CT muscles, but of the PCA muscles bilaterally as well. Evidence of PCA activity during phonation of "eee" is considered abnormal synkinetic activity. In contrast, TA activity can occur during a sniff, but it should not represent the predominant activity of the TA (i.e., more motor units should be recruited in the TA during phonation).

The utility of LEMG is as follows:

1. LEMG can differentiate between VFP, synkinetic laryngeal muscular activity, and vocal fold CA joint fixation
2. LEMG can be useful in determining the prognosis for recovery of vocal fold mobility, which can assist in treatment planning
3. LEMG can determine if the cause is peripheral or central in origin, because myopathic processes demonstrate unique EMG findings
4. LEMG can determine which vocal fold has the most robust neuromotor status. This assists in determining which vocal fold should be selected for any destructive, glottic enlargement procedure (see below).

Because of the tentative airway status in patients with BVFP, caution should be taken if LEMG is to be performed in these patients in the clinic setting.

Laryngoscopy and Palpation for Vocal Fold Mobility

Despite the expanding role of LEMG in the evaluation of BVFI, laryngoscopy with examination under anesthesia (either general or local) still provides clinically useful information. This examination should include inspection of the IA space for scarring, along with palpation of the vocal folds for passive mobility. It is important to note that IA scarring, CA joint fixation, and VFP can all coexist in the same patient. An abnormal LEMG suggests paralysis as the cause of vocal fold immobility, but it *does not* rule out PGS and/or CA joint fixation as a contributing factor. The only reliable method to evaluate for PGS and/or joint fixation is to examine the posterior commissure, and test for passive vocal fold mobility (88).

When performed in the OR, the evaluation should be carried out *without* an endotracheal tube in place and *without* the laryngoscope suspended to obtain an unobscured view of the glottis; jet ventilation can be used for patients who do not have a tracheostomy in place. In patients with PGS, the posterior glottic space is obliterated by scar tissue, giving the residual glottic airway a triangular shape (Fig. 69.13). In contrast, patients with BVFP (no stenosis) have an airway that resembles an ice cream cone, with the



Figure 69.13 Larygoscopic view of the larynx in a patient with PGS. Note the triangular appearance of the glottic aperture caused by the loss of the posterior (respiratory) glottic region.

preservation of the posterior glottic space representing the scoop of ice cream (Fig. 69.14).

Palpation of the CA joint is performed by using a sturdy instrument (e.g., a large cup forceps in the OR or an Abrams cannula in the office), placing it adjacent to the vocal process and swiftly pushing the vocal process laterally. With this maneuver, the surgeon can gauge the degree of effort required to laterally displace the vocal process as well as the speed of the recoil of the tissue in a medial direction. This same procedure should be done on the contralateral side and used to compare the degree of stiffness and range of motion of the CA joint. During this maneuver, the posterior glottis and contralateral vocal fold should be observed. In patients with PGS or IA scarring, the posterior commissure and contralateral arytenoid cartilage will be moved to the midline during the vocal process palpation because of the entire posterior glottic complex being fused with scar tissue.



Figure 69.14 Laryngoscopic view of a normal larynx. The airway has roughly the shape of an ice cream cone.

Management

Initial Management of the Airway

The management strategy for BVFP varies, depending on a variety of factors described in the treatment planning for UVFP (Table 69.3), with one key difference. The main determinant for intervention is the status of the patient's airway. A patient with BVFP who rapidly develops progressive stridor and air hunger needs immediate intervention. Generally, endotracheal intubation is preferred as the initial management. It is important to note that intubation is used to secure the airway in cases of BVFP, but *not* when PGS is present. Intubation gives the medical team valuable time to gather more data on the patient, so that an informed decision can be made regarding short- or long-term airway management strategies. Although a temptation to secure the airway with a tracheostomy exists, some cases of bilateral RLN neuropraxic injury can be managed expectantly with intubation and sedation in an Intensive Care Unit setting, IV corticosteroids, and controlled extubation in the OR several days later. This is a particularly appealing strategy when the patient has a fresh neck wound after thyroidectomy. In general, if symptomatic BVFP is still present 5 to 10 days after iatrogenic injury, securing the airway with a tracheostomy or possibly a temporizing measure (listed below) is a reasonable plan of action. LEMG can be useful to plan early treatment versus observation (in anticipation that recovery of mobility in one or both vocal folds may occur).

Temporizing (Reversible) Treatments

Tracheostomy

Tracheostomy is an excellent treatment to secure the airway until adequate time passes for spontaneous recovery to occur (6 to 12 months). In general, it is not a good long-term strategy, because most patients are unhappy with permanent tracheostomy. This is especially true in light of the many endoscopic treatments that can preserve reasonable voice quality and allow for decannulation.

Endo-Extralaryngeal Suture Lateralization

Endo-extralaryngeal suture lateralization, as popularized by Lichtenberger and Toohill (88), is a viable option for temporizing the patient's airway in select cases of BVFP. The technique uses a nonabsorbable suture placed endoscopically above and below the posterior vocal fold at the region of the vocal process. The suture can be brought out over the thyroid ala, or through the skin of the neck and secured over a button externally. Suture tension can be adjusted intraoperatively and postoperatively to fine tune the degree of vocal fold lateralization or airway aperture.

Laryngeal Botox Injection

In carefully selected cases of BVFP, where airway obstruction is not imminent and airway symptoms are principally exertional, laryngeal Botox injection into the TA–LCA muscular complex may result in minor airway improvement (89) that lasts 2 to 4 months. The symptomatic

improvement is thought to result from blocking of synkinetic TA activity during inspiration. Side effects are breathy dysphonia, aspiration of liquids, or both, which are temporary in nature. A suggested dose to achieve symptomatic improvement is 2.5 mouse units in each vocal fold (90).

Long-Term Surgical Solutions

An important concept must be brought to the attention of the patient during preoperative counseling: almost all procedures designed to treat BVFP, except tracheostomy, result in some degree of dysphonia. In general, surgical interventions cannot simultaneously result in improvement in airway without some degree of loss of vocal function; one is generally improved at the expense of the other. The vocal folds can be approximated more closely to improve the voice, but the airway narrows. Similarly, the vocal folds can be separated to open the airway, but the voice suffers. This concept must be explained to the patient, so that realistic expectations can be established preoperatively. Any discussion of surgical treatment of BVFP that does not involve the "airway for voice" equation is flawed.

Transverse Cordotomy

Endoscopic CO_2 laser transverse cordotomy (TC) is an excellent surgical option. Originally described by Kashima (91) in 1991, this technique is technically less demanding than an endoscopic laser arytenoidectomy, and appears to result in comparable airway enlargement. Vocal quality in patients who have undergone TC does worsen, becoming slightly more breathy and rough, but most patients maintain a reasonably good conversational voice (92). The procedure consists of microlaryngoscopy with a CO_2 laser TC anterior to the vocal process. The cordotomy must be extended far laterally, including division of the medial aspect of the false vocal fold. The goal is to detach as much of the TA muscle from the arytenoid cartilage as possible (Fig. 69.15). The TA muscle retracts anteriorly, and heals over several weeks, leaving a rounded tear-shaped opening anterior to the arytenoid (Fig. 69.16). Although the increase in airway diameter is only a few millimeters at best, this results in significant improvement in the patient's airway. The procedure can be repeated ipsilaterally or contralaterally if further airway opening is indicated. A tracheostomy is not often necessary perioperatively (91). Although TC has been used principally in adults, Friedman et al. (93) have reported success with a variant of TC (an additional wedge of tissue is removed) in a small number of pediatric patients.

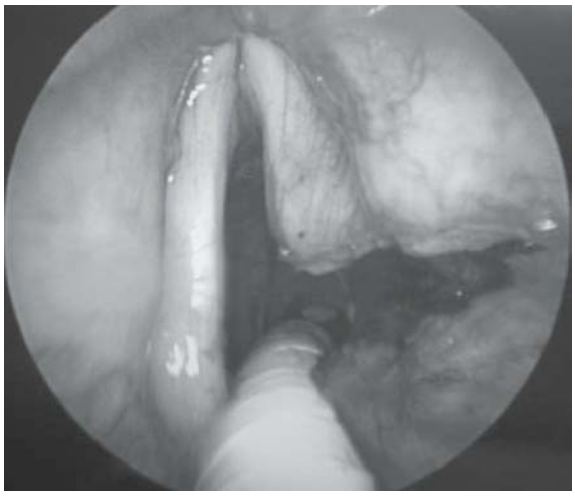


Figure 69.15 Intraoperative photo of the larynx following a right CO_2 laser posterior cordotomy. Note the cordotomy extends far laterally into the musculature of the false vocal fold.

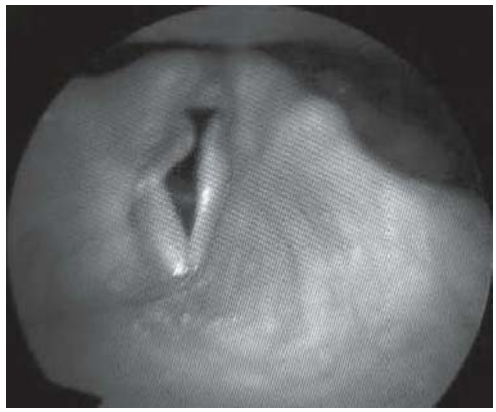


Figure 69.16 Fiberoptic laryngoscopy of patient 3 months after cordotomy for BVFP. Note the widened glottic aperture as the healed right vocal fold is in a lateralized position.

Endoscopic Laser Arytenoidectomy

Endoscopic Total Laser Arytenoidectomy. Endoscopic laser arytenoidectomy, which was introduced in 1984 by Ossoff et al. (94,95), led to a fundamental shift in the treatment paradigm of BVFP. The endoscopic arytenoidectomy shifted the treatment of BVFP from an external framework approach (Woodman procedure) to an endoscopic, laser-assisted procedure. The CO_2 laser technique provided better hemostasis than previous cold techniques, and was the catalyst that led to a resurgence of endoscopic surgical approaches for glottic stenosis and BVFP. The entire arytenoid cartilage is ablated (Fig. 69.17), and a small wedge is removed from the posterior vocal fold, along with a small cut just lateral to the wedge "to facilitate lateralization of the vocal cord during healing." The long-term success rate of this technique is 86%, and vocal quality was judged subjectively as "good." Although this technique was a mainstay in the treatment of BVFP for a decade, it has largely been replaced by the TC, or partial arytenoidectomy, since the mid-1990s.

Endoscopic Laser Partial Arytenoidectomy. The endoscopic laser partial arytenoidectomy is a variant of the technique of total endoscopic laser arytenoidectomy that preserves a portion of the arytenoid. Theoretically, this reduces the risk of aspiration, while achieving comparable voice and airway results. Originally described by Crumley (96), the "medial arytenoidectomy" preserves the lateral aspect of the arytenoid. Another modification by Remacle et al. (97) involves preserving the posterior body of the arytenoid. The results of this technique are comparable to TC in terms



Figure 69.17 Intraoperative photograph of a left CO_2 laser total arytenoidectomy.

of improvement of dyspnea without significant voice or swallowing difficulties and low complication rates (98).

Laryngeal Pacing

Perhaps the most promising treatment for BVFP is laryngeal pacing. This process involves a programmable pulse generator that is implanted beneath the skin and delivers electrical stimulation to the PCA muscle during inspiration once triggered by an electrode on the diaphragm. This resultant larger glottal airway opening allows improved ventilation without significant decrement in voice (99). Laryngeal pacing may ultimately prove to be the optimal solution for a difficult clinical problem that has frustrated otolaryngologists for decades. An initial small multi-institutional trial demonstrated that five out of six patients receiving an implantable stimulation device experienced reestablishment of normal oral airflow, allowing three of these patients to be decannulated (100). Recent small prospective canine studies report long-term complete rehabilitation of ventilation and exercise tolerance without aspiration (101,102). Technical limitations of the pacing hardware currently prevent this technique from being utilized as part of routine clinical care.

Arytenoid Abduction

In 2007, Woodson and Weiss (103) introduced the use of an arytenoid abduction suture procedure to reposition the vocal process to enlarge the glottal airway while allowing continued vocal fold adduction during phonation. In their initial study of six patients with BVFP, all patients demonstrated airway improvement, including three patients who were able to avoid tracheotomy and two of three patients with preexisting tracheotomies who were able to be decannulated (103). In her follow-up report, Woodson described continued success with this procedure in 7 of 11 additional patients and identified risk factors for poor outcome following this procedure including prolonged tracheotomy and "electromyographic evidence of inspiratory activity of adductor muscles." No patients developed aspiration or dysphagia (104).

Flap-Type Tracheostomy

It should be noted that all of the "static" laser treatments for BVFP (TC, arytenoidectomy) result in suboptimal airway caliber and worsened voice when compared with tracheostomy. It is important to remind patients that no surgery (with the possible exception of laryngeal pacing) can provide the caliber of airway and preserve the quality of voice as well as a tracheostomy. Patients should be given the option of tracheostomy when discussing the treatment options for BVFP. Clearly, most patients who seek an otolaryngology consult to discuss treatment for their BVFP consider a tracheostomy an unacceptable option. They simply need to be aware that endoscopic treatments for their condition represent a compromise in voice and airway in order to achieve successful decannulation. In those patients who are medically infirm or have significant pulmonary comorbidity (e.g., chronic obstructive pulmonary disease, obstructive sleep apnea), tracheostomy is usually the most appropriate treatment. A modified flap-type tracheostomy, as described by Miller et al.(105), with an indwelling Hood stoma stent is the ideal way to optimize patient acceptance of long-term tracheostomy in these cases.

SUMMARY

The evaluation and management of UVFP and BVFP have evolved considerably over the past decade. LEMG is an integral part of the workup in VFP, as its role in diagnosis and prognosis for recovery provides valuable insight. The surgical armamentarium for the treatment of UVFP continues to expand, with the introduction of multiple injectable substances for augmentation over the past decade. These innovations, coupled with the resurgence and refinement in office-based injection augmentation of the vocal folds, have shifted the treatment of UVFP from a "watch and wait" stance to that of early intervention. In addition, framework surgery (e.g., ML and AA) has emerged as the "gold standard" for long-term management of poorly compensated UVFP.

In the case of BVFP, TC and partial arytenoidectomy appear to be the most effective static procedures for improving airway with minimal negative impact on voice quality. Other novel treatment techniques continue to be investigated currently.

HIGHLIGHTS

- VFP most commonly occurs from an abnormality of the peripheral nervous system providing innervation to the larynx, specifically the vagus or RLN.
- UVFP and BVFP often have a shared etiology (e.g., surgical, malignancy, idiopathic). However, their

symptoms vary significantly with UVFP presenting with primary symptoms of voice and swallowing dysfunction, and BVFP presenting with symptoms related to airway restriction.

- VFP evaluation requires an exclusion of a malignancy as a causative factor. This evaluation process often requires imaging of the brain and the entire course of the vagus and RLNs.
- LEMG can provide important diagnostic and prognostic information regarding VFP with shortening the time period before proceeding with permanent treatment.
- Treatment options for UVFP include voice therapy, vocal fold injection (temporary or permanent), and laryngeal framework surgery (ML or arytenoid cartilage adduction).
- Evaluation of patients with BVFI requires a differentiation between the clinical entities of BVFP and PGS.
- Surgical enlargement of the glottic airway in cases of BVFP typically involves a trade-off of decreased voice quality for improved airway.

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70 Neurologic Disorders of the Larynx

John P. Ney *Tanya K. Meyer*

The laryngopharynx coordinates the four basic physiologic functions of the upper aerodigestive tract: airway protection, breathing, swallowing, and phonation. Accurate execution of these tasks depends on proper movement and valving function of the larynx, proper contractile function of the pharynx, and intact sensation of these structures. Neurologic disorders of the laryngopharynx are largely disorders of function (and therefore movement) rather than anatomy and may result from a focal disease process or present as a local manifestation of a systemic disorder. Many diseases produce a stereotypical pattern of abnormal function in the context of historical clues that should be recognized (1).

It is important to understand as an otolaryngologist which disorders are related to end organ dysfunction and which may be due to central dysfunction. It is not unusual for a patient who cannot create normal speech due to a cortical stroke (such as apraxia or dysarthria) to be referred for "hoarseness." Such an individual may have nothing wrong with his or her larynx or with vocal fold motion or structure but is unable to produce speech output due to cortical disease.

Phonation, articulation, speech, and language are interrelated tasks that require progressively higher orders of brain function (Fig. 70.1). Phonation, defined as the production of sound by the vocal apparatus (usually but not exclusively the vocal folds), is driven by airflow from the lungs. The resultant sound is modified and amplified through resonation within the sinonaso-, oro-, and hypopharyngeal spaces. Articulation further modulates this sound with the palate, tongue, lips, and teeth to produce specific phonemes. Speech requires pronunciation of words from a collection of phonemes, and language involves meaningful groupings of words into phrases to communicate ideas. The mechanics of phonation and articulation are principally influenced by structural defects (such as surgical defects in the tongue or palate), lower motor neuron disorders (vocal fold paralysis), and brainstem function, whereas language requires control by the cerebral cortex.

NEUROANATOMY AND THE LARYNX

Understanding the implications of neurologic disease of the larynx begins with a working familiarity of the neuroanatomical structures critical to laryngeal function (Fig. 70.2).

Primary motor control of the larynx and receipt of sensory information is accomplished through descending and ascending pathways in the central and peripheral nervous system. The cerebral cortex, divided by Brodmann into a number of areas based on location and function, is the origin of motor commands. The preparatory stages of phonation involve the selection of phonemes in the superior posterior temporal and inferior parietal lobes. Grammatical speech is formulated in Broca's area (Brodmann areas 44, 45) at the inferior frontal gyrus along the sylvian fissure. This information is communicated to the supplementary motor area in the frontal cortex (Brodmann area 6), which receives inputs from the thalamus (and indirectly from the cerebellum and basal ganglia) for motor modulation, and then to the pyramidal (corticobulbar) neurons in the primary motor cortex (Brodmann area 4). These are the upper motor neurons (UMN) involved in laryngeal control. The processes of these cortical neurons descend through the subcortical white matter to the medial aspect of the anterior midbrain in an area called the cerebral peduncles. These corticobulbar fibers continue their caudal path through the anterior pons where they interact with fibers that originate in the cerebellum, and then a portion cross the midline (decussate), synapsing on the neurons in bilateral nucleus ambiguus of the posterolateral caudal medulla. It is important to repeat that the corticobulbar

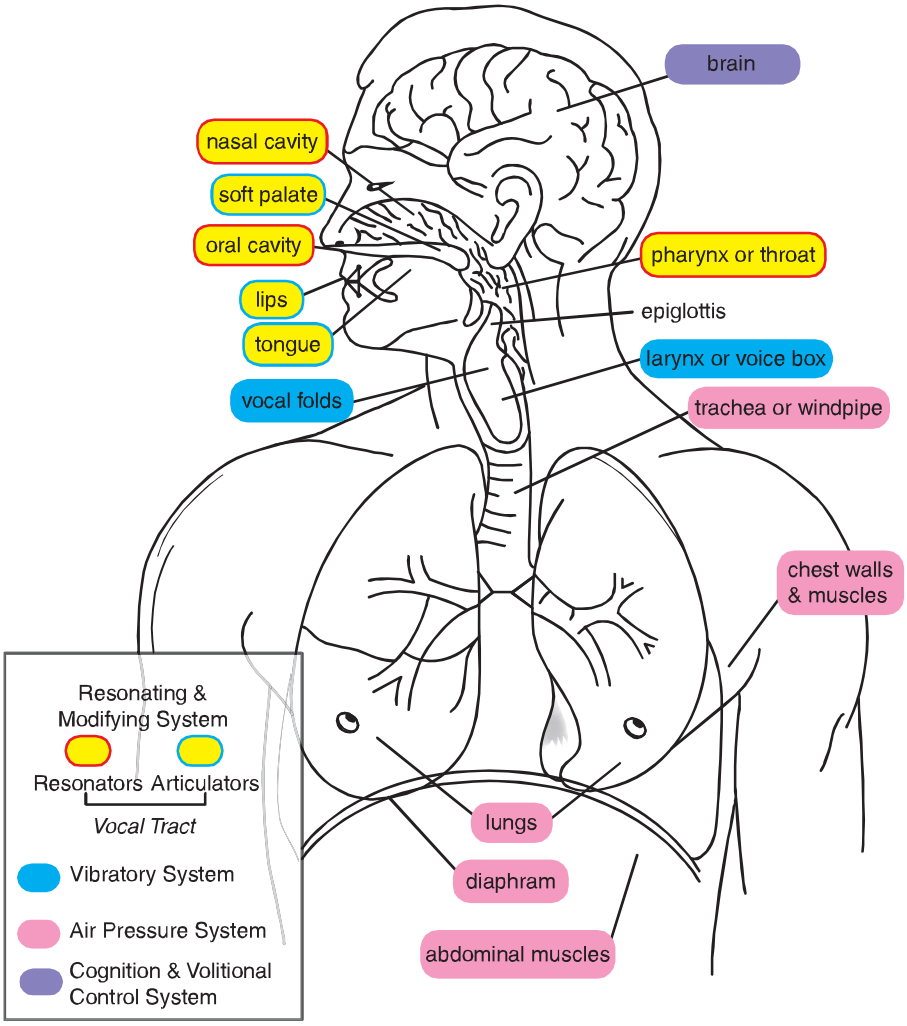


Figure 70.1 The human vocal process. Human vocal communication—effortless for a healthy adult—is the end result of a complex cognitive process leading to a highly coordinated series of motor actions of the thorax, larynx, pharynx, and mouth. The first step is volitional planning of a given vocalization in the cerebrum. The lungs, chest wall, and diaphragm then provide airflow to the vocal apparatus (usually the larynx) that provides a vibration source or a sound source. The resultant sounds are then shaped and modified by the resonating cavities of the upper airway (oral, nasal, and pharyngeal cavities) and by the articulators (palate, lips, teeth, tongue). Disease at any level can lead to a communication deficit. A stroke affects motor planning in the cerebrum, asthma or pulmonary disease can affect the air pressure system, lesions on the vocal cords will affect vibration, and disease of the upper airway or oral cavity can affect articulation or resonation (think of an individual after glossectomy, or an individual with a cleft palate, which changes vocal resonance).

fibers from one side of the cortex synapse on the neurons of both (bilateral) nucleus ambiguus in the brainstem.

Cell bodies in the nucleus ambiguus are the lower motor neurons and axons (referred to by neuroanatomists as special visceral efferents) for motor control of the larynx through the vagus nerve (cranial nerve X). The vagus exits the anterior brainstem just lateral of midline above the foramen magnum, traversing cerebrospinal fluid, and exiting the skull via the jugular foramen. The vagus travels in the carotid sheath with the carotid artery and jugular vein and gives off the superior laryngeal nerve and the recurrent laryngeal nerves. The superior laryngeal nerve branches medially off the vagus, splitting into the (sensory) internal superior laryngeal nerve, which pierces the thyrohyoid membrane, and the (motor) external superior laryngeal nerve, which descends to innervate the cricothyroideus muscle. The recurrent laryngeal nerve (RLN) branches from the vagus to loop around the arch of the aorta on the left, and around the subclavian artery on the right. The recurrent nerves then ascend in the trachea–esophageal groove posterior to the thyroid gland to innervate all the intrinsic laryngeal musculature save the cricothyroideus.

General sensory information from the larynx mimics the primary motor control pathways largely in reverse. The internal branch of the superior laryngeal nerve provides sensation above the vocal folds, and the RLN provides sensation to the subglottis and proximal trachea. These afferent impulses ascend via the vagus to the bipolar neuronal cell bodies in the inferior vagal ganglion located within the carotid sheath and the jugular foramen to enter the brainstem in the caudal medulla and synapse with neurons in the contralateral spinal trigeminal nucleus. They then ascend in the trigeminothalamic tract to the thalamus, and finally arrive at the primary sensory cortex located in the postcentral gyrus, Brodmann area 3, 1, 2.

The cerebellum and extrapyramidal systems integrate sensory and motor information to exert a modulating influence on laryngeal function. A series of inhibitory and excitatory checks and balances in the basal ganglia allows for second-to-second gradation of laryngeal motor control. The basal ganglia are located in the subcortex of the cerebrum, adjacent to the midbrain and the thalamus. The basal ganglia consist of the globus pallidus, putamen, and caudate. These have further interaction with the substantia nigra located

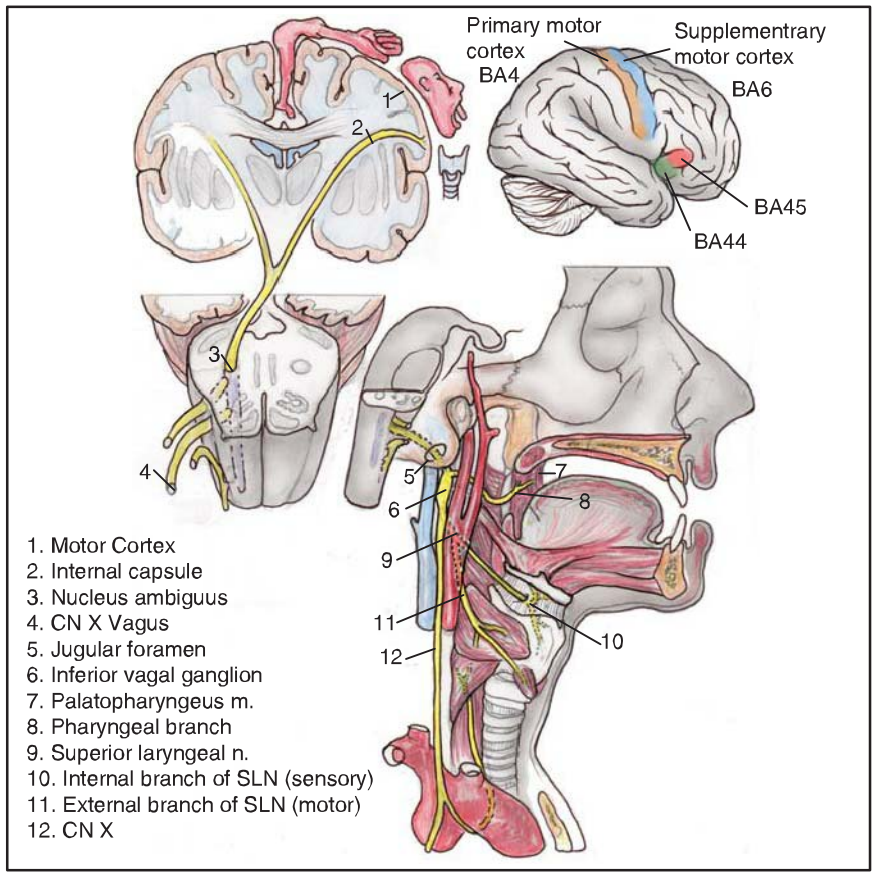


Figure 70.2 The pathway of the vagus.

in the anterior midbrain, the subthalamic nucleus, and the thalamus. In general, sensory information arrives from the cortex to the caudate and putamen, and excitatory impulses are sent to the globus pallidus with inhibitory adjustment from the substantia nigra (particularly the dopaminergic *pars compacta* region). The globus pallidus, with influence from the subthalamic nucleus, exerts a net inhibitory effect on the motor portion of the thalamus, which projects to the frontal planning regions of the cortex. For the cerebellum, sensory information is relayed through the medulla, ultimately projecting to the cerebellar hemispheres and the dentate nucleus, the most lateral deep cerebellar nucleus. Projections are also received from the parietal cortex. These, in turn, are further modulated by inputs from corticobulbar fibers in the pons, and project to the ventral lateral nucleus of the thalamus, which sends inputs back to the motor planning and primary motor areas of the cortex.

Function follows from anatomy. Motor neurons have two primary purposes, the first of which is establishing control over muscular function, and the second is providing basal tone to those muscles. UMN, originating in the cortex and terminating in the brainstem, have an inhibitory influence on lower motor neurons, acting to reduce tone in effector muscles. Lower motor neurons, in turn, provide the resting tonal stimulation to maintain muscle mass and tension. The "motor unit" consists of the total complement of axons, corresponding neuromuscular junctions, and contractile muscle fibers innervated by a single lower motor neuron. Interruption of the upper and lower motor neuron pathways creates significantly different abnormalities.

A UMN lesion to the corticobulbar tracts (at the contralateral cortex, the subcortical cerebral hemispheres, the cerebral peduncles, or the pons), would create spasticity and increased muscle tone with poor control. The voice would have a variable and unpredictable quality, which would be highly frustrating to the patient. There is not a characteristic laryngoscopic appearance—but the patient may show variable laryngeal motion depending on whether the task is a vegetative task (cough) or volitional task (speech). UMN lesions can be unilateral or bilateral, occur in combination, or in isolation, and demonstrate a wide spectrum of potential presentations depending on neurologic structures compromised.

In contrast, a lower motor neuron lesion in which any component of the motor unit is disrupted (the motor neuron, the peripheral nerve, neuromuscular junction, or effector muscle fibers) would result in atrophied, flaccid musculature devoid of tone. If skeletal muscle fibers are denervated, the motor units may depolarize spontaneously, resulting in fasciculations. Patients complain of a weak, breathy, or diplophonic voice (the voice is heard at two distinct vibratory frequencies because each cord is at a different tension), and be unable to perform a glottal stop or valsalva maneuver. Endoscopic examination of

the larynx would reveal impaired mobility of the vocal fold with possible bowing or flaccidity of the same fold and pooling of secretions in the ipsilateral pyriform sinus.

Lesions to the sensory pathways results in impaired gag, inability to clear secretions, and pooling of saliva. Patients may have gurgling speech, profound dysphagia, and absent or poorly productive cough.

The effects of lesions of the basal ganglia and cerebellum involve modulation of the frequency and smoothness of laryngeal movement. Due to the complex role of the basal ganglia, lesions involving its component structures present with laryngeal motion abnormalities that may be either hypokinetic or hyperkinetic. Hypokinetic disorders (parkinsonism) may yield a soft, breathy, monotonous voice, and difficulty initiating speech, with vocal fold bowing on phonation. Hyperkinetic disorders (e.g., dystonia, Huntington's), may manifest with rapid unexpected vocal fold spasms with poor phonatory control. Disorders involving cerebellar pathways result in ataxic speech, with a disruption in fine control of volume and pitch, and a vocal tremor.

GENERAL APPROACH TO DIAGNOSIS AND TREATMENT

The diagnosis of neurologic disease of the larynx rests largely on the traditional history and physical examination (Table 70.1). Of particular importance are changes the patient has noticed in strength and movement outside of issues with phonation, as neurologic disease is rarely limited to just the larynx. A broad neurologic assessment and consultation with a neurologist may be warranted. Beyond the history and physical (which includes endoscopy), radiologic imaging, sensory testing and laryngeal electromyography (LEMG) can add additional information. Flexible transnasal laryngoscopy is preferable to transoral rigid laryngoscopy because the former alters laryngeal mechanics the least and allows the examination to be carried out across multiple laryngeal tasks.

Neurologic diseases can be classified on the basis of the neuroanatomical structures and systems affected. Not uncommonly, disorders may span a number of neuroanatomical structures, creating a mixed picture of dysfunction.

TABLE 70.1 NEUROLARYNGOLOGY EXAMINATION

Neurologic examination

- Evaluate gait as patient walks to room
- Complete head and neck examination
- Cranial nerve examination:
  - Pay special attention to the tongue for tone and fasciculations: atrophy, flaccidity, and fasciculations indicate a LMN lesion, spasticity a UMN lesion
  - Look for twitching, dystonic posturing, or synkinesis of facial musculature
  - Pa, Pa, Pa: labial function
  - Ta, Ta, Ta/Ga, Ga, Ga: tip or posterior tongue function
  - Kitty cat: soft palate function
- Look at outstretched hands for tremor

Vocal examination

- Listen for fluidity (central), quality of articulation (central or peripheral), quality of the vocal signal (peripheral, laryngeal posturing, mucosal lesion)
- Differentiate hyperfunction, adductor spasms, abductor spasms, tremor
  - Hyperfunction will give a strained quality that does not change significantly from one word to the next
  - Tremor will be rhythmic
  - Adductor spasms are best heard during voiced sounds, such as the /ay/ in 80
  - Abductor spasms can be elicited with a vowel following a voiceless consonant. In the word taxi, there will be involuntary breathiness during the /a/ sound after the voiceless consonant t.

Fiberoptic examination

- Stop at level of the palate and evaluate for closure; have patient say "kitty cat"
- With the patient breathing quietly through the nose, evaluate the glottis at rest for tremor or paradoxical motion
- Evaluate for pooling of secretions
- Evaluate glottal closure pattern, vocal fold motion, and supraglottic hyperfunction
- Repeat vocal tasks during visualization and include
  - Glissando (sliding from low to high pitch): evaluates cricothyroid (CT) function
  - "Sniff: /i/" maneuver alternates adduction with abduction and will emphasize movement abnormalities such as a subtle paresis
  - Ask for purposeful inspiratory stridor, which may unveil lesions on the undersurface on the TVF
  - Agility and fatigability of vocal folds: alternate the sounds /pa/ - /ta/ - /ka/ past the point at which the patient is out of breath, assessing mobility, symmetry of motion, dexterity, and evidence of fatigue with repetition
- At the end of the exam, gently touch the aryepiglottic folds with the tip of the endoscope to assess for laryngeal sensation

CT, cricothyroid; LMN, lower motor neuron; TVF, true vocal fold; UMN, upper motor neuron.

The following categories focuses on disease entities most commonly associated with neurolaryngologic dysfunction, but is by no means exhaustive.

DISORDERS AFFECTING THE CENTRAL NERVOUS SYSTEM

Neurologic disorders of the central nervous system (CNS) are categorized on the basis of the systems affected. Lesions to the primary motor system (corticobulbar/corticospinal UMN, also known as pyramidal) primarily create spastic dysfunction, while lesions to the basal ganglia (extrapyramidal) result in disturbed control of function that may be hypo or hyperkinetic. (i.e., Parkinson disease would be hypokinetic, dystonia or tremor would be hyperkinetic). Disorders affecting the cerebellum and its outflow tracts in the brainstem and subcortical regions result in ataxic dysfunction. Some disorders are heterogeneous, resulting from inflammation or vascular occlusion to a number of important structures, with resulting combinations of dysfunction.

Spastic Disorders

Spastic disorders result from lesions or degeneration of UMN (pyramidal cells) and their projections in the corticobulbar pathway that extends from the cortex to the medulla. Stroke, the sudden onset of symptoms due to vascular compromise of cerebral tissue, commonly affects the motor pathways in addition to other structures and is discussed in the section under mixed CNS disorders. Amyotrophic lateral sclerosis (ALS), the most common nonvascular cause of spasticity, is a neurodegenerative disorder affecting both upper and lower motor neurons, and is discussed in detail under the section on peripheral nervous system disorders.

"Pseudobulbar palsy" refers to weakness of the bulbar musculature with hyperreflexia (hyperactive gag and brisk jaw jerk), indicating a UMN cause. This usually results from a lesion affecting the corticobulbar fibers. A true bulbar palsy would be due to compromise of lower motor neurons. Please see the explanation of bulbar palsy in the section on peripheral nervous system below.

Symptoms of pseudobulbar palsy include an exaggerated jaw jerk and gag reflex, and a spastic tongue that is contracted with a pointed tip but cannot be moved rapidly from side to side. Emotional lability (unprovoked crying or laughter), subcortical cognitive impairments, and dysarthria with thick, slurred, labored, and sometimes explosive articulation can be present. Marked hypernasality can exist, but palatal and pharyngeal reflexes are preserved. Dysphagia, dysarthria, nasal intonation, and nasal regurgitation are common.

Although often secondary to multiple bilateral vascular lesions above the brainstem, pseudobulbar palsy can also be caused by motor neuron disease. It is important to note that any disease involving the corticobulbar pathways can cause pseudobulbar palsy including multiple sclerosis (MS), neoplasm, encephalitis, and vascular disease.

Primary Lateral Sclerosis

Primary lateral sclerosis is a motor neuron disorder affecting UMN only and typically presents with spastic involvement of the lower extremities. There is often progression to spasticity of the bulbar musculature (2), giving the classic features of pseudobulbar palsy including spastic speech and dysphagia with pronounced emotional lability. The disorder is rare, accounting for a small percentage of all motor neuron disorders, and typically progresses very slowly (in contrast to ALS (3)). The cause is largely unknown. Differential diagnosis includes retroviral infection from HIV or human T-cell leukemia virus-I, MS, and adrenoleukomyelopathy. Antispasmodic pharmacotherapies such as baclofen (oral or intrathecal), or tizanidine can be helpful in ameliorating the spastic symptoms.

Hypokinetic (Parkinsonian) Disorders

Parkinsonism

Parkinsonism refers to the presentation of muscular rigidity and slowed movement (bradykinesia), with or without tremor. All forms involve damage to the pathways in the basal ganglia and brainstem, resulting in a net-inhibitory effect on movement and muscular function. Causes of secondary parkinsonism include stroke (usually accumulation of multiple basal ganglia lacunar infarcts), postencephalitic, paraneoplastic, traumatic (boxer's encephalopathy), drug-induced (phenothiazines and other antipsychotic medications), and toxic (pesticides and designer drugs such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a meperidine analog) effects. Parkinsonism also includes a number of genetic and neurodegenerative disorders referred to as Parkinson Plus syndromes. These include Shy-Drager Syndrome (multiple systems atrophy or MSA), dementia with Lewy bodies, and progressive supranuclear palsy. Parkinson disease refers to idiopathic parkinsonism and is by far the most common hypokinetic movement disorder and also the most amenable to treatment. MSA is also relevant to otolaryngologists for its association with airway difficulties.

Parkinson Disease

Parkinson disease has a prevalence of 0.3% to 0.4% of the U.S. population (4) and affects up to 2% of people over age 60 across all ethnic groups with an equal sex distribution. Up to 80% demonstrate vocal difficulties, with 30% finding it the most disabling part of the disorder. The classic symptoms include a pill rolling tremor, cog-wheel rigidity, masklike facies, small handwriting, decreased blinking, flexed posture with shuffling gait, and reduced arm swing.

Pathologically, Parkinson disease is associated with the accumulation of inclusion granules of abnormal alpha-synuclein protein in the autonomic and motor centers of the medulla oblongata. In later stages of disease, there are additional changes in the substantia nigra, basal forebrain, and ultimately, the frontal cortex (5). Autopsy examination shows loss of pigmentation of the substantia nigra, and

cellular degeneration in the globus pallidus and putamen, with prominent Lewy body formation. Parkinson disease becomes symptomatic when the loss of substantia nigra dopaminergic neurons reaches about 70%. The cause for aberrant alpha-synuclein deposition in Parkinson disease is not known, but there are rare familial forms of the disease that include an autosomal dominant mutation in the alpha-synuclein gene (4q21) and an autosomal recessive mutation of the parkin gene (6q25.2-q27).

The vocal characteristics of Parkinson disease include a soft breathy monotone voice perceived by the patient to be of normal loudness. This is caused by poor effort from a bradykinetic bellows mechanism (chest wall and diaphragm) exacerbated by an inaccurate perception of personal speech effort. Additional components include vocal tremor, poor articulation, stuttering quality, difficulty initiating speech, and swallowing difficulties.

Laryngoscopy shows vocal fold bowing with a spindle-shaped glottal gap on phonation (Fig. 70.3). Other findings include pooled hypopharyngeal secretions, decreased sensation, diminished cough reflex with aspiration, and poor coordination of the vocal folds with respiratory effort. Identification of vocal fold motion impairment suggests a parkinsonism plus syndrome, specifically MSA.

Pharmacotherapy for Parkinson disease aims to increase the amount of dopamine available in the synaptic cleft for neurotransmission to the basal ganglia. This can be accomplished by the use of the dopamine precursor levodopa (L-dopa, usually taken as an oral preparation with carbidopa, which inhibits peripheral metabolism of L-dopa), which is converted in the brain into dopamine by remaining substantia nigra cells. Other medications include dopamine agonists such as pramipexole and apomorphine (the latter available as an intravenous [IV] preparation), and therapies that prevent degradation and reuptake of dopamine once available in the synaptic cleft including the monoamine oxide type B inhibitor (selegiline) and catechol-O-methyltransferase inhibitors (entacapone). Thoughtful use of these medications is necessary, as spikes in dopamine levels can cause overflow movements including chorea and dyskinesias, while nadirs can result in ignition failure (inability to initiate movement) and freezing episodes.

L-dopa has had mixed results in dysphonia, although most studies have shown no statistical improvement (6). Vocal fold augmentation or medialization laryngoplasty (7) may improve loudness and maximal phonation time if sufficient respiratory drive for phonation exists, but in general it has demonstrated only temporary effectiveness (most likely because of progression of disease). Laryngeal surgery does not improve articulatory function or prosody. Deep brain stimulation has shown variable improvement in speech, despite significant changes in limb movements (8,9). Only behavioral therapy has shown a consistent positive effect on voice and speech function of patients with Parkinson disease.

Lee Silverman Voice Therapy (LSVT) is the most well studied of the behavioral techniques for Parkinson disease (Table 70.2). The program works both by increasing patients' physical efforts and also, theoretically, by resetting their sensory perception of their own vocal output. In the original study, 35 patients were randomized into placebo and treatment groups. At 2 years, the patients in the LSVT group sustained or improved vocal intensity over pretreatment levels, whereas the placebo group deteriorated (10). Swallowing function also appears to be improved after treatment (11).

Multiple Systems Atrophy

MSA combines parkinsonism and autonomic dysfunction. Patients with MSA suffer profound autonomic failure, usually manifesting as severe orthostatic hypotension, disturbance of sphincter control (urinary or fecal incontinence), and impotence. MSA-P (parkinsonian, previously "striatonigral degeneration") has more resting tremor and parkinsonian features, and may be difficult to distinguish from Parkinson disease, save that these patients have a poor response to dopamine-related therapies. MSA-C (cerebellar, or olivopontocerebellar atrophy), has a greater degree of cerebellar ataxia. The prevalence is up to 5/100,000

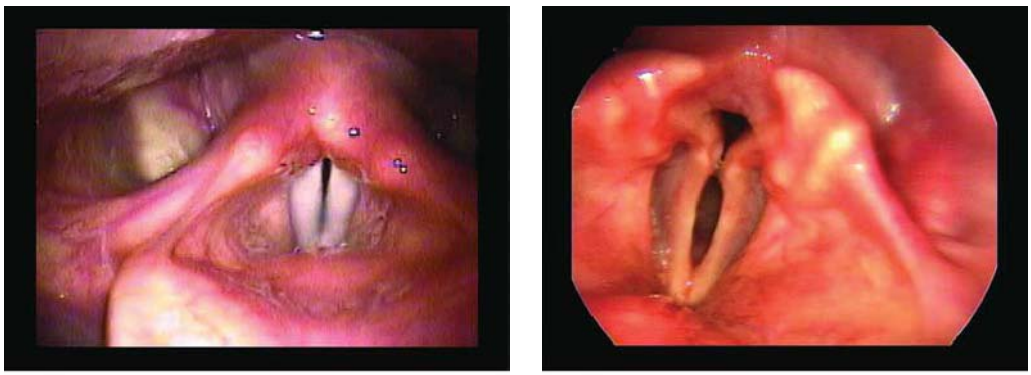


Figure 70.3 Vocal fold bowing with Parkinson disease. **A:** Normal larynx in adduction, note the near complete closure of the membranous vocal folds and also the alignment of the vocal process of the arytenoid cartilages. **B:** This individual has the characteristic vocal fold bowing of parkinsonism—there is approximation of the tip of the vocal process of the arytenoids, but a prominent glottal gap at the midmembranous vocal fold and often (as seen here) a marked posterior glottal chink.

TABLE 70.2 LEE SILVERMAN VOICE THERAPY

Three major features contribute to the voice disorder in individuals with parkinson disease:

1. Global scale-down of neural drive to the speech mechanism, resulting in a soft monotone voice (bradykinesia)
2. Inaccurate sensory perception of self-effort involved in vocalization, which prevents the individual from accurately monitoring vocal output
   "My voice is not too soft, my spouse needs a hearing aid"
3. Difficulty with independently generating the correct effort to produce adequate vocalization
   "I can't speak this loud, I feel I am shouting"

Five essential LSVT concepts:

- Increasing amplitude of phonatory output (think loud, be loud)
- Improving sensory perception of effort (think loud)
- Administering treatment in high-effort style (recalibration)
- Administering treatment intensively (four times a week for 16 sessions in 1 month)
- Quantifying all speech and voice output (sound meter)

persons (12). Like Parkinson disease, the pathogenetic mediator is the abnormal deposition of alpha-synuclein in intracellular inclusions (referred to as glial cytoplasmic inclusions, not Lewy bodies). Many patients have orofacial or craniocervical dystonia associated with a characteristic quivering, high-pitched dysarthria. Decreased sensation of the laryngopharynx and a diminished cough reflex may permit recurrent aspiration. Vocal fold immobility in a patient with parkinsonism is highly suggestive of MSA (13). Inspiratory stridor develops in about 30% of patients.

These individuals develop many sleep disorders, including obstructive and central sleep apnea, hypoxemia, phasic swings of systemic arterial pressure, reduced rapid eye movement (REM) sleep, and REM sleep behavior disorder. When obstructive sleep apnea occurs in patients with MSA, there is significant risk of sudden death (14), and tracheotomy is recommended. The disease progresses more rapidly than Parkinson disease, with average survival of less than 9 years.

Hyperkinetic Disorders

Dystonia

Dystonia is a chronic neurologic disorder of central motor processing within the basal ganglia (extrapyramidal system) characterized by involuntarily sustained muscle contractions of agonist and antagonist muscles causing twisting and repetitive movements or abnormal postures. Anxiety will aggravate the movements; sedatives may mitigate the movements; and posturing characteristically disappears during sleep. Dystonia can be focal (spasmodic dysphonia, writer's cramp), regional (cervical dystonia), or generalized, and can be idiopathic or secondary to a wide variety of causes, including hereditary syndromes (Dystonia gene [DYT1] gene locus), stroke, trauma, and drug effects.

Spasmodic Dysphonia

Spasmodic dysphonia is a focal task-specific laryngeal dystonia with involuntary contractions of the intrinsic laryngeal musculature. If the contractions in the adductor musculature predominate, it is termed "adductor spasmodic dysphonia" (AddSD) and is characterized by a harsh, strained, and strangled quality with voice breaks. If the contractions in the abductor musculature predominate, it is termed abductor spasmodic dysphonia (ABdSD), which is characterized by sustained breathiness with breathy voice breaks. The dystonic (spasmodic) muscle contractions generally do not affect nonspeech laryngeal functions such as breathing, singing, swallowing, or coughing.

AddSD was first described by Traube in 1871 in a female having a "spastic form of nervous hoarseness" (*spastiche form der nervosen helserkeit*). Spasmodic dysphonia historically has been considered to have a psychogenic cause owing to the fluctuation in symptoms and frequent coexistence of anxiety and depression. However, in 1976, Dedo described the dramatic response (although temporary) of the disease to RLN section, providing proof of an organic cause (15). In many patients, the symptoms of anxiety and depression normalize after successful treatment of their spasmodic dysphonia (16). Although the exact pathophysiology of dystonia is unknown, some autopsy studies have detected altered levels of neurotransmitters in the caudate, putamen, globus pallidus, and dentate nuclei, supporting the current theory that the site of pathology involves the basal ganglia (17,18). Furthermore, recent studies suggest that dystonias involve cerebellar pathways that modulate extrapyramidal function (19).

Spasmodic dysphonia is an adult onset disorder with a female predominance. When classified, 83% of cases are AddSD, 17% ABdSD, with rare mixed cases and rare cases of breathing dystonia. Spasmodic dysphonia is associated with essential tremor in 30% of patients and with other forms of dystonia, such as blepharospasm or writer's cramp, in 14% of patients (20). Up to 23% of patients with spasmodic dysphonia report a family history of dystonia or other movement disorders (21).

Spasmodic dysphonia affects the speaking voice but spares other vocal tasks such as singing, character speech

(e.g., speaking in falsetto like Minnie Mouse), or yelling. Patients describe more difficulty with speaking over the telephone, public speaking, and communication during stressful situations. Alcohol or sedatives can reduce voice breaks, and speech during sleep is normal. Patients describe a "strangled" feeling when trying to speak, and have great difficulty "getting the words out." Individuals with spasmodic dysphonia have a wide range of vocal patterns, depending on the severity of the spasms, compensatory vocal strategies used, and presence of overlying tremor. Some patients with AddSD use a low, breathy voice as a compensatory mechanism and sound similar to patients with ABdSD. Occasionally, it can be difficult to distinguish organic spasmodic dysphonia from psychogenic voice disorders or muscle tension dysphonia.

The vocal characteristics of AddSD include strangled breaks in connected speech, especially prominent with words that begin with vowels. Eliciting phrases would include counting from 80 to 90, and the sentence "We eat eggs every day." The vocal characteristics of ABdSD include breathy breaks in connected speech, especially for vowels following a voiceless consonant. Eliciting phrases would include "The puppy bit the tape" and "Harry had a hard head." The examiner should listen for delayed onset of phonation after the voiceless consonants p, t, and h.

Diagnosis is made by history, vocal characteristics, and flexible transnasal laryngeal examination across multiple speech tasks. Patients with AddSD demonstrate inappropriate adduction of vocal folds with hyperfunction of the supraglottis. Patients with ABdSD demonstrate inappropriate vocal fold abduction during connected speech. Some individuals are able to suppress symptoms with a sensory trick (*geste antagonist*) such as voicing while chewing, biting the tongue, or holding a finger in the corner of the mouth. Similarly, insertion of a flexible scope may diminish involuntary contractions and normalize speech. Associated neurologic disease should be excluded through neurologic consultation, preferably with a movement disorders specialist.

Botulinum toxin injection into the affected laryngeal muscles is the treatment of choice for the symptoms of spasmodic dysphonia, and results in vocal improvement in up to 90% of patients (21,22). For AddSD, the thyroarytenoid-lateral cricoarytenoid muscle complex (TA-LCA) is most commonly injected; for ABdSD, the posterior cricoarytenoid (PCA) is injected. Complications are caused by excessive glottal weakness and breathiness with TA-LCA injections, stridor with PCA injections, and dysphagia to liquids if the toxin has diffused to the adjacent constrictors. Resistance to toxin at doses used to treat spasmodic dysphonia is rare, and most treatment failures are related to technical problems (improper dosing or placement of toxin).

With a successful injection, patients can expect reduction in voice breaks, effort required for speaking, and the uncomfortable strangling sensation. The adductor or abductor muscle group can be specifically targeted, and the dose titrated to provide just enough weakness to relieve spasm without causing excessive weakness and subsequent breathiness (Add) or stridor (ABd). Results are critically dependent on achieving sufficient weakness to ameliorate spasm without causing undue side effects.

Injections are most commonly performed transcutaneously using electromyography (EMG) guidance to ensure proper placement within the correct muscle, although some groups use anatomic landmarks only (23). Although any serotype and brand of botulinum toxin can give the desired results, dosages may differ significantly. The most common brands in current clinical use are BOTOX® (Allergan, Irvine), which is botulinum toxin type A, and Myobloc® (Solstice, Louisville), which is rima botulinum toxin type B. It is important to note that, as of the writing of this chapter, although these pharmaceuticals are scientifically and clinically accepted for use in the treatment of laryngeal dystonia, they are only Food and Drug Administration (FDA) approved in the treatment of blepharospasm, cervical dystonia, and glabellar lines. For AddSD, the average dose is 1 U of botulinum toxin type A to bilateral thyroarytenoid muscles, with the range between 0.05 to 10 U (22). Most patients receive bilateral injections via the cricothyroid membrane every 3 to 4 months, although some individuals find benefit from unilateral injections at shorter intervals. Side effects include breathiness and difficulty swallowing liquids, which emerge in 1 to 3 days and can last up to 2 weeks. For ABdSD, the average dose is 2 to 5 U unilaterally into the PCA (22). (See the LEMG section for a detailed explanation of injection techniques.) The side effects are stridor with airway compromise (from weakening the sole abductor musculature) and dysphagia. For this reason, unilateral injections are usually given to reduce the chance of airway compromise until the patient's reaction to injections are better known to the treating clinician (24). All patients must be evaluated by transnasal laryngoscopy to assess glottal adequacy before injection of the PCA.

There are several surgical therapies for spasmodic dysphonia that prevent glottal closure through destruction of branches of the RLN (25), resection and thinning of the dystonic musculature (26), altering the laryngeal framework (27) (type II thyroplasty), or reinnervation of the dystonic musculature with a branch of the ansa cervicalis (28). These therapies have been reported to provide good symptomatic relief in carefully selected patients. Unfortunately, to date, all successful treatments for spasmodic dysphonia have focused on symptomatic amelioration of the laryngeal end organ, and have not been effective in correcting the underlying disease process in the brain. Botulinum toxin injections remain the gold standard treatment for this group of patients and the only treatment for AddSD demonstrated to be effective by a controlled clinical trial (29).

Essential Tremor

Essential tremor is a common, benign, and likely inherited movement disorder with a female predominance (30). Oscillatory 4 to 8 Hz shaking of the hands and rhythmic head titubation are the most commonly affected areas. Thirty percent of afflicted persons will have symptomatic vocal involvement. Vocal symptoms are related to tremor

in the muscles in the larynx, pharynx, soft palate, and the strap muscles of the neck. Although aggravated by anxiety, public speaking, telephone use, and mitigated by alcohol and benzodiazepines, tremor differs from spasmodic dysphonia by its rhythmicity and presence across all speech tasks. Most patients with essential tremor are treated with systemic agents (propranolol and primidone); however, in our experience vocal tremor does not respond as well as head or hand tremor to medical management. Injections of botulinum toxin may be useful to "dampen" the tremor by weakening the affected musculature, but oscillatory movements will persist at diminished amplitude.

Tic Disorders

Tics are sudden, recurrent, quick, abnormal movements or vocalizations that abruptly interrupt normal (31) activity. Largely thought of as a phenomenon of childhood with male predominance, upwards of 30% of children may have transient tics. Many adults have unrecognized simple tics, making the prevalence difficult to characterize. Simple phonic tics include throat clearing, snores, squeals, coughs, and belching noises. There is a compulsion to perform a movement, which is relieved once the movement is completed. Tics can be temporarily suppressed, although doing so will cause anxiety. They are usually aggravated by stress, anger, and excitement, and can decrease with relaxation and sleep. Tic disorder, a clinical diagnosis, often exhibits a good response to medical therapies including tetrabenazine, clonazepam, and botulinum toxin.

Gilles de la Tourette syndrome is a tic disorder with associated behavioral abnormalities (96% by age 11). Tourette's generally emerges in early childhood, peaks by age 10, and regresses in about half of patients by adulthood. Compulsive personality disorder, attention deficit disorder, and anxiety disorders are present in most of these individuals. Complex phonic tics may be present, including palilalia (repetition of one's last word or syllable), echolalia (repetition of someone else's last words) and coprolalia (obscenities), although coprolalia is likely present in less than 20%.

Myoclonus

Oculopalatolaryngopharyngeal myoclonus is an uncommon disorder consisting of twitch-like, rhythmic contractions of the soft palate, pharynx, and larynx at a rate of one or two contractions per second. This condition may affect only the palate, or all of the laryngopharynx. This condition can be part of a seizure disorder, be posttraumatic, or be caused by a viral, toxic, or metabolic encephalopathy, where a lesion interrupts the pathways between the olivary nuclei in the medulla, the dentate nucleus in the cerebellum, and the red nucleus in the midbrain (Mollaret triangle). Speech may be choppy with intermittent hypernasality from palatal dysfunction. Often, the chief complaint will be persistent clicking in the ear. The palate and vocal folds can be treated with injections of botulinum toxin to decrease the severity of the contractions, but Eustachian tube dysfunction and velopharyngeal insufficiency are important limitations. Systemic medications can be helpful.

Ataxic Disorders

Disorders of the cerebellum and its outflow tracts create ataxic laryngeal dysfunction, usually through the influence of toxins (alcohol), the presence of tumors of the posterior fossa, genetic conditions, or stroke. The clinical picture is one of poor control of speech volume and pitch, with uncoordinated laryngeal muscle contractions.

Friedreich Ataxia

Friedreich ataxia (FA) is an autosomal recessive congenital disorder caused by a mutation in the gene *FXN* (32) that codes for a protein essential for proper functioning of mitochondria. FA is the most common inherited ataxia. Prevalence is 1 to 2/100,000, and age of onset is generally in mid to late childhood. Although the target of the dysfunctional protein is unknown, the dentate nucleus of the cerebellum and the dorsal root ganglia outside the spinal cord are most affected, causing severe difficulties with proprioception (awareness of body in space) and limb, girdle, and vocal ataxia. Treatment is supportive.

Arnold-Chiari Malformations

Arnold-Chiari malformations are the most important of the posterior fossa deformities, and of the four types, Chiari I and II are encountered most commonly. Individuals with Chiari I have cerebellar tonsillar herniation 5 mm below the foramen magnum without other brain malformation. This occurs with an incidence of 1% (33) and can cause brainstem and vagal compression.

Symptoms, which often do not develop until adult life, include tussive head pain (increased intracranial pressure), visual changes, syncope, dizziness, dysphagia and hoarseness (cranial nerve X), absent gag reflex (cranial nerve IX), and ataxia. There is a high incidence of associated syringomyelia (cavitation of the central parts of the spinal cord usually in the cervical region) (Fig. 70.4).

In Chiari II, the posterior fossa is small and the cerebellum, pons, and medulla are displaced to varying degrees into the cervical canal. Infants present with brainstem dysfunction, including swallowing difficulties, slow feeding, repeated aspirations, and breathing difficulties (e.g., apnea and stridor) from vocal fold paresis. Older children and adults may have extremity weakness, sensory changes, and swallowing difficulties. In selected patients, surgical decompression of the posterior fossa will allow neurologic recovery.

Mixed Disorders

Stroke

A stroke refers to a sudden interruption of blood flow to a portion of the brain causing neurologic deficits that become maximal within seconds to minutes. Stroke is the

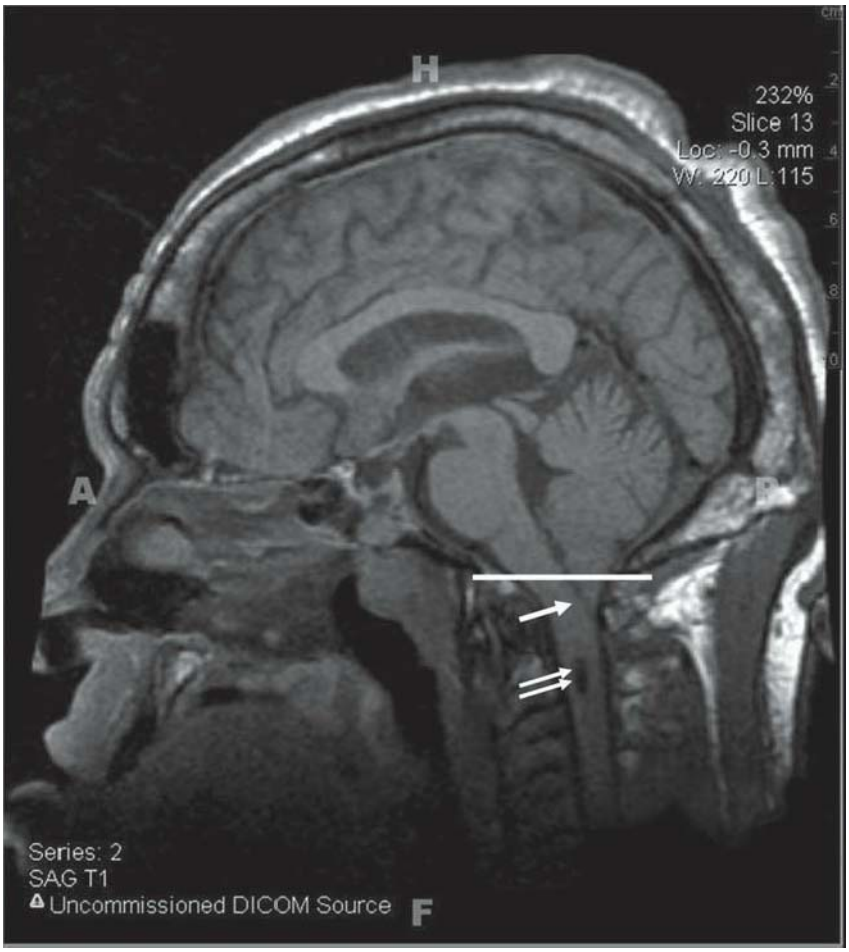


Figure 70.4 Sagittal T1-weighted MRI showing the presence of a Chiari type I malformation associated with a cervical syrinx (*double arrow*) and herniated cerebellar tonsils (*single arrow*) through the level of the foramen magnum (*white line*). (Courtesy of M. Michel and M. Kocak. Medical College of Wisconsin, Milwaukee.)

third leading cause of death in the United States and affects more than half a million persons per year. Eighty-five percent of strokes are ischemic, from reduction or absence in blood flow to one of the arteries supplying the cerebrum, cerebellum, or brainstem. The remaining 15% of strokes are hemorrhagic, either from overt hemorrhage or conversion of a prior infarct after reperfusion. Ischemic strokes are generally further divided into large vessel (affecting an arterial distribution) or lacunar (affecting small penetrating arteries). The etiologies of large vessel and lacunar infarcts differ. Large vessel infarcts are generally embolic, referring to a clot or occlusion that travels from another source—typically atheromas in the carotid arteries or cardioembolism due to atrial fibrillation. Lacunar infarctions are typically *in situ* thromboses caused by gradual arterial sclerosis from chronic hypertension.

The neurologic deficits of strokes arise from the location of brain tissue affected. Large-vessel infarctions, particularly of the middle cerebral artery (MCA), can have a devastating effect on language comprehension and formulation, as well as speech production affecting Broca or Wernicke areas and the connections between them. MCA distribution infarcts may result in hemiparalysis as they affect the primary motor cortex and the descending corticobulbar tracts. Lacunar infarctions, on the other hand, generally affect the deeper structures at the base of the brain, particularly the basal ganglia, and often have a better prognosis for recovery. Although a single lacunar infarction in the basal ganglia is unlikely to cause a movement disorder, the accumulation of multiple lacunes may result in a "vascular parkinsonism," which responds poorly to L-dopa. Lacunar infarctions may also affect the corticobulbar pathways in an area that runs near the basal ganglia, called the internal capsule, causing contralateral weakness of the hemibody, face, tongue, or vocal fold paresis.

Infarctions of the vertebrobasilar circulation involve the brainstem, which can have particular implications for laryngeal function. In particular, a posterior–inferior cerebellar artery (PICA) infarction affects the lateral medulla (Wallenberg syndrome), lesioning the nucleus ambiguus, nucleus solitarius, and the tracts providing sensory information. This can cause a severe unilateral vocal fold paralysis, as well as other features such as chronic hiccups. PICA infarctions often occur in association with vertebral artery dissections, and dissection should be looked for, particularly in younger patients. Hemorrhagic infarctions have a similar etiology to lacunar infarcts, and most often occur in the basal ganglia, followed by the thalamus, and the cerebellum in frequency of location. Because they may introduce a large volume of blood to a limited space, hemorrhages may increase intracranial pressure and compress nearby structures such as the brainstem, impairing

consciousness and vital functions. Decompressive surgery for acute hemorrhages to prevent brainstem herniation can be life-saving.

Diagnosis of stroke is initially clinical and then confirmed with computed tomography (CT) or magnetic resonance imaging (MRI). Although MRI is the more sensitive of the two modalities, CT is invaluable in the acute diagnosis of hemorrhage. Ischemic infarcts should be followed up with imaging of carotid arteries to rule out atherosclerotic plaques, and further evaluation for cardiac lesions responsible for embolism such as atrial fibrillation.

Acutely embolic ischemic infarctions can be treated with IV or intra-arterial (IA) thrombolytic agents such as tissue-plasminogen activator (TPA) or streptokinase, although both of these treatments are time sensitive (usually less than 4 hours for IV-TPA, less than 6 hours for IA-TPA). Subacute and chronic treatment is geared toward prevention of further strokes, and mostly involves platelet inhibition with aspirin, clopidogrel, or aspirin-dipyridamole in combination. Carotid end-arterectomy and stenting may prevent further embolism from carotid atheromas, and warfarin, heparinoid, or direct thrombin inhibitor-based anticoagulation is indicated for prevention of cardioembolism (usually from atrial fibrillation). In the chronic phase, the role of the otolaryngologist is to ameliorate symptoms of spasticity, movement abnormalities, and paralysis, described elsewhere in this chapter.

Multiple Sclerosis and other Demyelinating Disorders

MS is defined by the presence of at least two neurologic deficits, separated by time and space. The disorder preferentially affects the oligodendroglia responsible for CNS myelin, but severe and chronic lesions may cause axonal damage. MS is the most common autoimmune disorder of the CNS, with a prevalence of 91/100,000 persons in the United States. Like many autoimmune disorders, the disease has a bimodal distribution, with the first incident peak in women in their 20s and 30s, and a second, smaller peak in men in their 40s and 50s. MS has a predilection for persons who grew up in northern climates (before age 15). Etiology of the autoimmune dysfunction is unknown, but may be related to human leukocyte antigen haplotype and viral exposures, and most recent research has found an association with vitamin D deficiency (34). Unlike stroke, the onset of neural dysfunction is more gradual, usually occurring over hours to days. Early in the course of MS, the deficits may improve over time, return the patient to baseline or at least remaining stable thereafter, creating a pattern of relapse and remission. The overall trajectory of neurologic dysfunction is usually progressive, and many patients ultimately experience a steady downward course (secondary progressive course). However, like stroke, the location of the lesion is responsible for the neurologic deficit. Typical locations for demyelinating lesions include the deep white matter, including corticospinal and corticobulbar tracts, the middle cerebellar peduncle (extending from the pons), the corpus callosum, and the optic nerves (which have oligodendroglia). Brainstem involvement is common, and may be responsible for extraocular motion abnormalities, tremor, spasticity, and weakness, depending on the exact location of the lesions. Demyelinating events that may serve as precursors to MS include optic neuritis (optic nerve inflammation with blurred vision and loss of intensity of color), internuclear ophthalmoplegia (double vision with ocular misalignment secondary to upper brainstem lesions), and transverse myelitis (sensory loss, weakness, and /or bowel or bladder dysfunction from spinal cord involvement). Most initial demyelinating events herald ultimate progression to MS.

A number of options exist for confirming MS diagnosis. MRI (Fig. 70.5) is the most used modality for diagnosis

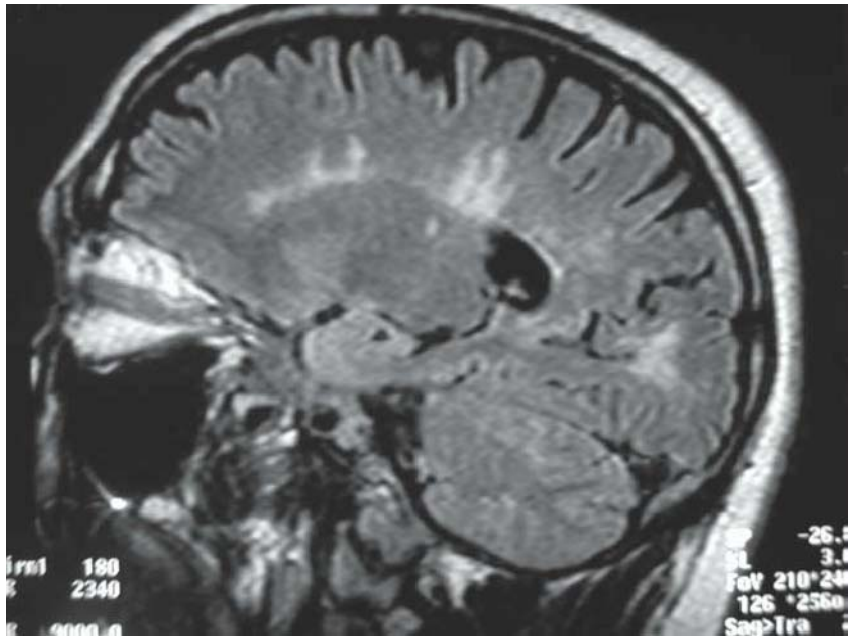


Figure 70.5 Sagittal Fluid Attenuated Inversion Recovery (FLAIR) image near midline, demonstrating signal abnormalities in the periventricular white matter oriented perpendicularly to the ventricular surface, typical for multiple sclerosis. An additional area of abnormality is also seen in the occipital white matter. (Courtesy of M. Kocak. Medical College of Wisconsin, Milwaukee.)

and staging of MS, and the Mcdonald criteria can categorize the probability of MS diagnosis based on the type, number, and location of active and chronic demyelinating lesions. With inconclusive MRI results, other testing may be indicated. Visual evoked potentials can confirm demyelinating damage from a prior optic neuritis by detecting a delay of the P100 waveform and examination of cerebrospinal fluid obtained from lumbar puncture may show biomarkers such as elevated immunoglobulin G levels and oligoclonal banding.

An acute exacerbation of MS may respond to 3 to 5 days of IV methylprednisolone, 1,000 mg, which will speed recovery from the exacerbation but not affect overall disease course. Disease-modifying therapies for chronic disease, including subcutaneous and intramuscular formulations of interferon-beta and glatiramer acetate, a copolymer, reduce the frequency and intensity of exacerbations, and diminish the number of demyelinating lesions on MRI. The monoclonal antibody natalizumab has been FDA-approved for the treatment of MS, and has shown a powerful effect in reduction of demyelinating lesions and altering the clinical course of MS. Natalizumab treatment is associated with activation of the parvovirus responsible for Progressive Multifocal Leukoencephalopathy, a potentially lethal condition. Therefore, natalizumab treatment should not be undertaken lightly.

Due to the frequent involvement of the brainstem and motor tracts in patients with MS, otolaryngologists have a crucial role in the evaluation of MS-related dysphagia and dysphonia. Pseudobulbar palsy and spasticity are common, as is an ataxic pattern of laryngeal function. Lower motor neuron-related paralysis may occur with lesions that affect the nucleus ambiguus, and sensory dysfunction with poor clearing of secretions, impaired cough and gag reflexes may occur.

Laryngeal Dysfunction Following Closed Head Injury

Traumatic brain injury produces diffuse damage to the neuronal connections among interactive brain structures. Some individuals may suffer laryngeal spasticity and hyperfunction (35), whereas others experience glottal incompetence caused by paresis or vocal fold atrophy often compounded by poor effort. Hypernasality caused by velopharyngeal insufficiency is also common.

DISORDERS AFFECTING THE PERIPHERAL NERVOUS SYSTEM

Peripheral nervous system disorders induce laryngeal dysfunction largely through their effect on the motor unit. Because the motor unit comprises the lower motor neuron in the brainstem, the peripheral nerve, the neuromuscular junction, and the sum of muscle fibers which it innervates, disturbance to any one of these structures can create vocal fold weakness or paralysis.

Bulbar Palsy

The term *"bulbar palsy"* refers specifically to paresis of cranial nerves IX–XII associated with the "bulb," which is a historical term for the medulla. The trigeminal and facial nerves can be involved but these are not strictly within the medulla. Weakness of the jaw, face, sternocleidomastoid, trapezius, tongue, pharynx, and larynx is prominent. Symptoms include dysphagia, dysarthria, nasal intonation with drooping of the palate, nasal regurgitation, absent jaw and gag reflex, pooling of saliva in the pharynx, a weak cough, and a wasted, fasciculating tongue with a rounded tip. This can occur in many disorders, including diphtheria, poliomyelitis, myasthenia gravis (MG), myotonic dystrophy, botulism, and Chiari malformation.

Motor Neuron Disorders

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig disease, is a progressive neurodegenerative disorder involving both the lower motor neuron cell bodies (anterior horn cells in the spinal cord, motor nuclei of the lower cranial nerves in the brainstem) and the UMN in the corticospinal or corticobulbar pathways. Because of the involvement of both upper and lower motor neurons, the picture can be a mixed one of both flaccid atrophy and spasticity. Disease onset is usually after the age of 50 and the process is usually fatal within 3 to 6 years (36). The annual incidence is 2/100,000, with a male predominance, 10% is inherited, and 1% of the total number affected is attributable to a mutation in the superoxide dismutase gene.

Weakness of the bulbar muscles is seen as the initial symptom in 20% of patients. Poor tongue function is common, manifesting as slurred speech, dysphagia, or drooling. Patients may have difficulty coughing and breathing, with weakness and eventual paralysis of respiratory function. Other symptoms include progressive weakness, atrophy, fasciculation, and hyperreflexia of limb musculature. Extraocular movements and bowel and bladder function are typically spared.

Riluzole, a sodium channel blocker, is currently the only medication approved for treatment of ALS, giving a 9% advantage in 1-year survival (37), but can have side effects including nausea and liver dysfunction. Most interventions are supportive such as anticholinergics for drooling, percutaneous endoscopic gastrostomy tube, and finally tracheotomy with ventilation. Motor neuron disease is progressive and usually has a fatal outcome within 3 to 5 years, most commonly from pulmonary infections.

Progressive Bulbar Palsy

Progressive bulbar palsy is a distinct type of adult onset motor neuron disease caused by lesions affecting the motor nuclei of the cranial nerves. Typically, the patient is spared UMN symptoms, such as spasticity and jaw hyperreflexia. Kennedy syndrome, or bulbospinal muscular atrophy is

an inherited motor neuron disease, associated with gynecomastia and primarily lower motor neuron degeneration. The disorder is X-linked, and is based on an accumulation of trinucleotide repeats.

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a group of genetic disorders from deletions in the survival motor neuron gene on chromosome 5, and is classified largely by time of presentation. SMA-I, Werdnig-Hoffman syndrome, is evident sometimes even in utero from decreased fetal movements, and is characterized by a "floppy," severely hypotonic infant with poor suck and weak cry. Bulbar muscle weakness is prominent, affecting feeding and causing continuous gurgling, ultimately placing the infant at high risk for aspiration pneumonia. Tongue fasciculations are common. Most infants with SMA-1 do not live beyond age 2. In SMA-II (arrested or intermediate) and III (Kugelberg-Welander), onset is later, from 18 months to 15 years of age, limb weakness and contractures is most prominent, although aspiration and respiratory compromise (usually involvement of intercostals rather than diaphragm) can occur.

Poliomyelitis

Poliomyelitis, now rare in developed countries since vaccination, is caused by a ribonucleic acid virus of the picornavirus group. After a flu-like prodromal phase, asymmetric weakness develops in the bulbar and respiratory muscles, with or without associated limb weakness. There is no sensory deficit. Management is supportive.

Postpolio Syndrome

Postpolio syndrome is characterized by recurrence some years later of the original illness, with increasing weakness of previously involved or seemingly uninvolved muscles. Treatment is supportive. The likely cause is further loss of anterior horn cells caused by aging from a pool that was depleted by the original infection.

Peripheral Neuropathies

Peripheral neuropathies affect the peripheral nerve distal to the neuronal cell bodies in the anterior horn cells and the dorsal root ganglia. The major etiologies of neuropathies are hereditary, toxic and metabolic (particularly diabetes), trauma, and infectious/immune-mediated (38).

Neuropathies typically fall into one of two categories: those that primarily affect the axon and those where damage is primarily to the myelin layer (myelinopathy). Axonal neuropathies exhibit length dependency, where the most distal portions of nerve are preferentially affected, often due to disruption of microtubular transport mechanisms that prevent the sustainment of the distal axon from the neuronal cell body. Antimitotic agents such as colchicine and vinca alkaloids particularly can cause this variety of damage, as can alcohol and diabetes. The length-dependency of many axonal neuropathies usually means that most axonal polyneuropathies will spare proximal nerves.

Myelinopathies, by contrast, often affect more proximal segments of nerve. Hereditary myelinopathies, such as Charcot-Marie Tooth type I, also called hereditary motor sensory neuropathy, are the result of dysfunctional peripheral myelin proteins, and affect myelin throughout the nerve. Acquired myelinopathy, such as Guillain-Barré syndrome (GBS)/acute demyelinating inflammatory polyneuropathy cause damage to some (often proximal) segments of myelin, sparing others.

Mononeuropathies, typically due to entrapment of the nerve in a bony canal or fibrous tunnel, or acutely from trauma in penetrating injury or nerve stretch injury, initially causes damage to the outer myelin (neurapraxia), but can result in injury to the axon as well. Following onset of acute nerve damage, evidence of electrophysiologic abnormalities in nerve conductions and EMG may require up to 3 weeks to occur.

Vocal Fold Paresis and Paralysis

The strict definition of vocal fold paresis and paralysis is motion impairment or complete lack of motion caused by damage or loss of *innervation* to muscle. In general use, these terms describe the *symptom* of motion impairment, which can be caused by nerve injury or mechanical fixation. More precise terminology would use the descriptor vocal fold motion impairment or vocal fold immobility until the etiology has been ascertained. Because it can be difficult to distinguish between paralysis and fixation by laryngoscopy alone, additional diagnostic measures may be necessary. LEMG may suggest paralysis (Fig. 70.6), fixation, or synkinesis. Direct laryngoscopy under anesthesia will permit evaluation for posterior glottic stenosis and palpation of the cricoarytenoid joint for ankylosis. If the cause is not obvious (trauma or iatrogenic), a typical workup would include a thorough history and imaging of the course of the vagus and RLN from skull base to mediastinum to search for possible lesions along the course of the nerve.

The clinical presentation of vocal fold paralysis varies from asymptomatic to severe laryngeal dysfunction. Patients may complain of an asthenic (weak), breathy, and diplophonic voice (the voice is heard at two distinct vibratory frequencies because each cord is at a different tension). Because the patients cannot approximate the vocal folds tightly (glottal incompetence) they will suffer phonatory shortness of breath due to rapid air escape and have a weak and incompetent cough. Because the RLN also contributes to innervation of the pharyngeal musculature and the cricopharyngeus muscle, dysphagia may be prominent. Additionally, loss of sensation in the hypopharynx secondary to superior laryngeal nerve compromise can result in pooling of secretions in the pyriforms and contribute to dysphagia and aspiration risk. Laryngoscopy reveals decreased mobility of the affected vocal cord, a glottal

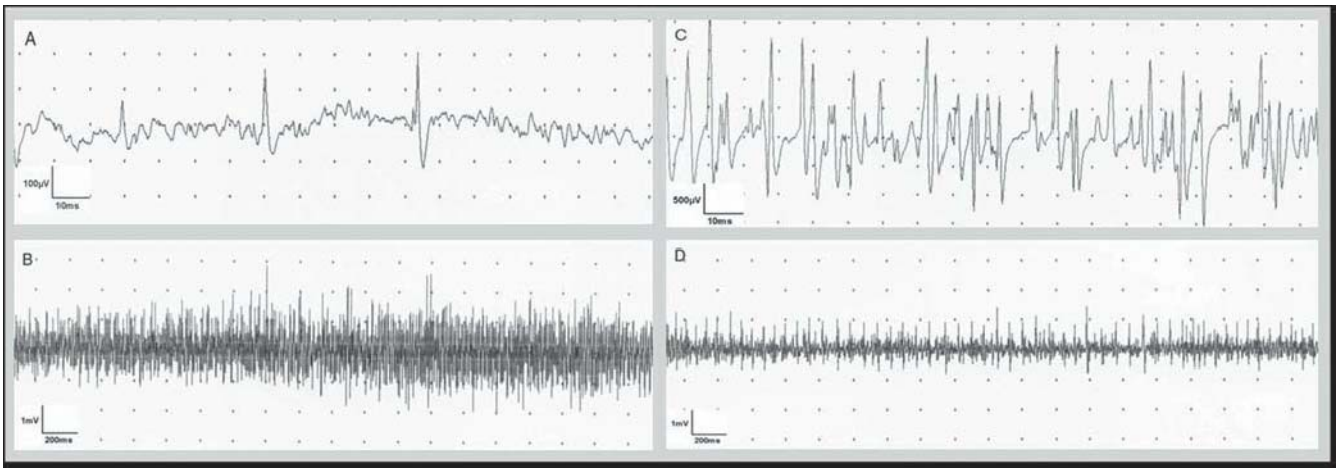


Figure 70.6 LEMG sequence of a patient with a left vocal fold paralysis caused by injury of the recurrent laryngeal nerve. **A:** Tracing of the electrical activity of the right thyroarytenoid muscle taken during quiet respiration, showing isolated firing of MUP of normal morphology. **B:** The normal, full interference pattern for the right thyroarytenoid, obliterating the baseline. **C:** Tracing of the electrical activity of the left thyroarytenoid muscle taken during phonatory effort shows multiple polyphasic giant waves indicative of reinnervation. **D:** A decreased interference pattern for the left thyroarytenoid, demonstrating the picket-fence pattern characteristic of neuropathy.

gap, pooling of secretions in the ipsilateral pyriform sinus, abnormalities in position of the arytenoid tower, and occasionally decreased sensation.

Because vocal fold paresis or paralysis often recovers spontaneously or patients develop satisfactory compensation, a logical treatment plan must be formulated to account for the natural progression of the injury. If potential for spontaneous recovery exists, a temporary augmentation procedure can provide immediate airway stabilization and restore glottal competence. This will improve vocalization, cough, swallow, and help prevent aspiration. If laryngeal EMG or the clinical scenario (such as latrogenic nerve transection) imply a poor chance of recovery, the patient would be a candidate for a more permanent rehabilitation procedure (see Chapter 69).

Bilateral vocal fold paralysis most often results from a surgical misadventure (thyroidectomy, esophagectomy). The voice may be close to normal, but patients can develop significant airway compromise from inability to abduct the vocal folds. Interestingly, even after bilateral injury, patients may tolerate the restricted airway for days to years before developing symptoms, which may then be misdiagnosed as asthma or bronchitis until laryngeal examination. Thus, it is always important to inquire about previous surgery—especially thyroidectomy, esophageal, or spine surgery—and examine the patient for revealing scars. If the airway compromise is severe, a tracheotomy may be required. This is sometimes done awake because it may not be absolutely evident if the embarrassment is caused by nerve injury, posterior glottic stenosis, or other laryngeal fixation. After the patient's airway has been secured, a direct laryngoscopy with evaluation of the cricoarytenoid joint should be performed. In less emergent circumstances, other vocal fold lateralization procedures can be considered (e.g., partial or total arytenoid ablative procedures, posterior cordotomy, an external lateralization stitch, or selective chemical neuromuscular denervation [39]) (see Chapter 62). These procedures are generally designed to maintain approximation of the anterior membranous vocal fold for phonation but increase the respiratory glottis.

Superior Laryngeal Nerve Paresis

Superior laryngeal nerve paresis manifests as sensory loss from the internal branch with motor weakness of the cricothyroideus muscle from the external branch of the RLN (Fig. 70.7). This can occur independently of recurrent nerve injury, and can be iatrogenic (thyroidectomy, neck dissection) or idiopathic. A unilateral sensory loss can cause throat clearing, coughing, and a globus sensation. A bilateral sensory loss can lead to severe, life-threatening aspiration. The vocal characteristics are caused by asymmetric cricothyroideus muscle function. Although individuals without complicated vocal demands may not notice any vocal defect, singers will complain of a ceiling effect (i.e., inability to reach their highest registers). Additionally, individuals may complain of vocal fatigue and diplophonia. On examination, pooling of secretions in the pyriform on the affected side reflects the sensory defect (40) The diagnosis can be confirmed by LEMG. Although some advocate voice therapy for unilateral loss and cricothyroid approximation for bilateral loss, no proven, useful medical or surgical interventions are available.

Acute Immune-Mediated Polyneuropathy—Guillain-Barré Syndrome

GBS is a heterogeneous grouping of immune-mediated inflammatory polyneuropathies generally characterized by motor, sensory, and autonomic dysfunction. In its most

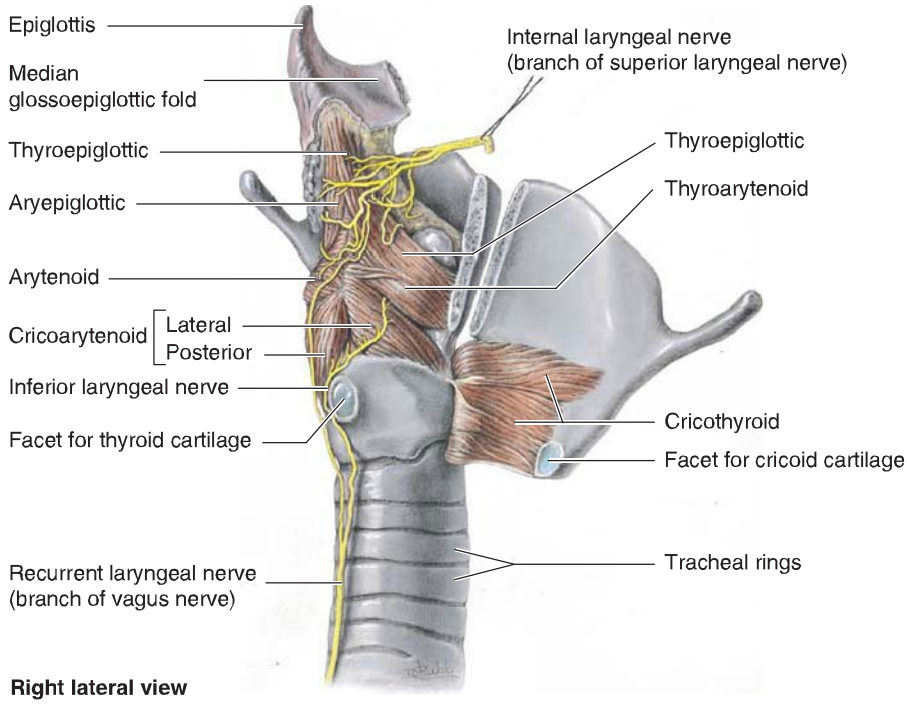


Figure 70.7 Details of the superior and recurrent laryngeal nerves. (From Moore KL, Dalley AF II. *Clinical oriented anatomy*, 4th ed. Baltimore, MD: Lippincott Williams & Wilkins, 1999.)

common form, GBS is characterized by progressive symmetric ascending muscle weakness, paralysis, and hyporeflexia with or without sensory or autonomic symptoms. In severe cases, muscle weakness may lead to respiratory failure.

GBS is a sporadic disorder with an incidence of 1 to 2 cases per 100,000 in North America and Europe and a 2:1 male predominance (41). In 60% of cases, acute inflammatory demyelinating polyneuropathy is preceded by a respiratory tract infection (e.g., cytomegalovirus, Epstein-Barr virus) or gastroenteritis (*Campylobacter jejuni*). The pathobiology of the disease is felt to result from postinfectious molecular mimicry in which nerve antigens are attacked by the immune system because they resemble antigens presented by microbes.

Miller Fisher syndrome is a variant of GBS that presents with the triad of ophthalmoplegia, ataxia, and areflexia. This form manifests as a descending paralysis, proceeding in the reverse order of the more common form of GBS and usually affects the eye muscles first. Up to 50% of patients will have bulbar palsy with prominent dysarthria and dysphagia (42).

The diagnosis is usually made by nerve conduction studies. With prompt treatment by IV immunoglobulins or plasmapheresis, together with supportive care, the majority of patients will recover completely. In the modern setting, acute mortality is about 2%. In general, slow spontaneous recovery occurs over a period of weeks or months. Most patients can expect complete recovery or minor sequelae; about 20% have a persistent disability. Individuals with Miller Fisher variant have an excellent prognosis.

Neuromuscular Junction

Myasthenia Gravis

MG has distinct implications for neurolaryngology, beginning with the first description in the 17th century by the English physician Thomas Willis, who described a woman who had transiently lost speech and was rendered "as mute as a fish." The disease has a prevalence of 14 to 20/100,000, and like many other autoimmune disorders, has a female predilection, with a bimodal incident distribution of young women in their 20s and 30s, and older men in their 40s and 50s. MG is associated with other autoimmune disorders, including Graves hyperthyroidism in about 10% of MG patients. Antibodies in MG are directed against the postsynaptic acetylcholine receptors, competitively inhibiting acetylcholine binding. These antibodies are produced from T cells that have their origin in the thymus.

MG patients complain of weakness that worsens toward the end of the day and with repeated activity or movement. Myasthenia affects proximal muscles more than distal muscles, and may involve extraocular muscles exclusively (ocular myasthenia), causing diplopia or ptosis. Patients with ocular myasthenia frequently progress to generalized muscle involvement.

If disease is localized to the throat, patients can have difficulty speaking, breathing, or swallowing, and examination of larynx and palate will reveal fatigue with repetitive movements. Because of the sustained contraction of the vocalis and cricothyroideus muscles required to maintain a high musical pitch, individuals with myasthenic involvement of these muscles fatigue quickly with a lowering of the pitch over a few seconds (43). Rhinolalia (hypernasal

voice) and nasal regurgitation of food are manifestations of myasthenic involvement of palatal musculature.

Diagnostic testing for MG include serologic, provocative, and electrophysiologic testing (44). Binding acetylcholine receptor antibodies (AchRAbs) can be detected in serum, and are positive in 85% of generalized myasthenics and 50% of patients with ocular MG. Blocking antibodies to the acetylcholine receptor are positive in approximately 1% of patients with negative binding AchRAbs. Antibodies to muscle-specific kinase may be positive in up to 40% of myasthenics with negative AchRAbs. The edrophonium (Tensilon) stimulation test involves injection of a small amount of a short-acting acetylcholine esterase inhibitor (edrophonium 0.05 to 0.1 mg/kg, slow push over 1 minute), which is deemed positive if the patient's weakness, ptosis, ocular misalignment, or vocal cord paresis transiently resolves or improves. Because edrophonium acts at both nicotinic and muscarinic acetylcholine receptors, premedication with atropine may be performed to prevent symptomatic bradycardia.

Additional electrophysiologic testing that aids in diagnosis includes repetitive nerve stimulation and single fiber EMG. These tests can be positive in many diseases of the peripheral nervous system, so is not specific for MG.

Early detection is invaluable because medical treatment is effective and potentially lifesaving. Exacerbations may result in respiratory compromise and require intensive care unit stay. Medications either act to increase the amount of acetylcholine in the synaptic cleft by inhibiting the breakdown enzyme acetylcholine esterase (pyridostigmine) or modifying immune response (steroids, steroid-sparing agents including mycophenolate and azathioprine, and intravenous immunoglobulin [IVIG] and plasma exchange for acute exacerbation). Thymectomy for thymic hyperplasia or thymoma may ameliorate the condition, or even be curative, in some cases.

Myasthenic Syndrome or Lambert-Eaton Syndrome

Lambert-Eaton Myasthenic Syndrome is a paraneoplastic condition primarily associated with small cell lung and other cancers (45). Antibodies against tumor antigens cross-react with epitopes on voltage-gated calcium channels and prevent transmission presynaptically. The patient presents with weakness that improves with exertion and repetitive movement, in contrast to MG. Treatment is 3,4 diaminopyridine to aid in acetylcholine release from the synaptic terminal. Steroids, IVIG, and plasmapheresis may be of some benefit in immune modulation. The syndrome may precede discovery of actual cancer by up to several years, and its presence warrants a search for a primary neoplasia.

Botulism

Botulism is the paralytic disease caused by poisoning with the toxin of the anaerobic, spore-forming, gram-positive rod *Clostridium botulinum*. Botulism most commonly occurs following ingestion of improperly home-canned food. Fulminating weakness, which begins 12 to 72 hours after ingestion of the toxin, is manifested initially by diplopia, ptosis, facial weakness, dysphagia, and rhinolalia, then progressing to respiratory failure. Weakness usually appears last in the limbs. Also present may be the anticholinergic symptoms of blurry vision, dry mouth, paralytic ileus, and postural hypotension. Symptoms can progress for several days. Antitoxin is available, although the effect on the disease course is unclear. Guanidine hydrochloride (facilitates release of acetylcholine from nerve endings) can improve muscle strength. Supportive care is the mainstay of treatment.

Botulinum Toxin Mechanism

The bacteria *C. botulinum* is an anaerobic, spore-forming, gram-positive rod that is a soil organism. Disease is caused by (a) inoculation of a wound with local proliferation of the bacterium and systemic spread of the toxin; (b) ingestion of the spores in improperly cooked food, with germination and growth in the gut and absorption of the toxin; or (c) ingestion of preformed toxin in improperly cooked foods with systemic absorption. The toxin is heat labile and can be inactivated by boiling for several minutes.

Seven serotypes (A–G) exist, which exert their paralytic effect by inhibiting the exocytotic release of acetylcholine at the neuromuscular junction, and may have inhibitory activity in the afferent transmission of pain by preventing the release of pain mediators such as substance P, calcitonin gene-related peptide, glutamate, or neurokinin A. The toxins are composed of a heavy and light chain. The heavy chain is responsible for neuron-specific binding and internalization, and the light chain is a protease that cleaves one of the fusion proteins responsible for vesicle docking, thus preventing neurotransmitter exocytosis. Specific serotypes target different docking proteins, botulinum toxin A and E target synaptosomal-associated protein 25 (SNAP-25), and botulinum toxin B, D, F, and G target synaptobrevin, and type C targets syntaxin. It takes approximately 3 months for the Snap-25 to become functional again, and 2 months for synaptobrevin to be regenerated, which correlates to the duration of muscular weakness seen clinically.

When neuromuscular transmission is initially interrupted, the axon responds by creating sprouts to establish new junctions. These new junctions allow weak stimulation at about 1 month. At approximately 90 days, the original terminals regain activity, resulting in regression of the sprouts.

The potency of the toxin is determined by *in vivo* mouse assays. One unit of the brand name BOTOX® (botulinum toxin A—Allergan) is defined as the amount of toxin required to kill 50% of a batch of female Swiss-Webster mice. The lethal dose in humans is estimated to be approximately 3,500 U of BOTOX®. Dysport (Ipsen Pharmaceuticals, Berkshire, England) is also botulinum toxin type A, but 1 U of BOTOX® is felt to be equivalent to 3 to 4 U of Dysport. Myobloc (Elan), which is botulinum toxin type B, has slightly different characteristics. It has a faster onset (24 hours vs. 1 to 3 days) and a shorter duration (2 months vs. 3 months). One unit of BOTOX® is felt to be equivalent to 54 U of Myobloc.

Individuals can form antibodies to the toxin, which appear to cause no harm in terms of anaphylactic reactivity, but do render the patients resistant to the paralytic effect of the toxin. Individuals immunoresistant to one serotype of toxin usually receive benefit from switching to another serotype.

Aminoglycoside Antibiotics

Large doses of aminoglycoside antibiotics can produce a clinical syndrome like botulism owing to prevention of acetylcholine release from nerve endings. This is likely related to calcium channel blockade. Symptoms resolve if the drug is discontinued. These antibiotics are best avoided in patients with disturbances of neuromuscular transmission and should be avoided in patients with MG.

Myopathic Disorders

Myopathies

Myopathies, primary disorders of muscle, are diseases that can be classified as muscular dystrophies, genetic disorders resulting in aberrant microcellular structure, or myositides, inflammatory muscle diseases. Myopathies generally affect more proximal muscles than distal muscles, and result in muscle weakness and atrophy. Diagnostic modalities include needle electromyography (nEMG), serum creatine kinase, myoglobin levels, and muscle biopsy.

Muscular Dystrophies

Muscular dystrophies are inherited myopathies that affect muscle membrane and cytoskeletal elements (46). They may have associated cardiomyopathies and other organ system dysfunction. They may be accompanied by mild to moderate elevations of serum creatine kinase. Examples of muscular dystrophies include X-linked *Duchenne* and *Becker* diseases that come from production of an abnormal dystrophin membrane protein. They affect boys in childhood and their teens. *Limb-girdle* and *facio-scapular-humeral muscular dystrophies* are inherited in various patterns, affect a variety of muscle proteins, including calpain, caveolin, and lamin, and affect people in the later teens and adulthood. The pattern of weakness and atrophy is evident in the named disorder.

Oculopharyngeal muscular dystrophy is a rare muscular dystrophy of variable inheritance pattern causing ptosis and ocular misalignment, as well as dysphagia and tongue weakness. Symptom onset is in the late teens to forties. Expansion of the trinucleotide repeat GCG on chromosome 14 encoding the protein polyalanine is implicated in the pathogenetic mechanism. *Myotonic dystrophies*, so named because of the presence of clinical and electrical myotonia due to muscle membrane abnormalities that create abnormal patterns of contraction and relaxation, may affect distal or proximal musculature. *Myotonic dystrophy type I* (DM1) affects distal hand muscles, neck flexors, and tongue and palate, beginning in early childhood. DM1 is caused by a trinucleotide repeat expansion on chromosome 19 affecting the myotonin kinase enzyme, while *myotonic dystrophy type 2* (DM2) also called proximal myotonic myopathy, is caused by an expansion of a tetranucleotide repeat affecting the zinc finger 9 membrane protein. DM2 has an onset in later childhood and has less face, tongue, and palate involvement.

Inflammatory Myopathies

Polymyositis and *dermatomyositis* are inflammatory myopathies often associated with lung carcinoma, autoimmune disorders, or polio. These myopathies are often associated with muscle pain, tenderness, dysphagia, and respiratory difficulties. Dermatomyositis is clinically distinguished from polymyositis by the presence of skin findings including a heliotrope rash and Gottron papules on the extensor surfaces of the hands but has a distinct pathophysiology. Dysphagia can be a presenting symptom (47), but most patients will often also have proximal muscle weakness as evidenced by difficulty in standing up from a seated position without using their arms to assist, or difficulty in sitting up from a supine position. Patients may have serum creatine kinase elevation several hundred times the normal indicative of the degree of muscle breakdown from the disorder; EMG shows evidence of myonecrosis and muscle biopsy will show inflammatory cells. The course can progress rapidly, and treatment with steroids and other immune modulators is indicated.

Inclusion body myositis (IBM), has an unusual distribution insofar as it has preference for the anterior thigh muscles and the finger flexors of the hands. Dysphagia, affecting the upper one-third of the esophagus is present in half of patients with IBM. Age of onset is usually after 50 years, and is slowly progressive over one to two decades. Muscle biopsy is distinct in showing the presence of rimmed vacuoles. IBM generally responds poorly to immune modulatory treatment (48).

ELECTROMYOGRAPHY OF LARYNGEAL AND PHARYNGEAL MUSCLES

nEMG is a valuable tool in the evaluation of laryngeal and pharyngeal musculature function. The nEMG evaluation has two primary functions: (a) evaluation of the stability of the muscle membrane and (b) evaluating changes to the motor unit. Remember that the motor unit is the summation of the motor neuron (from the nucleus ambiguus), the axon, and all the muscle fibers it supplies. Therefore, characterizing any alterations to the motor unit waveforms may be diagnostic of a motor neuron disorder, damage to the peripheral nerve axon, or an intrinsic muscle lesion.

nEMG detects electrical potentials at the recording electrode, relative to the potentials at the reference electrode, and the difference between potentials at these two sites is displayed. This effectively cancels out any ambient electrical activity not specific to the reference site. The output is digitally processed for presentation on a computer screen and loudspeaker for both visual and audio interpretation.

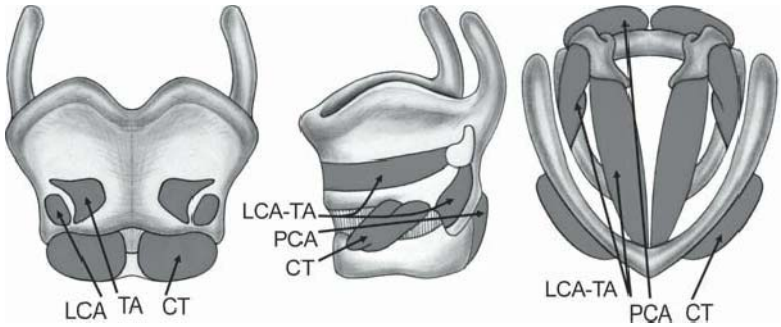


Figure 70.8 Needle electrode placement for the thyroarytenoid (*TA*), cricothyroid (*CT*), lateral cricoarytenoid (*LCA*), and posterior cricoarytenoid (*PCA*).

Laryngeal nEMG (LEMG) is performed using a 25 to 27 gauge monopolar needle recording electrode with a surface reference electrode or a concentric needle (with its own reference). Both require a surface ground electrode. The monopolar needle is Teflon-coated, glides through muscle with greater ease, and also has a greater recording volume. The concentric needle has both recording and reference electrodes contained in the needle, is not coated in Teflon, and has a recording volume of roughly half the size of the monopolar needle. A 37-mm length needle is sufficient for most patients. Electrical waveforms recorded from a monopolar needle are wider and larger than those from a concentric needle, but a concentric generally yields a more precise recording for evaluation of waveforms, particularly for concerns of myopathy.

For LEMG, a needle electrode is inserted through the skin and into the muscle of interest. Proper insertion is verified by asking the patient to perform appropriate verification tasks such as vocalization (for the thyroarytenoid) or sniffing (for the PCA). EMG evaluation consists of sampling electrical activity during three events: needle insertion into the selected muscle, spontaneous electrical activity when the muscle is at rest, and volitional electrical activity during muscle contraction.

Technique

In general, three muscle groups are sampled during routine LEMG: the cricothyroid reflects superior laryngeal nerve function, and the TA-LCA and PCA reflect RLN function.

The cricothyroid muscle is accessed by inserting the needle electrode 5 mm lateral to midline at the lower edge of the cricoid cartilage and directing the tip of the needle toward the inferior tuberculum of the thyroid cartilage. Correct placement is verified by increased activity with glissando. The TA-LCA muscle is accessed by inserting the needle through the cricothyroid membrane at the midline and directing the tip submucosally and laterally toward the superior thyroid corneau. Correct placement is verified by increased activity with phonation. The PCA can be accessed laterally by laryngeal rotation or transglottically by piercing the posterior lamina of the cricoid cartilage. Correct placement is verified by increased activity during sniffing but not during phonation (Fig. 70.8).

When the needle is felt to be in the muscle of interest, the patient is asked to rest and breathe quietly to evaluate for spontaneous activity. In general, complete relaxation of a healthy striated muscle gives no EMG activity, or only minimal nonpropagated depolarizations owing to proximity to the motor endplate. Muscles that have had neuropathic damage with denervation will develop abnormal spontaneous activity such as fibrillation potentials and positive sharp waves approximately 2 to 3 weeks after injury, which will persist until reinnervation occurs or until the motor endplates of the muscle degenerate (Fig. 70.9).

Volitional activity is measured by asking the patient to perform selected vocal tasks. The resultant motor unit potentials (MUPs) are evaluated for phase, duration, amplitude, and the interference or recruitment pattern.

A normal MUP is bi- or triphasic (phases are counted by noting the number of times the potential crosses the baseline). Greater than four phases is abnormal and termed polyphasic. Polyphasia occurs when the single muscle fibers are not well synchronized. Although this can occur for many different reasons, it most often occurs following denervation of muscle fibers, as adjacent axons sprout to reinnervate the orphaned muscle fibers after a neuropathic injury. Over time, the polyphrasia resolves as the motor

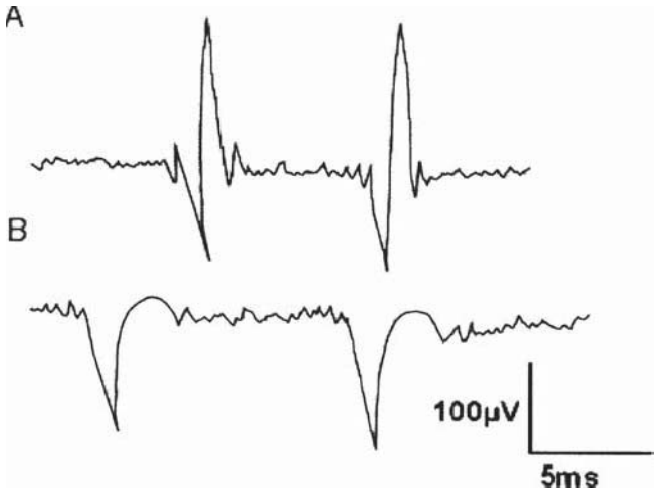


Figure 70.9 Diagrams of abnormal spontaneous activity suggestive of denervation. **A:** Fibrillation potential. **B:** Positive sharp wave.

unit consolidates into a unit of wider duration and greater amplitude than what existed prior to the injury. Thus "polys" and "giant MUPs" characterize neuropathic injury.

In myopathic conditions, the number of functioning muscle fibers in a motor unit decreases and the amplitude of the associated MUP also decreases. Myopathic MUPs, therefore, are often polyphasic, but have decreased amplitude and duration (brief, small amplitude polyphasic potentials [BSAPs]; Fig. 70.10).

Finally, the recruitment pattern is determined. As a muscle is contracted intensely, the frequency of motor unit firing will increase, filling the display screen with MUPs such that individual patterns are not discernible and the baseline is obliterated. A *full recruitment* pattern is normal. In a neuropathic process, there is loss of motor units and despite full firing of all available units, the baseline will not be obliterated yielding a *reduced recruitment* pattern. This pattern visually appears as a picket fence on the EMG screen, and the auditory signal sounds like the dragging of a stick along a picket fence or the monotonous firing of a machine gun. In this case, a single motor unit may have to fire at a greater rate to produce the same muscle power that several normally recruited units would create. So, reduced recruitment indicates a decrease in functioning motor units. With a myopathic process, there is no loss of motor units, but the power of an individual motor unit is less than normal. Therefore, more motor units are more quickly engaged to produce the same amount of power as a normal motor unit, hence termed *early recruitment*. This produces an interference pattern that is reduced in amplitude but still able to obliterate the baseline (Fig. 70.11).

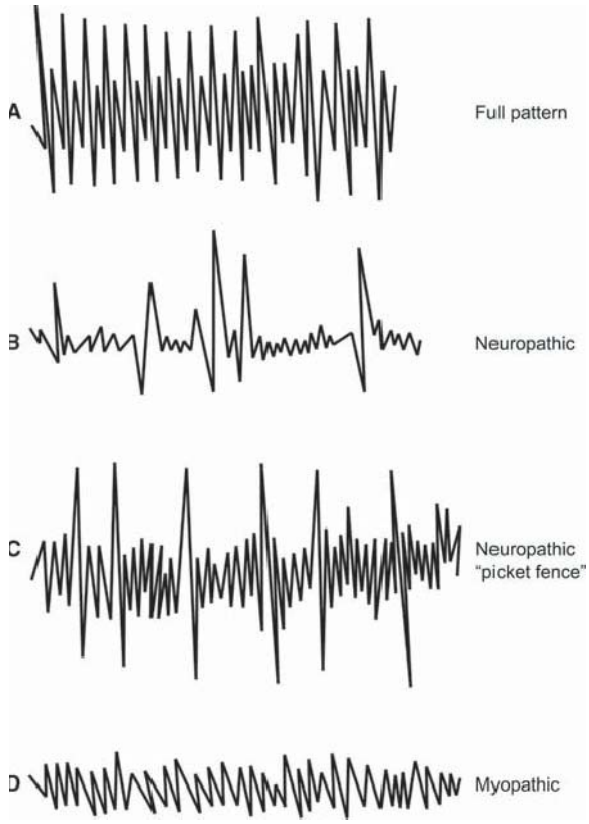


Figure 70.11 Examples of recruitment patterns. **A:** Normal pattern with a full interference pattern obliterating the baseline. **B:** Reduced recruitment seen with a neuropathic process. Note that the baseline is not obliterated. **C:** "Picket-fence" pattern characteristic of a neuropathic process. **D:** Early recruitment pattern seen with a myopathic process. The baseline is obliterated quickly with an overall lower amplitude.

Uses in Laryngology

1. Paralysis versus fixation: Vocal fold paralysis should have the EMG findings of neuropathy, whereas cricoarytenoid arthritis, dislocation, and posterior glottic scarring should yield a normal EMG pattern (49,50).
2. Prognosis of paralysis (51): In general, laryngeal EMG better predicts which patients will NOT recover vocal fold motion and are thus candidates for early rehabilitation. Presence of spontaneous activity (fibrillations and positive sharp waves), polyphasic potentials, absence of normal MUPs, synkinesis (52), and a decreased recruit-

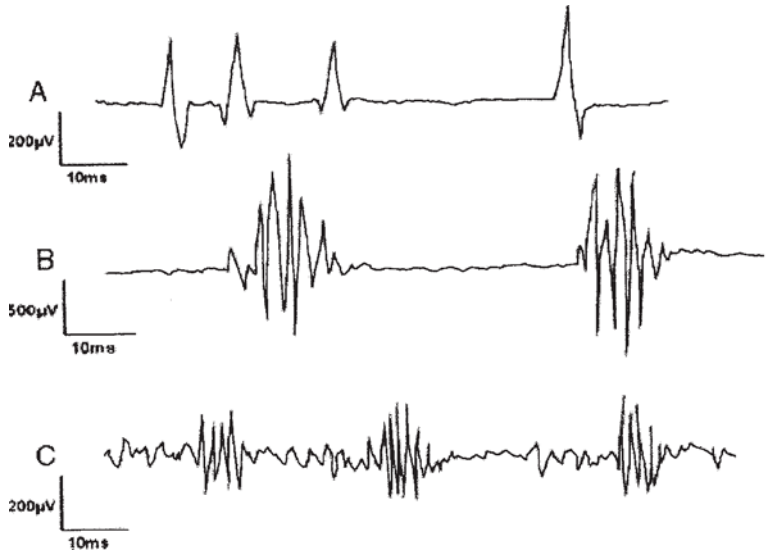


Figure 70.10 Examples of MUP. **A:** Normal units. **B:** Neuropathic units. **C:** Myopathic units.

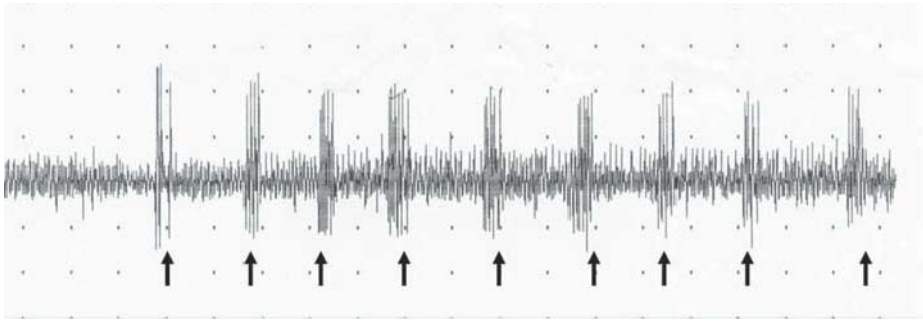


Figure 70.12 Synkinesis. A recording from the thyroarytenoid muscle of a patient with long-standing vocal fold immobility, demonstrating inappropriate activation when the patient is asked to sniff (*arrows*), an abductory task during which the thyroarytenoid muscle is normally not active.

ment pattern are indications that the nerve damage is severe and may not recover. Presence of normal MUPs, a normal recruitment pattern, and absence of spontaneous activity indicate a good chance of return of function. A mixed pattern gives an intermediate prognosis. This information must be interpreted in light of the clinical history and time course (53). Recent advances in quantitative laryngeal EMG demonstrate significant improvements in ability to prognosticate return of function (54).

3. Site of lesion localization: EMG testing of the cricothyroid muscle compared with the thyroarytenoid muscle allows isolation of the two components of vagal innervation to the larynx. A high injury will show abnormalities in the EMG pattern of both muscles, and an isolated superior or recurrent injury will show an abnormal pattern in one muscle only.
4. Synkinesis: EMG testing of the TA-LCA muscle and the PCA muscle will show inappropriate activation of muscle groups with certain laryngeal gestures. So, the TA-LCA will be activated with sniffing, or the PCA will be activated with voicing. This is felt to be caused by misdirected regeneration of nerve fibers between abductor and adductor muscle groups (52) (Fig. 70.12).
5. Identification of appropriate muscles for BOTOX injection.
6. EMG can be used to determine a neurologic diagnosis (MG, ALS, myopathy).
7. Intraoperative nerve monitoring.
8. Biofeedback in speech and swallowing disorders.
9. EMG can determine the relative levels of functional neuromuscular innervation of each vocal fold. This information can influence surgical and procedural decision making for laryngeal reinnervation, vocal fold augmentation, arytenoid adduction, or a destructive glottic enlargement procedure.

TABLE 70.3 NEUROLARYNGEAL DISORDERS, BY LARYNGEAL PRESENTATION

Presentation	Spastic	Hypokinetic	Hyperkinetic	Ataxic	Paresis/Paralysis
Vocal Fold Appearance	Variable	Rigid/bowing on phonation	Hyperabducted	Uncoordinated, decreased mobility	Atrophied, flaccid, fasciculating
Anatomical Structures Involved	UMN/corticobulbar tracts	Basal ganglia	Basal ganglia	Cerebellum	Brainstem—nucleus ambiguus; peripheral nerve; neuromuscular junction; muscle
Example Disorders	PLS, ALS, stroke, MS	Parkinson disease, MSA	Dystonia, tremor, myoclonus	Friedreich ataxia, stroke, MS	ALS, brainstem stroke, GBS, superior laryngeal nerve injury, MG, polymyositis
Treatment	Botulinum toxin, voice and swallowing therapy vocal fold medialization	Voice and swallowing therapy, vocal fold medialization	Botulinum toxin, voice and swallowing therapy	Voice and swallowing therapy, vocal fold medialization	Tracheostomy(severe), vocal fold medialization or lateralization, voice and swallowing therapy

UMN, Upper Motor Neuron; PLS, Primary Lateral Sclerosis; ALS, Amyotrophic Lateral Sclerosis; MS, Multiple Sclerosis; MSA, Multiple Systems Atrophy; GBS, Guillian-Barre Syndrome; LSVT, Lee Silverman Vocal Therapy.

HIGHLIGHTS

- The accurate diagnosis of neurologic disease of the larynx relies on both history and physical examination, with adjunctive testing, LEMG, and neurology consultation.
- Flexible transnasal laryngoscopy is the preferred method of laryngeal evaluation for neurologic disease. Transoral rigid laryngoscopy or mirror examination significantly alters laryngeal mechanics owing to tongue traction and inability of the patient to perform normal speech and vocal tasks.
- Neurologic disorders of the larynx are, for the most part, disorders of function as determined by the structure disrupted (Table 70.3).
- Behavioral therapy (LSVT) is the only treatment modality that has shown a consistently positive and lasting effect on the vocal function in many parkinsonian patients.
- An individual with parkinsonian features and vocal fold immobility should be evaluated for multisystem atrophy. If these individuals develop sleep disorders, they are at risk for sudden death.
- Vocal fold paralysis can be diagnosed in an individual with vocal fold immobility when it can be shown by history or examination that there has been damage to the RLN, EMG evidence indicates denervation, or palpation of the cricoarytenoid joint confirms lack of fixation.
- Spasmodic dysphonia is a focal laryngeal dystonia. Botulinum toxin injections into the laryngeal musculature are the treatment of choice, and have both peripheral and central neurologic effects. Vocal spasms are ameliorated by weakening the dystonic musculature, and CNS function is modulated through changes in peripheral feedback. Surgical therapy yields transient results and speech and medical therapy are useful only as an adjunct to toxin injection.
- LEMG is a useful adjunct in the diagnosis of neurologic disease of the larynx and is critical to guide medical and surgical treatments. LEMG is especially helpful in the prognostication of recovery from vocal fold paralysis.

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71 Voice Therapy for the Treatment of Voice Disorders

Jackie Gartner-Schmidt

The otolaryngologist and speech–language pathologist are critical members of the voice care team (1). The role of each, however, is different. Patients enter the medical setting with the medical intervention model in mind; namely, is there a medicine or surgery that will fix their voice problem? Whereas otolaryngologists take responsibility for effecting change either medically or surgically, a speech–language pathologist teaches patients to adopt responsibility for behavioral change because, in its most basic sense, voice therapy teaches patients to modify faulty or compensatory vocal behavior. Persuading patients to become responsible for their vocal behaviors may be difficult, but it is paramount to successful voice therapy (2–4). Otolaryngologists are the first people to impress this message to their patients: voice therapy is often successful but requires active participation from the patient. Unfortunately, there are high rates of attrition in voice therapy (5–7). It is important for otolaryngologists to refrain from saying "I want you to *try* voice therapy" as often this verbiage can plant the seeds of noncompliance and attrition. In addition, because most patients assume the medical model of rehabilitation, a rapid restoration (i.e., "quick fix") of voice is expected. Behavioral modification is not a "quick fix" and patients need to understand this basic premise.

A common question posed by otolaryngologists to speech–language pathologists is, "What do you do in voice therapy?" In this chapter, a model of the component parts of voice therapy will first be illustrated followed by a condensed description of some of the most commonly used voice therapies and their applications to specific voice disorders. In addition, approximate treatment durations, reference to appropriate referrals, and limitations to therapeutic success will be discussed.

The Venn diagram in Figure 71.1 illustrates the key categories of any voice therapy program: increase vocal hygiene, decrease phonotrauma, and increase coordinated voice production. Although the circles delineate separate entities, they are not mutually exclusive. This model is very similar to the component parts (i.e., categories) of voice therapy. The speech–language pathologist determines which category (i.e., circle) to work with the patient, so modification of the appropriate maladaptive behaviors can be emphasized. The speech–language pathologist must also realize that patients may be in more than one circle. The first two circles, increase vocal hygiene and decrease phonotrauma, represent indirect approaches to voice therapy, whereby the speech–language pathologist essentially educates the patient concerning how his or her laryngeal mechanism works and what may cause harm. The third circle, increase coordinated vocal production, represents a direct approach to voice therapy; here, the speech–language pathologist directly alters the patient's speaking technique in an attempt to increase vocal quality and efficiency. Indirect voice therapy usually requires 1 to 2 weekly sessions, whereas direct voice therapy usually requires 4 to 6 sessions (e.g., weekly sessions are ideal but not mandatory). This therapy schedule mirrors preoperative and postoperative therapy, in that patients generally receive 1 to 2 sessions of preoperative voice therapy and 4 to 6 sessions of postoperative therapy. Patients may also benefit from a subsequent series of voice therapy (1 to 3 sessions) months after the initial voice therapy to evaluate transfer and retention of the new vocal behaviors.

VOCAL HYGIENE

Vocal hygiene is the foundation of voice therapy. Patients are taught to take care of their vocal fold tissues by keeping hydrated and limiting laryngeal irritants. The best voice therapy starts with the patient taking active control of his or her vocal health. In addition, good vocal hygiene may decrease susceptibility to postoperative scarring (8). Two general topics are included in this circle: hydration and laryngopharyngeal reflux (LPR).

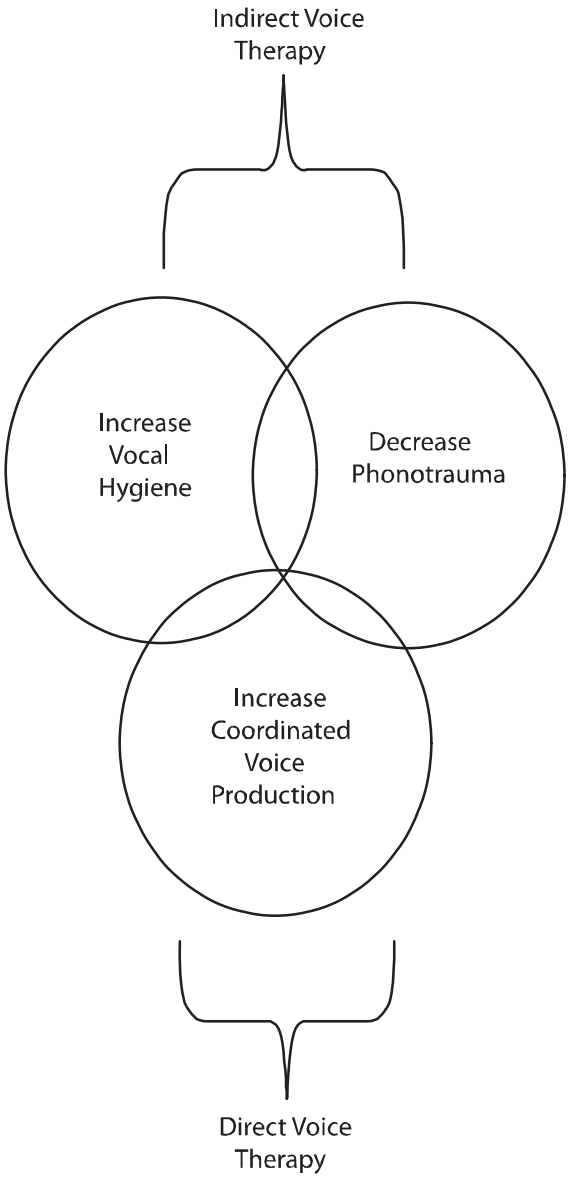


Figure 71.1 Model for voice therapy: three categories.

Hydration

Laryngeal sicca is increased viscosity of laryngeal secretions and is a result of the reduction of water in the body. Patients should be educated concerning why drinking water is important to the physiology of vocal production; they should not simply be told "to drink 8 glasses of water a day." Increased viscosity of secretions may cause increased viscosity of vocal fold surfaces and, in turn, cause increased heat, friction, and edema of the vocal folds, which may increase the risk of phonotrauma (9). Research has shown that hydrated vocal folds vibrate with less subglottic pressure than do nonhydrated vocal folds, especially at high pitches (10–14). Hydrated vocal folds are less predisposed to trauma than dry vocal folds and show more resilience from trauma (i.e., phonotrauma) than dry vocal folds (9,12–15). Interested readers are referred to a review article by Leydon et al. (16). Patients may hydrate internally (i.e., drink water), externally (i.e., steam shower, steam inhaler, and/or hot water vaporizer), or both, based on medical history and individual need. Hygiene programs should be individualized for each patient. For example, if a patient is diagnosed with congestive heart failure, they may not be able to drink large quantities of water. In addition, smoking cigarettes or other substances should be eliminated. Engaging in voice therapy when patients continue to use laryngeal irritants (e.g., smoking) is obviously counterproductive to therapeutic success.

Laryngopharyngeal Reflux

Patients diagnosed with LPR should be medicated (e.g., proton pump inhibitors, H_2 blockers, antacids) for this disease and engage in behavioral LPR treatment if needed (see Chapter 59). LPR may inflame the vocal folds, change the biomechanics of phonation, and potentially influence vocal fold pathologies (17). Initiating voice therapy with the healthiest vocal folds possible is the launch pad of therapy. Voice therapy is often used in conjunction with medical intervention in this circle.

DECREASE PHONOTRAUMA

The second circle is entitled decrease phonotrauma (vocal abuse/overuse) and is defined as a voice produced with too much effort for increased durations of time or at an inordinately high volume, often resulting in organically based vocal fold pathology. Phonotraumatic vocal behaviors may result in benign vocal fold lesions (e.g., nodules, cysts, fibrous mass, polyps) and scar. Such vocal behaviors as screaming, yelling, throat clearing, continued voicing while sick, vocalization during vigorous exercising, vocal overuse, and speaking over background noise are examples. Although modern-day voice therapy is much more than a "do/don't" list, the prevailing "don't" recommendation in voice therapy is "don't scream." High-pitched screaming may result in vocal fold hemorrhage. Vocal overuse may also cause vascular changes (i.e., vascular permeability) in the vocal folds, which may predispose patients to have small and large hemorrhages, often recurrent in nature. Cumulative microtrauma to the vocal fold tissues may result in scarring, sulcus vocalis, or both. Voice therapy is often used in conjunction with surgical intervention for phonotraumatic lesions in this circle.

Patients should be educated concerning the first two circles (increase vocal hygiene and decrease phonotrauma) in the first and second sessions of voice therapy. If patients show difficulty with compliance to increasing vocal hygiene and decreasing phonotrauma, prognosis for improvement in voice therapy is guarded.

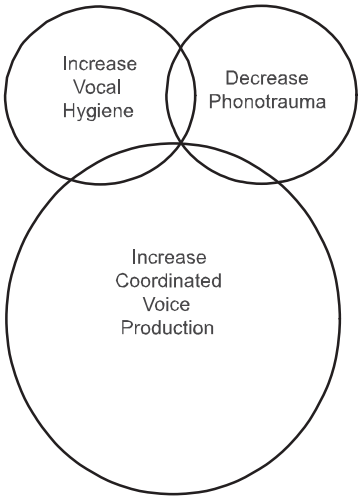


Figure 71.2 Interaction between the three categories of voice therapy.

INCREASE COORDINATED VOICE PRODUCTION

The third circle, increase coordinated vocal production (vocal misuse), is the crux of voice therapy. Uncoordinated vocal production is defined as an abnormal-sounding voice production resulting from the imbalance of respiration, phonation, and resonation. As illustrated in Figure 71.2, patients may have initially engaged in phonotraumatic behaviors and developed benign vocal fold lesions only to perpetuate their problems by producing voice in an unbalanced manner. Although faulty hygienic and phonotraumatic behaviors may have decreased, the patient now uses maladaptive compensatory voicing techniques, which places them in the third circle. Alternatively, patients may have a normal larynx but produce voice in an unbalanced manner. Examples of this include primary muscle tension dysphonia (MTD) and, the most extreme case, functional aphonia. Examples of poor balance between respiration, phonation, and resonation include "holding breath back" at the level of the vocal folds and respiratory mechanism (e.g., faulty airflow management), extra intrinsic and extrinsic laryngeal muscular tension (e.g., high larynx and glottal/supraglottic constriction), and abnormal pitch and intensity. These examples frequently define MTD. Often patients will complain of vocal fatigue and general tightness/constriction in the neck region. It is important not only to ask patients about the sound of their voice production but also about the "feel" of their voice production. Some patients are not so bothered by the sound of their voice but rather the feel.

VOICE THERAPY APPROACHES

The following is a brief synopsis of a variety of different voice therapy approaches that "rebalance" the voice production system. The types of therapies listed in the following are not intended to be comprehensive nor instructive in nature; instead, they are a description of the most commonly used voice therapies. "Typical" voice disorders may be paired with specific voice therapies; however, there is no general agreement among speech–language pathologists about which voice therapies to use with specific voice disorders. In part, this is because the medical disorder (e.g., nodules or vocal fold paralysis) does not necessarily determine how the patient uses his or her mechanism. Thus, it is much more important to treat the vocal behavior versus the voice disorder. Most speech–language pathologists use a combination of the therapies listed and do not use one therapy in particular. Although the following list defines each specific therapy, voice therapy is not "cookbook care." Each patient presents with individual needs, and some therapies work better with some patients than others.

Accent Method

The accent method, originally developed by Smith and Thyme (18), focuses on rhythmic breathing as the primary control mechanism and pairs body movement with respiration and phonation to rebalance the system. The method trains patients to produce easy voicing, abdominal breathing movements (by alternating contraction and release), and open throat postures. These productions are achieved by using rhythmic vocalizations of consonant sounds (called accents), in combination with body movements (e.g., swaying arms or rocking back and forth), while stressing respiratory support for each accent. Proponents of this method report that patients acquire optimal respiratory support, coordination of exhalation and phonatory onset, and phonatory effort (19). Research investigating the efficacy of the accent method shows good outcomes (19,20).

Anatomic/Physiologic Explanation

The rhythmic pairing of timing with respiration and phonation may promote motor learning of new phonatory behaviors (21).

Application

The accent method may be used to treat benign lesions, MTD, vocal fatigue, paradoxical vocal fold motion, and mild glottal incompetence.

Confidential Voice

Confidential voice therapy is used to reduce the force of vocal fold collision and excessive laryngeal hyperfunction during phonation. A breathy voice produced with slightly abducted vocal folds (22) is the therapeutic goal. The slight abduction of the vocal folds results in increased airflow, decreased loudness, and decreased collision force. Although a breathy voice is not the final goal of therapy, it is encouraged for a prescribed period to promote mucosal healing. Confidential voice therapy allows surgical

sites to heal without strong collision forces/stress impact, decreases lesion size, eliminates excessive muscular activity, and increases awareness of habitual loudness levels.

Anatomic/Physiologic Explanation

Producing a breathy voice results in slightly abducted vocal folds, which results in smaller amplitudes of vibration and decreased collision force/stress impact. As a result, the vocal folds should be protected from further injury and allowed to heal.

Application

Confidential voice therapy may be used to treat benign lesions, MTD, and it can be used during the postoperative period of voice reinstatement. It is not appropriate for patients with voice problems related to glottal incompetence. Also, confidential voice is only used for a period of time to promote vocal fold healing; once that period is finished, the voice production is shaped into a healthy vocal production by other therapies mentioned in this chapter. A soft, breathy voice is not an appropriate goal of any voice therapy technique.

Lee Silverman Voice Treatment

Lee Silverman voice treatment (LSVT) is the most researched voice therapy protocol to date. LSVT was developed to address the hypokinetic dysphonia most frequently associated with Parkinson disease. LSVT is a systematic voice therapy approach that focuses on increasing loudness during four sessions per week for 4 weeks (23–25). Patients are trained to "recalibrate" their habitual speaking volume to one louder because the loudness that they think is normal is, in reality, too quiet. Having patients use a very loud voice also improves their articulatory precision and inflection. Treatment and home practice are intensive, and a high degree of independent compliance is required by the patient. The efficacy of this treatment has been well researched (23–27). It should be mentioned that there is a modified version of LSVT called Pitch Limiting Voice Treatment, which requires patients to voice in a low and loud pitch to increase loudness and speech intelligibility (28). Two other therapy programs designed from the LSVT theoretical framework are LSVT (LOUD) and LSVT (BIG) that may be used with patients with Parkinson disease, the aging voice, and other conditions including stroke, multiple sclerosis, cerebral palsy, and Down syndrome (29).

Anatomic/Physiologic Explanation

Loud speech tends not only to be more intense but also more intelligible. Many of the characteristics of speech produced in noise (i.e., loud speech) are perceptually more intelligible than conversational speech produced in quiet (29). When patients are asked to speak loudly, not only does vocal fold closure increase but articulatory precision also improves.

Applications

LSVT has been most researched on patients with Parkinson disease; however, LSVT may be useful for patients with atypical Parkinson disease and other types of neurologic disorders.

Manual Circumlaryngeal Techniques

Manual circumlaryngeal techniques (30) are direct hands-on approaches in which the larynx is repositioned during phonation while observing changes in voice. These techniques are used when extrinsic and intrinsic laryngeal muscle dysregulation (imbalance) contribute to an abnormal-sounding voice. When muscle tension pulls the larynx out of the neutral position, the larynx is suspended high in the neck and the hyoid–laryngeal sling is tight. Symptoms of excessive laryngeal muscle tension are usually neck tenderness, soreness, and tightness. Unilateral symptoms are common. On palpation, focal areas of tenderness may be felt in the thyrohyoid musculature, along the superior horns of the thyroid cartilage and the inferior border of the hyoid bone. The thyrohyoid space is often narrowed as a result of laryngeal elevation. There are three laryngeal reposturing maneuvers: (a) "push-back" maneuver, (b) "pull-down" maneuver, and (c) "medial compression and downward traction." Brief manual laryngeal reposturing, sustained pressure, or downward traction while the patient phonates interferes with habituated patterns of muscle imbalance. Moments of voice improvement are identified, shaped, and reinforced with manual laryngeal manipulations (i.e., digital cueing). Then the digital cues are faded while the patient learns to rely on vibrotactile, kinesthetic, and auditory feedback to maintain improved voice, muscle balance, and laryngeal positioning.

Speech–language pathologists may also use manual laryngeal tension reduction (i.e., circumlaryngeal massage) (31) which differs from manual circumlaryngeal techniques because rather than reposturing the laryngeal mechanisms, direct massage to the laryngeal area is done. This is elaborated by Morrison and Rammage (32). Circumlaryngeal massage is achieved by placing the thumb and forefinger over the tips of the hyoid bone while using circular motion to massage inferiorly to the thyrohyoid space and posterior borders of the thyroid cartilage. Roy and Leeper (33) showed almost normal return of voice following a single session in 93% of 17 participants with hyperfunctional dysphonia. Further, Roy et al. (34) reported significant value in both short- and long-term gains using manual circumlaryngeal therapy for functional dysphonia, with brief episodes of relapse in 68% of the participants.

Anatomic/Physiologic Explanation

The "push-back" maneuver uses digital compression in the posterior direction within the region of the hyoid bone. The "pull-down" maneuver impedes laryngeal elevation

by applying downward traction over the superior border of the thyroid cartilage. The medial compression and downward traction maneuver puts pressure directly over the posterior aspect of the thyroid cartilage and thyrohyoid space. Circumlaryngeal massage may directly stretch the laryngeal muscles and effect relaxation.

Applications

Manual circumlaryngeal techniques and circumlaryngeal massage were originated for patients with MTD and muscle tension aphonia, but they may also be effective in patients with organic lesions who have developed maladaptive compensatory excessive muscle tension.

Resonant Voice

Several speech–language pathologists and voice trainers have used some form of resonant/frontal focus voice therapy (i.e., general class of resonant voice therapies), which is initiated by having patients hum on nasal sounds (m, n, ng) and prolong voiced fricatives (z, v). Resonant voice or "voice with forward focus" usually refers to an easy voice production that is associated with vibratory sensations in the anterior facial bones (35). The Lessac-Madsen Resonant Voice Therapy (LMRVT) (36) is probably most well known. The therapy program was developed through a convergence of basic science and performing arts traditions and consists of three critical issues: (a) physiology (biomechanics), (b) learning, and (c) patient compliance. The target in LMRVT is "barely adducted" or "barely abducted" vocal fold configuration, facilitated by the use of "resonant voice," which is defined as "easy" voice production with perceptible anterior oral vibrations (36). This glottal configuration produces the greatest amount of acoustic output with the least amount of intravocal fold impact stress associated with phonation (37,38). In LMRVT, emphasis is placed on experiential learning using sensory awareness and principles of motor learning (39–41). Formal written instructions for patients and patient self-monitoring devices are used to increase compliance. Eight weekly therapy sessions are prescribed. Verdolini-Marston et al. (42) investigated the effectiveness of confidential voice therapy and resonant voice therapy in patients with vocal fold nodules. Phonatory effort, auditory-perceptual analysis, and laryngeal appearance on stroboscopy all improved regardless of the type of treatment.

Anatomic/Physiologic Explanation

Several studies show that easy, resonant voice is produced with vocal folds that are barely touching or barely separated vocal folds, which tend to optimize the relation between voice output intensity and vocal fold impact intensity (38). This glottal configuration appears to produce the strongest, clearest voice with the least amount of effort. Thus, resonant voice may be defined as having large-amplitude vocal fold oscillations with decreased vocal fold impact stress.

Application

Resonant voice may be used with patients who have benign vocal fold lesions, mild glottal incompetence, and hyperfunctional (e.g., MTD) voice disorders.

Respiratory Retraining

Relaxed "open-throat breathing" was described by Florence Blager (43) for patients diagnosed with paradoxical vocal fold motion disorder (PVFMD). Christopher et al. (44) also described a form of speech therapy that focused on breathing with the abdominal muscles during inspiration and reduction of the muscular effort of the oropharyngeal muscle groups. Later, Martin et al. (43) elaborated this therapy into a multistepped therapy program focusing on exhalation. The keys to therapy include muscle relaxation; open-throat breathing, retraining the breathing cycle to increase the patient's awareness of relaxed rhythmic inhalation/exhalation and to reduce the laryngeal and respiratory effort associated with breathing. Open-throat breathing can be achieved by inhaling through the nose with a relaxed tongue posture or inhaling with pursed lips (e.g., like sucking a thick milk shake up through a straw) and prolonging audible exhalation through pursed lips on an unvoiced /u/ or by producing a voiceless fricative like /s/, /f/ or "sh." Patients are taught both "rescue breathing techniques" when in an attack, as well as rhythmic breathing to "prevent" an attack. Emphasis is also placed on gentle movement of the abdomen in breathing and extra attention is paid to exhalation. Often, videonasoendoscopic biofeedback is used with this patient population to show them that they are in control of their vocal folds.

Anatomic/Physiologic Explanation

The activities in respiratory retraining focus the patient's attention on the rhythm of respiration. Nasal inhalation and pursed mouth breathing encourage wider glottal abduction than oral inhalation and a more open-throat posture. Attention to the exhalation phase of breathing focuses attention away from dyspnea on inhalation and primes the parasympathetic nervous system for relaxation.

Application

Respiratory retraining is mostly used with patients diagnosed with PVFMD.

Flow Phonation

Flow phonation (45) was adapted from a therapy called Stretch and Flow Phonation developed by Stone and Casteel (46). Flow phonation is a model of intervention that focuses on airflow management. Many patients present with breath-holding tendencies that are either the cause of their voice problems (e.g., MTD or functional aphonia), in conjunction with another diagnosis (e.g., benign midmembranous lesions), and/or maladaptive

compensatory responses to physiologic limitations of their laryngeal mechanism. The model incorporates four simple skills that increase awareness of "breath-holding" habits.

Skill One: Airflow Release—encouraging patients to let unvoiced airflow through the glottis in a consistent steady manner (i.e., "let go").There are many ways to accomplish this task (e.g., sustaining a voiceless /u/, sighing, gargling, sustaining voiceless fricatives [e.g., /s/, /f/], etc.). Attention to the effects of the airflow at the mouth via sensation of flow at the lips, a piece of tissue or finger at the lips is encouraged.

Skill Two: Breathy Phonation—the parameter of voicing is added and the result is breathy phonation. Having patients recognize that they are not holding their breath is the key.

Skill Three: Flow Phonation—fading the breathy voice quality is accomplished by simply asking the patient to produce a louder voice without increasing effort while continuing to feel airflow at the lips. This last skill level results in a balanced "normal" voice production. Discriminating between breathy phonation and flow phonation is important in this step.

Skill Four: Articulatory Precision—asking patients to concentrate on articulatory precision seems to facilitate the sensation of airflow energy at the front of the mouth while maintaining decreased throat constriction. If patients can *feel* the airflow energies of most consonants and not feel throat tightness, transfer of flow phonation to conversational speech occurs.

Anatomic/Physiologic Explanation

By focusing on egressive airflow, patients learn not to hold their breath while they speak. This model elicits laryngeal function with an absence of excessive laryngeal and respiratory muscle activity that has become associated with habitual phonation and shapes the relaxed laryngeal function into behavior that results in coordinated vocal production.

Application

Flow phonation may be used with patients with functional aphonia, MTD, and mild atrophy and it also may be effective in patients with benign vocal fold lesions.

Vocal Function Exercises

In the 1950s, Briess (47,48) developed voice therapy techniques based on specific laryngeal muscles. The most recent publication on vocal function exercises demonstrates how Stemple et al. (49) adapted this therapy program into a series of vocal function exercises (VFEs). These VFEs are a series of systematic vocal manipulations, similar in theory to physical therapy for the vocal folds, intended to strengthen and balance the laryngeal musculature and to improve the efficiency between the interaction of airflow, vocal fold vibration, and resonance. There are four steps to the program: (a) vocal warm-up by sustaining the vowel "ee" for as long as possible, (b) stretching of the laryngeal muscles by gliding from the lowest note to the highest note on the word "knoll," (c) contracting of the laryngeal muscles by gliding from the highest note to the lowest note on the word "knoll," and (d) building muscular power by sustaining musical notes for as long as possible on the word "knoll" minus the "kn." The exercises are performed two times each and are repeated twice a day. The exercises are to be done softly without excess strain. Stemple et al. (50) investigated the efficacy of VFEs on young adult females with no vocal fold pathology or voice complaint and proposed that VFEs, based on significant improvement in measures, may improve laryngeal muscle and respiratory effort and supraglottic placement of tone. Another study (51) suggested a beneficial role for VFE for singers.

Anatomic/Physiologic Explanation

Practice on maximal prolongations should improve strength and endurance of vocal fold muscles and the coordination of respiration and phonation. By performing pitch glides to high and low pitches, the cricothyroid and thyroarytenoid muscles should be lengthened and shortened, inducing flexibility and strength.

Application

VFEs may be used on patients with benign vocal fold lesions, mild glottal incompetence, and MTD.

Semioccluded Vocal Tract Therapies

Semioccluded vocal tract (SOVT) therapies can be described as an umbrella term for vocal exercises that employ a semiocclusion in the vocal tract either in the front (i.e., lips/tongue) or the back (i.e., epilarynx tube). Examples of common SOVT exercises are humming, lip bubbles, tongue trills, straw phonation, sustained fricatives (/z/, /v/), etc.

Anatomic/Physiologic Explanation

A semiocclusion heightens the sound source (vocal folds) and vocal tract interaction in that these semiocclusions (front or back) dictate vocal fold oscillation in which the vocal folds are slightly abducted by back pressure caused behind the semiocclusion. Thus, positive pressure above the true vocal folds lower the pressures needed to start and sustain phonation (52).

Application

Almost all voice disorders can be helped by this general grouping of therapies, as well as the nonspecific complaint of vocal fatigue.

APPROPRIATE REFERRALS FOR VOICE THERAPY

Not all patients are appropriate patients for voice therapy. A proper referral is the key to successful therapy. Voice therapy begins with an accurate diagnosis and referral from an otolaryngologist. The otolaryngologist diagnoses the voice disorder, and the speech–language pathologist evaluates the vocal behavior while determining stimulability for improvement. Just as an otolaryngologist may "think twice" about doing laryngeal surgery on certain patients, speech–language pathologists also "think twice" about voice therapy for certain voice disorders. Although most patients benefit from a brief session (1 to 2) of indirect voice therapy (increase vocal hygiene and decrease phonotrauma), multiple voice therapy sessions are often misguided for certain voice disorders. Referrals that may result in limited voice therapy success may be categorized under the following two headings: patient factors and laryngeal status. *Patient factors* refer to such things as motivation for change, positive attitude, compliance to behavioral modification, adherence to homework, hearing loss, and accepting responsibility for change. *Laryngeal status* refers to the physiologic integrity of the laryngeal mechanism. Table 71.1 compares voice disorders that typically get better from voice therapy and do not need surgical management with voice disorders that typically require surgical management with or without voice therapy. The following voice disorders represent organic problems that are less amenable to voice therapy as a result of physiologic limits of the larynx.

Chronic Vocal Fold Scar/Sulcus Vocalis

Although some speech–language pathologists offer such voice therapy exercises as trills and pitch extension glides as possible strategies to loosen scarred mucosa by creating greater force for vocal fold oscillation and actively stretching the scarred mucosa, anecdotal results of such exercises show limited success. In addition, there are no articles published on this topic. Whether phonation affects the biologic process of vocal fold wound healing is a question still unanswered, although basic science studies may be laying groundwork for future investigations into this area, namely, how phonation effects the tissue biology of vocal folds (53).

Papilloma

As a result of the multiple surgeries and subsequent increase in scar tissue, therapy is limited in success, as discussed above.

Severe Reinke Edema

Reinke edema is often found in patients who smoke, have LPR, or engage in phonotrauma (i.e., vocal abuse). Whereas voice therapy may be helpful in reducing phonotrauma, patients with severe (extensive) Reinke edema have significant anatomic abnormalities of the vocal folds that limit the success of voice therapy.

Cysts, Fibrous Masses, and Polyps

Typically, a specific diagnosis of what type of vocal fold lesion is present is not made until after voice therapy and sometimes not until surgery (see Chapter 68). Thus, the indication for a full course of therapeutic voice therapy is not made on the specific diagnosis. Most patients with benign, midmembranous vocal fold lesion(s) should be treated with voice therapy prior to being considered for surgery. Often the lesion(s) will not substantively change in size but therapy results in improved voice function and thus surgery is not indicated. In contrast, some lesions are "unfavorable" sole voice therapy candidates; these are lesions that very large and exophytic or cause a severe

TABLE 71.1 COMPARISONS OF WHICH VOICE DISORDERS ARE MORE OR LESS AMENABLE TO VOICE THERAPY

Voice Disorders Amenable to Voice Therapy (Infrequent Surgical Management)	Voice Disorders Less Amenable to Voice Therapy (Frequent Surgical Management Required)[a]
Nodules	Cysts, polyps, fibrous masses, pseudocyst
Primary muscle tension dysphonia	Scar/sulcus
Functional aphonia (muscle tension aphonia)	Papilloma
Mild vocal fold atrophy	Moderate-to-severe atrophy
Paradoxical vocal fold motion disorder	Reinke edema
Parkinson disease	Paralysis/dense paresis
	Spasmodic dysphonia/vocal essential tremor

[a]Although patients may require a brief session of voice therapy, to be educated about their current laryngeal mechanism and engaged in indirect voice therapy, possibly reduce edema around the lesions for better surgical success, and to be instructed in ways to reduce compensatory extralaryngeal tensions, voice therapy most likely will not resolve the problem.

amount of mucosal stiffness (most likely due to their involvement with the vocal ligament). These patient are best approached with a short course of voice therapy (1 to 3 sessions) followed by a reevaluation prior to proceeding with additional voice therapy or progressing to phonomicrosurgery (see Chapter 68).

Spasmodic Dysphonia/Essential Tremor

In general, voice therapy does not work well for this patient population. However, diagnostic voice therapy is often needed to disentangle MTD from spasmodic dysphonia (SD). A novel approach to helping a client with vocal essential tremor (54) is discussed in this case report.

Vocal Fold Paralysis in a Paramedian Position

Controversy continues to surround the role of voice therapy for unilateral vocal fold paralysis (55). Success in voice therapy seems to be based on the position of the paralyzed vocal fold (median, paramedian, intermediate, and level mismatch), differing bulk/mass of the vocal folds, and vocal fold tension of the paralyzed fold. A well-positioned paralyzed fold in the median position is most prognostic for therapeutic success. Even after surgery for vocal fold paralysis via laryngeal framework surgery (e.g., thyroplasty type I) or injectable augmentation, therapy may remain problematic. Complete glottal closure resulting from surgery does not address the dynamic nature of vocal fold vibration (e.g., issues of tissue bulk/mass, tension, and glottal plane differences between the vocal folds).

Moderate-to-Severe Vocal Fold Atrophy Associated with Aging

Biologic aging of the vocal folds may be seen in the elderly population with glottal incompetence as the prevailing laryngeal finding. If the vocal folds are severely affected by a glottal gap, surgical augmentation is often needed before starting voice therapy. However, decreased muscle tone is often the more perplexing of problems because surgical augmentation may decrease a glottal gap but decreased tonicity is hard to help both surgically and behaviorally. Sadly, sometimes neither treatment works (56).

Primary versus Secondary Muscle Tension Dysphonia

Primary MTD is seen in patients with an otherwise normal larynx. Primary MTD responds extremely well to voice therapy. However, secondary MTD (57) is an adaptive compensatory response to an underlying glottal incompetence. Voice therapy is often limited in success. For example, if a patient shows supraglottal medial and anterior/posterior constriction as a result of vocal fold atrophy, scarring, or vocal fold paralysis, voice therapy may be limited until the underlying primary laryngeal disorder is surgically altered.

A caveat to the applicability of voice therapy to the previously mentioned voice disorders is that sometimes patients need a brief session of voice therapy to be educated about their current laryngeal mechanism and its limitations—in particular, the tradeoff between sound versus feel of voice production. For example, in many of the voice disorders, patients will use extralaryngeal tension/constriction to compensate for their glottal sound source limitations. These extralaryngeal compensations usually come with a price tag of vocal fatigue/pain. Thus, patients may be able to sound louder and clearer with vocal effort, but it will cost them in vocal fatigue. Alternatively, patients may be taught to relax their extralaryngeal tension but may pay a price by having a significantly softer voice with less clarity. It is important for patients to understand this tradeoff.

LIMITATIONS TO VOICE THERAPY SUCCESS

Assuming an appropriate referral, the following list of prognostic considerations is offered. First, the patient must be stimulable for behavioral change. Can the speech–language pathologist elicit a better-sounding and healthier voice production from the patient? Second, the patient must be motivated for behavioral change and accept responsibility for the same. The patient is in control of his or her own laryngeal mechanism and does the majority of "work" in voice therapy. Unless this is understood at the beginning of voice therapy, success may be limited. Third, the patient must be compliant with voice exercise homework. Voice therapy requires behavioral modification. In turn, it is only by practice that the new vocal behaviors are entrained. Fourth, appropriate goals for voice therapy should be established immediately. Unfortunately, the physiologic limitations of the patient's laryngeal mechanism may preclude a return of the patient's premorbid voice. In other words, the vocal folds may be damaged to the extent that "normal" or premorbid voice characteristics will never occur. The patient should be instructed as to any limitations to success. Fifth, emotion, personality, stress, and anxiety may be component parts of many voice disorders (58), both as an etiology and consequence. Acceptance of this reality and concomitant therapy with a trained psychological counselor may be necessary. Sixth, although voice therapy can be very effective, there are speech–language pathologists who are better at voice therapy than others. A certified, licensed speech–language pathologist who specializes in voice should perform voice therapy. Referring patients to speech–language pathologists with little training or interest in voice wastes the patient's time and health care funds and inevitably fails. Table 71.2 summarizes these points.

TABLE 71.2 VOICE THERAPY: REASONS FOR SUCCESS OF FAILURE

Success	Failure
Appropriate referral • Stimulable for a better voice • Wants to avoid surgery—motivated to change voice production • Compliant to vocal hygiene, LPR treatment, decreasing phonotrauma, and daily homework • Takes responsibility for change	*Inappropriate referral* • Not stimulable for a better voice • Decreased motivation for change (i.e., wants a "quick fix") • Noncompliant to vocal hygiene, LPR, treatment, decreasing phonotrauma, and homework • Will not accept responsibility • Hearing loss • Possible concomitant emotional/psychological problems • Accurate referral to an inexperienced speech–language pathologist • Medical–legal issues not resolved (e.g., secondary gain)

WHAT CONNOTES SUCCESS IN VOICE THERAPY?

The answer to the question "What connotes success in voice therapy?" is riddled with unknowns. Because there is a paucity of prospective, randomized clinical trials concerning voice therapy efficacy, the answer to this question seems to be driven by expert opinion rather than data. Anecdotally, most professionals believe that success in voice therapy is defined as a return to a functional level of voicing rather than a change of the laryngeal mechanism. For example, a patient may get functionally better without a reduction in lesion size.

SUMMARY

Otolaryngologists, speech–language pathologists, and patients are witness to the success of voice therapy. However, the success is limited by a lack of data to support positive outcomes. Much-needed efficacy studies are under way to verify the anecdotal success of voice therapy. This chapter is not intended to be an all-inclusive list of all voice therapies; it is a synthesis of some of the most commonly used therapies and prerequisites for success. In general, when an otolaryngologist makes an appropriate voice therapy referral to a speech–language pathologist who specializes in voice, behavioral voice therapy is highly effective in treating patients with voice disorders.

HIGHLIGHTS

- Voice therapy teaches patients to modify phonotraumatic/inefficient vocal behavior and requires compliance to daily exercises; voice therapy is not a "quick fix."
- Voice therapy requires that patients assume responsibility for their vocal behavior.
- The three key categories of any voice therapy program include the following: increasing vocal hygiene, decreasing phonotrauma, and increasing coordinated voice production.
- Indirect voice therapy includes educating the patient about how his or her laryngeal mechanism functions, identifying what may cause them harm (e.g., dehydration, smoking, LPR), and establishing realistic therapeutic goals; it usually lasts 1 to 2 weekly sessions.
- Direct voice therapy includes actively altering the patient's speaking technique through various exercises and manipulations to increase vocal quality and efficiency; it usually lasts 4 to 6 weekly sessions.
- There are many different voice therapies, and most speech–language pathologists use a combination of same; voice therapy techniques should be chosen for the patient's voicing *behavior* and not the laryngeal disorder.
- Not all patients are appropriate referrals for voice therapy. Although most patients benefit from a short course of voice therapy, multiple direct voice therapy sessions for such voice disorders as vocal fold scar/sulcus vocalis, recurrent respiratory papillomatosis, severe Reinke edema, fibrous masses, spasmodic dysphonia, vocal fold paralysis with severe glottal incompetence, severe atrophy, and secondary MTD are limited in success.
- Successful voice therapy involves the following: an appropriate referral to a speech–language pathologist specializing in voice, a patient stimulable for a better sounding and/or feeling voice, and a motivated patient who takes responsibility for behavioral change.

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Care of the Professional Voice

72

Julina Ongkasuwan *Mark S. Courey*

A thorough understanding of the principles of laryngeal anatomy, physiology, and sound production provides an excellent background on which to build diagnostic and therapeutic strategies for all types of laryngeal disorders. In the 21st century, it is no longer adequate for otolaryngologists to treat voice complaints differently in different types of voice users. Rather, the appropriate management for all voice disorders is based on a thorough understanding of voice-production principles. The otolaryngologist/laryngologist must have a basic understanding of voice requirements and physiologic demands for all patients from the child to the opera singer. With this knowledge, the otolaryngologist can make correct decisions in the management of all voice problems from transient edema secondary to overuse to the management of vocal fold lesions.

ANATOMY AND PHYSIOLOGY OF VOICE PRODUCTION

While details of laryngeal anatomy, development, and physiology have been previously presented, it is helpful to reemphasize certain concepts.

Extrinsic Laryngeal Musculature

The series of strap muscles attaching to the outside of the laryngeal framework are referred to as the extrinsic laryngeal musculature. These are paired and consist of the sternohyoid, sternothyroid, and thyrohyoid muscles (Fig. 72.1). They are innervated by the ansa cervicalis, which arises as a branch from cranial nerve (CN) XII. For the purposes of voice production, these muscles are believed to influence laryngeal position within the neck. Laryngeal position affects the length of the vocal tract, which in turn alters the resonance characteristics of the voice. It also should be noted that the tongue and floor of mouth musculature, including the paired digastric muscles, geniohyoid, genioglossus, hyoglossus, and mylohyoid, all attach to the top the external laryngeal framework on the hyoid bone. Although these are not part of the extrinsic laryngeal musculature, they influence the laryngeal position within the neck because of their attachment on the hyoid bone. These muscles also receive a portion of their motor innervation through branches of CN XII, and they function primarily to move the tongue for articulation of speech. Because both muscle groups controlling laryngeal height and articulation are innervated by the same motor system, overlap or stimulus generalization may occur during speech production. To produce a balanced or pleasing sound, the professional voice user must learn to control laryngeal height for resonance separately from the tongue movement for speech articulation (1).

It also is important to consider the pharyngeal musculature. The inferior constrictor attaches to the posterior aspect of the thyroid framework. This muscle plays a role in shaping the pharynx during speech production and, along with the middle and superior constrictor, also alters laryngeal height and closure patterns. The constrictors receive motor innervation from branches of CN X, which also controls the intrinsic laryngeal musculature. Therefore, stimulus generalization also may occur as the professional voice user attempts to separate intrinsic laryngeal function from pharyngeal shape and laryngeal height for resonation characteristics.

Intrinsic Laryngeal Musculature

The paired intrinsic muscles attach to the arytenoids and the cricoid and thyroid cartilages. As are most muscles, they are named for the origins and insertions. First, the thyroarytenoid (TA) muscles originate near the most anterior portion of the thyroid cartilage and insert on the side of the vocal process of the arytenoid and the middle and upper body (Fig. 72.2). This muscle is innervated by CN X.

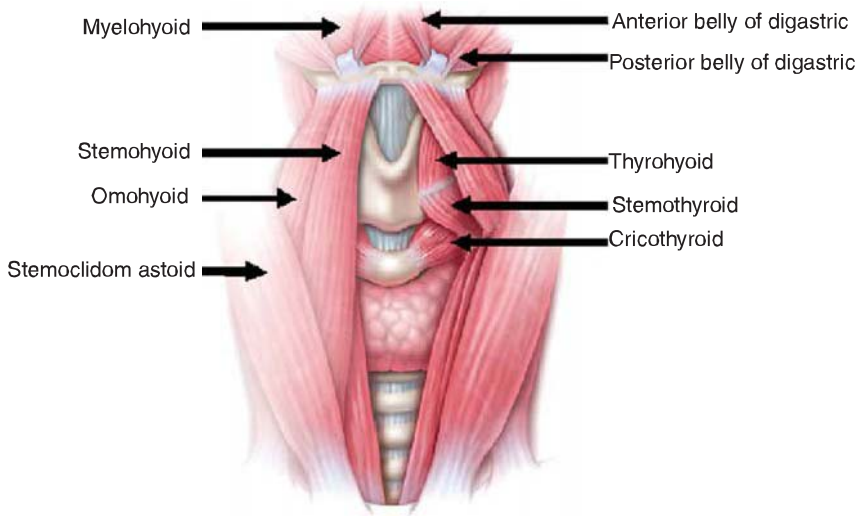


Figure 72.1 Extrinsic laryngeal musculature.

Through muscular activation, the distance between the arytenoid and thyroid cartilages is shortened. This occurs primarily by pulling the arytenoid forward on the cricoid ring. As the distance shortens, the mucosal membrane overlying the muscle is thickened, and the extracellular matrix proteins are brought into the closer approximation with each other. The thickening of the tissue will affect its characteristics of vibration.

The lateral cricoarytenoid (LCA) muscle originates on the lateral aspect of the cricoid ring and the inserts onto the muscular process of the arytenoid (Fig. 72.2). These paired muscles receive motor innervation through CN X. As the muscle contracts, the muscular process is pulled laterally and inferiorly. This action displaces the vocal process medially and inferiorly because of the angle of the cricoarytenoid joint. As the vocal fold adducts, the anterior aspect remains fixed at the anterior portion of the thyroid cartilage, but the posterior aspect moves inward and inferiorly.

The interarytenoid (IA) muscle is also innervated by CN X and attaches to the upper bodies of the arytenoid on the posterior and medial surfaces (Fig. 72.2). The muscle fibers run both obliquely and transversely. As the IA contracts, the upper portions of the arytenoid bodies tilt toward the midline. This action approximates the tissue slightly above the plane of the vocal process. In men, with thick mucosa and large cartilaginous structures secondary to the androgenic effects of testosterone, the entire space between the vocal processes is obliterated. In women, with more delicate structures, because of the relatively limited androgen effects of estrogen, the space is not filled or obliterated completely and is often viewed as an opening behind the vocal process or is referred to as an "open posterior chink." This phenomenon has been reported in up to 76% of middle aged women (Fig. 72.3) (2).

The posterior cricoarytenoid is the only abductor of the vocal fold. It originates on the posterior aspect of the cricoid

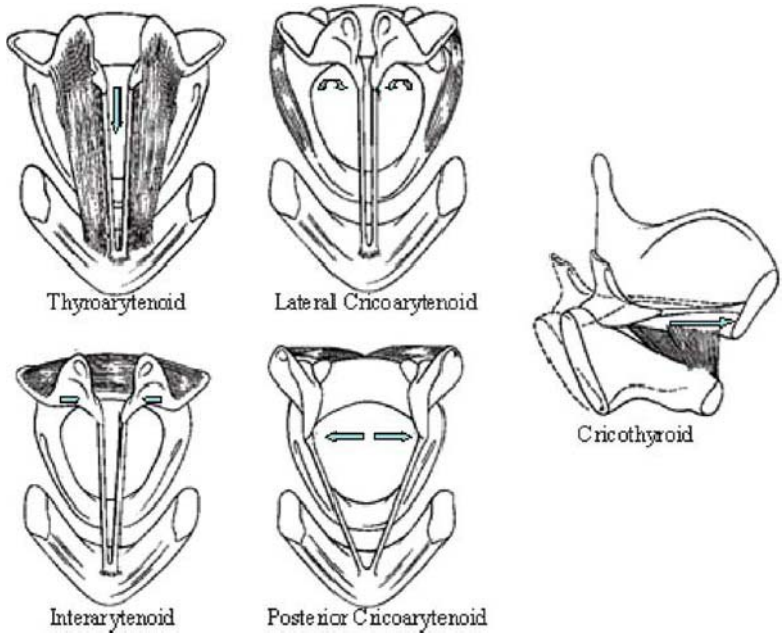


Figure 72.2 Intrinsic laryngeal muscles.

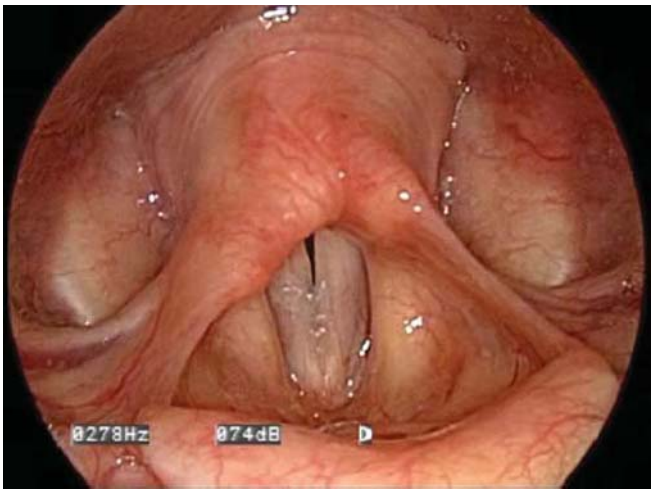


Figure 72.3 Posterior glottic chink.

ring and attaches to the muscular process on the posterior aspect of the arytenoid (Fig. 72.2). Contraction, stimulated by the recurrent laryngeal nerve from CN X, results in medial and inferior displacement of the muscular process. This results in lateral and upward displacement of the vocal process and, with it, the posterior aspect of the vocal fold.

Finally, the cricothyroid (CT) muscle originates on the anterior aspect of the cricoid ring and attaches at the anterior aspect of the thyroid cartilage at the inferior tubercle (Fig. 72.2). Contraction is regulated by the external branch of the superior laryngeal nerve, which is a branch of CN X. As the CT muscle contracts, the thyroid lamina is pulled closer to the cricoid ring. The cricoid ring sits anterior to the thyroid lamina. As the thyroid lamina is displaced forward, the vocal fold is stretched. The action tenses the vocal fold and thins the mucosal cover, decreasing the mass of the vocal fold available to participate in the vibration. This is analogous to the action of a rubber band. As the rubber band is stretched, it becomes tenser, and its thickness or lateral dimension, and width or vertical dimension, are reduced.

Minor Intrinsic Laryngeal Cartilages

The minor intrinsic laryngeal cartilages, which include the corniculate, cuneiform, and epiglottis, do not function directly in voice production. Their presence most likely results in alteration of the configuration and stiffness of the vocal tract, which ultimately affects the shape and therefore the resonance quality of the vocal tract (1).

PRINCIPLES OF SOUND PRODUCTION

Sound production of all types requires three basic components: a power source, a vibratory source, and a resonator (Fig. 72.4). In human voice production, the exhaled air from the lungs serves as the power source that drives vocal fold vibration, the vibratory source. The true vocal folds produce a faint primary sounds source, which is then

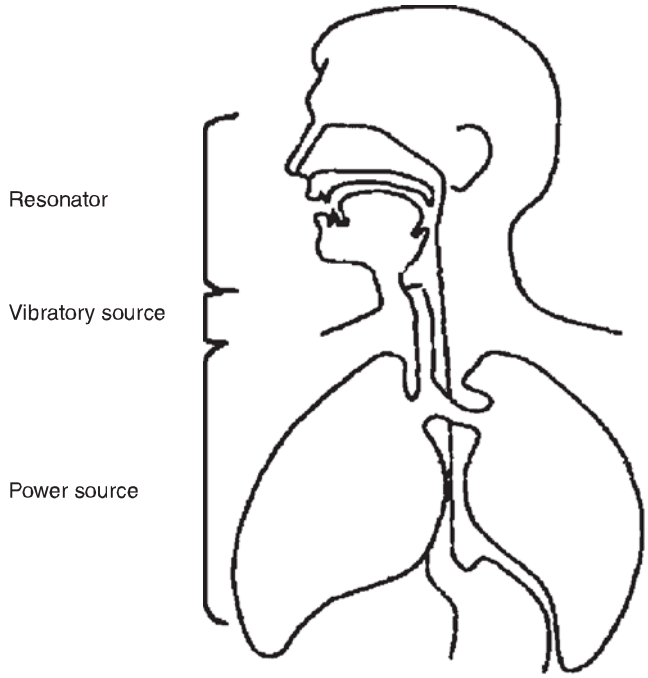


Figure 72.4 Vocal tract.

modulated by the third component, the resonating chamber or the supraglottic vocal tract. The supraglottic vocal tract is formed by the supraglottic larynx, the pharynx, and the oral cavity. If no resonating chamber were present, the primary sound source would produce a buzzing-type sound similar to a faint duck call.

Human communication can be divided into language, speech, and voice. Specifically, language production requires cognitive skills regulated by the cerebral cortex. Patients integrate higher cortical functions to express themselves through words and actions familiar to a certain region in which they were educated. Speech production refers to the articulation of words to produce language. It involves the supraglottic vocal tract for resonation and articulation of sounds produced at the glottis level. It is under the control of the cerebral cortex but is regulated by the coordinating centers in the basal ganglia and brain stem (3). Voice is produced through vocal fold vibration and specifically refers to the sound that emanates from the vocal folds as they are held in approximation and passively vibrated by the air that flows between them. Sounds produced by vocal fold vibration are termed *voiced sounds*. Commonly these are the vowels and voice consonants that require vocal fold adduction. Adduction and tension are regulated by cerebral cortical activity and are coordinated through the basal ganglia as well.

Harmonic Sound Source

Patients can present with problems of language, speech, voice, or a combination of these. In the professional voice user, we are most often concerned with problems of voice

TABLE 72.1 EXAMPLE OF FUNDAMENTAL FREQUENCY, OVERTONES, AND HARMONICS

Frequency (Hz)	Order	Overtones	Harmonic Numbering
440	$n = 1$	Fundamental	First Harmonic (H1) or F_0
880	$n = 2$	First overtone	Second Harmonic (H2)
1320	$n = 3$	Second overtone	Third Harmonic (H3)
1760	$n = 4$	Third overtone	Fourth Harmonic (H4)

production. Vocal fold vibratory activity is critical for voice production, as it provides the primary sound source, which is modulated by actions of the vocal tract (4). Vocal fold vibrations produce a complex tone. That is, they vibrate at a set of frequencies that have a whole-number mathematic relation between them. The primary frequency of vibration is termed the *fundamental frequency* (F_0), and is closely related to the perceived pitch of the voice. Each whole-number multiple of the F_0 is called an overtone. The terminology is such that the F_0 is labeled the first harmonic (H_1), and each multiple of that frequency is the second, third, fourth, fifth harmonic (H_2, H_3, H_4, H_5, etc.), and so on to infinity (Table 72.1).

Formant Frequencies

The harmonic spectrum is presented to the vocal tract. Because of the length, shape, and distal opening of the vocal tract, certain of these harmonics are amplified or resonated, and others are dampened or attenuated (4). This pattern, known as the *spectral envelope*, creates the sounds that we hear in speech production. The amplified or resonated harmonic regions of the spectral envelope are called the *formant* regions. The first two formant regions are responsible for vowel differentiation, whereas the third through the fifth regions are responsible for the quality of the sounds (timbre). The different sounds of speech are produced by alterations in the length, shape, and mouth opening of the vocal tract. This is under voluntary control. The vocal professional learns to alter the shape of the vocal tract to produce the target sound quality.

The formant regions can be evaluated through spectral analysis of the vocal signal. The spectrogram is a visual representation of the audible sounds. It is a plot of frequency and intensity changes of sound over time (5). To produce a spectrogram, the sound emanating from the vocal tract is broken into various frequency regions as it is passed through a variable bandpass filter. The filter identifies the audible frequency regions between 0 and 8,000 Hz. The harmonic frequencies within this region are represented on the *y*-axis and time is represented on the *x*-axis. Intensity of the various harmonics is represented by darker frequency bands on the graph. The darker bands represent the amplified harmonics and are called the formant regions.

Vowels have characteristic first- and second-formant frequencies. These are represented as F1 and F2. The vowel is determined by the absolute F1 and F2 as well as the relative distance between them (Fig. 72.5). Harmonics are selectively amplified by changes in the length, shape, and distal opening characteristics of the vocal tract. The higher formants (F3 to F5) are responsible for the timbre of the sounds and differences in the sound characteristics between speakers. Classically trained singers learn to cluster the third, fourth, and fifth formant regions to amplify the harmonic sounds frequencies between 2,800 and 3,500 Hz (6). Amplified sound in this frequency range is preferentially detected by the human ear over other sounds. It is known as the *singer's formant*, and is produced by learned behavior through which the classically trained singer, through movements in the tongue, pharynx, and lips, manipulates the vocal tract into a certain shape to amplify selectively the harmonics in the desired regions (7).

Although the quality of the spectral envelope is largely influenced by the shape, length, and distal opening of the vocal tract, it also is affected by the richness and quality of the harmonic spectrum presented to it as the sound source. Therefore, the vocal professional must be able to regulate

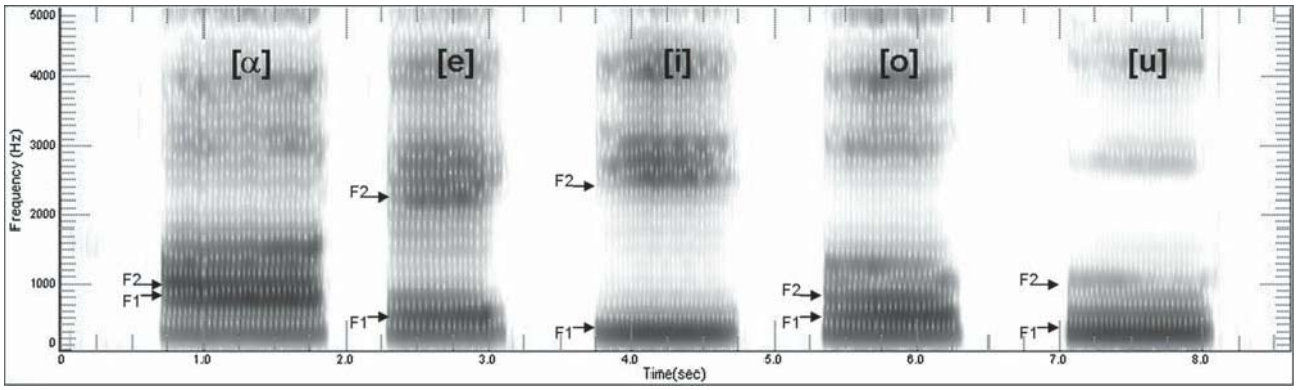


Figure 72.5 Spectrogram.

the harmonic source spectrum from the larynx, as well as the shape of the supraglottal vocal tract. Through manipulations of these two organ systems, all human speech sounds for professional and nonprofessional voice are produced (8).

MECHANISM OF VOICE PRODUCTION

We previously discussed the actions of the supraglottic vocal tract. Specifically, in speech production, the speaker moves the tongue, pharynx, and lips to alter the shape, length, and distal opening of the vocal tract. In this manner, the formant regions are manipulated to amplify the desired harmonics produced by the sound source. The speaker also manipulates the sound source to enhance the harmonic spectrum presented to the vocal tract (9). Manipulation of the vibratory source is accomplished in all styles of voice production with the same basic mechanisms. These mechanisms include control of subglottic pressure, control of vocal fold approximation, and control of vocal fold tension (Table 72.2).

Subglottic Pressure

Subglottic pressure is the pressure immediately below the vocal folds during vocal fold vibration. It is generated by a combination of the force of the expelled air and by the force of vocal fold closure used to resist the outflow of the air (Fig. 72.6). Subglottic pressure correlates directly with the volume of the sound that is produced by the sound source (10). Sound is a disturbance in the pressure–density equilibrium of the atmosphere. Greater disturbances result in louder sounds. During the closed phase of vocal fold vibration, as the mucosal surfaces are approximated, the disturbance in the pressure–density equilibrium is minimal. As the air explodes through the glottis, the pressure–density disturbance is maximized. Higher subglottic pressures built up through prolonged closure explodes through the glottis and result in a more rapid change and a greater disturbance in the pressure–density equilibrium. Both the absolute degree of change and the rate of change are important. A louder sound source presents more intense harmonics to the resonating chamber. The spectral envelop is altered because the more intense harmonics are better amplified. In this manner, all of the formants, including those in the 2,800 to 3,500 Hz range, which are preferentially identified by the human ear, are amplified. Thus, all of the formants are boosted by a loud sound source (6).

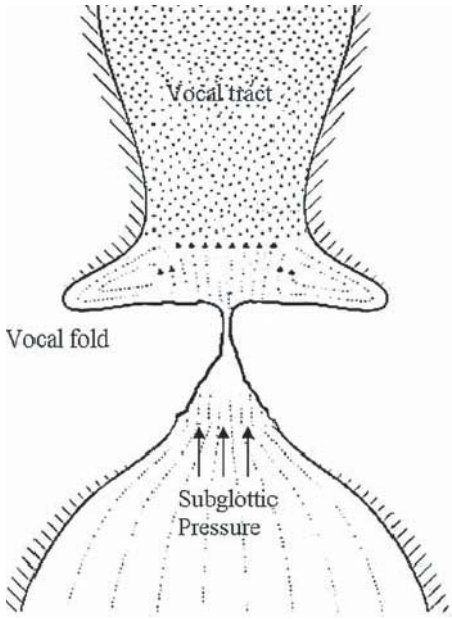


Figure 72.6 Subglottic pressure.

TABLE 72.2 MANIPULATION OF THE VIBRATORY SOURCE

Subglottic pressure
Respiratory support
Vocal fold contraction
Vocal fold approximation
Vocal fold tension

Control of Subglottic Pressure with Respiratory Support

Singers can create more volume and therefore more amplification of the harmonics by increasing the subglottic pressure. Professional voice users, and all voice producers for that matter, control the rate of exhalation during voice production by allowing incremental relaxation of the muscles that expand the thorax. The diaphragm is the primary muscle used to expand the thorax. It is assisted by the actions of the intercostal muscles, which spread the ribs, and the spinal accessory muscles, which elevate the clavicles and first and second ribs. During inspiration, the thorax is expanded beyond its resting volume. Air is drawn into the lungs by the negative pressure created through expansion. As the diaphragm and intercostal muscles are relaxed, the thorax passively recoils to its resting size. During voice production, the rate of recoil is resisted through incremental relaxation of the muscles of inspiration and through contracting the muscles of the abdominal cavity. This phenomenon is referred to as *respiratory support* and is believed to be the most efficient mechanism for the regulation of subglottic pressure.

Control of Subglottic Pressure with Vocal Fold Contraction

However, during all types of voice production, increases in forces of vocal fold adduction, which resist air escape and overclose the larynx, can also be used to increase subglottic

pressure, and with it, the volume of the sound source. This mechanism for increasing subglottic pressure is believed to be inefficient and may result in excess muscular fatigue through hypercontraction of the TA muscles, LCA muscles, or both, which most often relax during phonation.

Vocal Fold Approximation

Overclosure states, through a combination of hypercontraction of the intrinsic and extrinsic laryngeal musculature, can be used to augment the degree of laryngeal closure, affect the length of the closure phase during vibration, and alter the shape of the resonating vocal tract. Thus they affect the sounds spectrum through altering the sound source as well as the shape of the vocal tract.

Vocal Fold Tension

Finally, laryngeal tension for frequency of vibration and pitch control is under voluntary regulation. Tension is adjusted primarily by contraction of the CT muscle, which results in anterior displacement of the anterior commissure and elongating or stretching the vocal fold. In addition, CT contraction causes a reduction in vocal fold mass available to participate in vibration through thinning of the vocal cover as it is elongated. Both these actions result in pitch elevation.

The coordinated vocal user and particularly the vocal professional learn to control their vocal mechanism efficiently so that excess TA muscle contraction is not used to affect pitch. The vocal folds are set into a position for vibration. The relative tension for the desired frequency of vibration is set by tone in the CT muscle, which is termed *prephonatory tuning*, and then air is passed through the vocal folds, and vibration begins. During the sound-production phase, the TA muscle relaxes, and the vocal folds are held in nearly approximated position by the activity of the IA muscle. This activation pattern has been studied and documented through laryngeal electromyography (11).

Vocal fold approximation, by the IA muscle, however, is opposed by activity of the CT muscle. As the CT contracts and the anterior portion of the TA is stretched forward, the posterior attachment to the arytenoids remains relatively fixed. Because the posterior border of the cricoid ring and the cricoarytenoid joint are angulated superiorly to inferiorly, continued unopposed contraction of the CT will lead to lateral displacement of the arytenoids and the posterior aspect of the vocal fold. As the vocal folds are spread apart by this action, the glottis width increases and vibration will stop unless the glottic distance is decreased through coordinated action of the intrinsic laryngeal musculature (LCA, TA) or the airflow from the lungs is increased (Fig. 72.7). Thus to maintain a continuum of pitches without allowing for a break in phonation, the coordinated vocal user balances the desired vocal fold tension against the abductory forces, so that the vocal folds maintain a nearly approximated aerodynamic position. In addition, the trained vocal professional is probably altering the speed of the air flow as well to help merge these vibratory ranges.

The vocal folds can be tensed and maintained in an artificially thick state. This will result in alterations of the vibratory patterns with prolonged closure. This prolonged closure phase will alter the sound source and may produce desirable harmonic characteristics. These intensified harmonics are more easily amplified by the vocal tract, and the singer's formant region is boosted. Because of the boost in this region, the sound is preferentially distinguished as human and is enjoyable. This phenomenon is frequently used by female commercial vocalists as they attempt to sing in a relatively high-pitched, robust voice. It is referred to as "belting." During belt voice production, a bright brassy sound is produced at the expense of laryngeal and cervical muscle hypercontraction. If the TA muscle is held overly tense during voicing, it may affect the vibratory characteristics of the

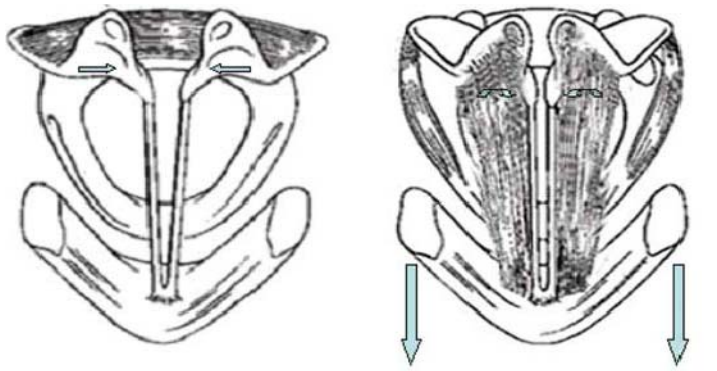


Figure 72.7 Using vocal fold tension to help control pitch.

overlying vocal ligament and cover by not passively cushioning the vibratory forces. A stiff underlying TA may increase the shear or compressive stress placed on the overlying ligament and cover, thus increasing the likelihood of injury.

VOCAL PERFORMANCE STYLES

People perform by using both the speaking and singing voice. As covered in the last section, these sounds are produced by using the same anatomic and physiologic principles. The successful performer must be able to manipulate both the sound source and the resonating vocal-tract characteristics to produce sound of the desired style.

Voice Classification

Regardless of style, voices can be categorized by the range of pitches they can produce. The average person can produce pitches over a 12- to 30-muscial note range. For the male voice, the average speaking vocal pitch hovers around 120 Hz, and for the female, approximately 200 Hz. The lowest note that a person can produce is frequently four to five notes below this average pitch range. Within individual people, however, significant variations are found in average pitch, their highest and lower pitch capability, and their overall pitch range. In total, these characteristics of voice, average pitch, and pitch range are described as the vocal profile. Men and women usually exhibit vocal profiles either higher or lower than the average pitch for their gender. For men, the lowest voices in classical singing are termed bass voices, the medium pitched voices are termed baritone voices, and the higher voices are termed tenor voices. In women, the lower voices are termed contralto or alto voices, whereas the higher voices are termed soprano voices (Fig. 72.8) (1).

Voice classifications are determined by several factors. These factors include the absolute pitch range, timbre characteristics, and vocal of vibratory break points within the voice. As stated previously, vibratory frequency or pitch of voice is proportional to the tension within the vibratory vocal fold and the mass of the vocal fold available to participate in vibration. The mass of our vocal folds is a physical characteristic within each of us. We then manipulate pitch (frequency of vibration) by adjusting tension with the vocal fold.

In singing terminology, the *chest voice* roughly correlates to the range in which the TA muscle relaxes, and the vocal folds are held in nearly approximated position by the IA. The *head voice* roughly correlated to the range in which the LCA and TA are employed to decrease the glottal distance as the CT lengthens the vocal folds (1). The area between these two ranges is termed the *mixed voice range*. At the beginning and the end of the mixed range, the notes involved are termed the *passaggio* or passage. These characteristic points help to determine the voice user's range and quality. In general, male voices have a smaller mixed voice range than do female voices, and females are asked/required to sing in their mixed voice range more commonly than are males. Male basses are usually required to sing below their mixed voice range, whereas tenors are required to sing above theirs. These passaggio points occur at relatively consistent frequency and are used along with the absolute high and low range to determine the voice class or type on the bass-to-soprano continuum (1).

Male baritone and bass voices have an additional register on top of the head voice referred to the as the falsetto voice. It is often described as breathy and less brilliant or full in sound. The majority of the vocal fold remains long

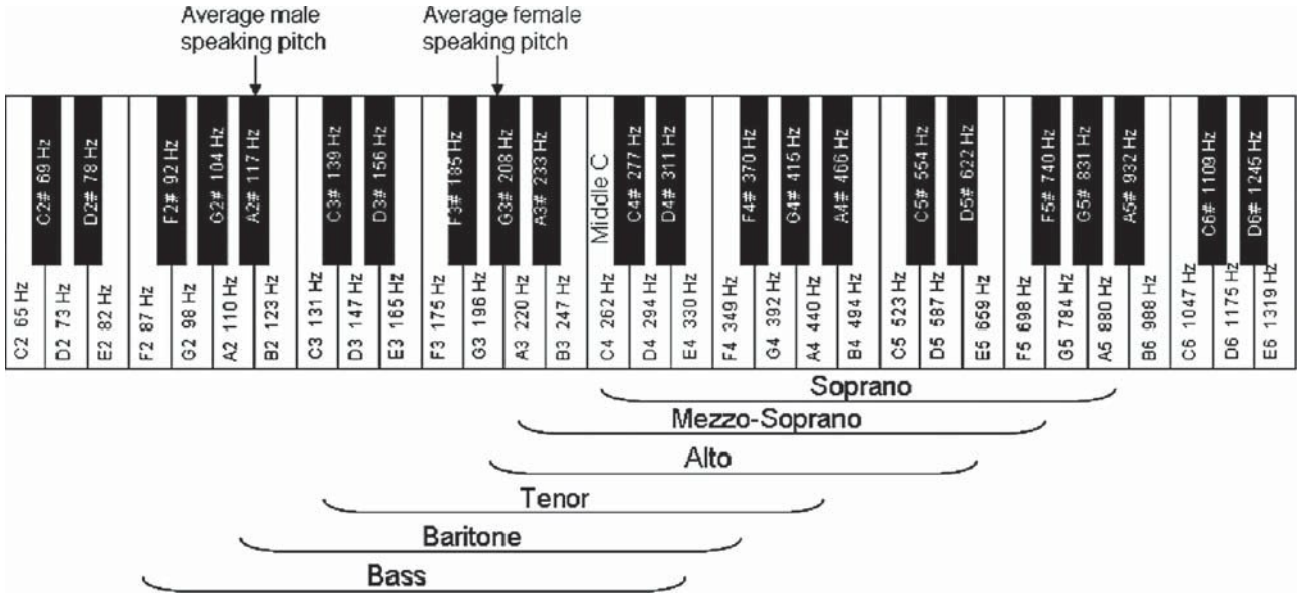


Figure 72.8 Voice classification by average pitch range.

TABLE 72.3 VOCAL REGISTERS

Chest voice	Lower register	TA muscle relaxes IA holds vocal fold approximated
Head voice	Higher register	CT lengthens the vocal folds LCA and TA hold vocal folds approximated
Mixed voice	Register between chest and head voice	
Passaggio	The beginning and end of mixed voice	
Falsetto (male)	Breathy, flute-like sound relatively free of overtones	Only the medial edges of the vocal folds vibrate
Whistle register (female)	Distant high-pitched bell-like sound	Vibration occurs only at the anterior portion of the vocal folds

and stiff with vibration occurring only at a thin medial edge with less complete vocal fold approximation compared to head voice. It is frequently used to imitate the female voice (1).

The male falsetto should not be confused with a female register above the upper voice often referred to as the flageolet register or whistle register. This also has a distinct timbre that is sometimes referred to as a distant high-pitched bell. When producing these pitches, the vocal folds lengthen and the posterior portion of the vocal folds are dampened. This register has been used by some commercial singers (Table 72.3) (1).

PERFORMANCE STYLES

In general, singing performers can be broken down into two basic types. These are classical styles and commercial styles of performance. Within the classical and commercial styles, many subtypes exist.

Historical Evolution of Performance Styles

The evolution of music performance demonstrates how these two styles of voice production developed. As human civilizations grew, history and daily events were often told through music. The original musicians, therefore, were traveling bards who would entertain and tell their stories to small groups of people. They would be rewarded through charitable contributions from the crowd and learned to tell their stories to music that the local population enjoyed. This was the original form of folk music and persists today through many styles.

During the Middle Ages, humans began to live more commonly in towns and cities. In addition, musical instruments where being developed. As such, musical composers began to develop music for many instruments to perform simultaneously. These pieces were often combined with human voices. As the number of musical instruments increased and the performance halls enlarged to accommodate larger audiences, the vocal performers needed to develop a technique that would allow their voices to carry to the back of the performance hall and be heard above the musical accompaniment. The call voice or the singer's formant was a natural way to accomplish this requirement. Within Europe, during the Middle Ages, many different schools of musical education developed in the various regions to train performers in distinct ways of producing and using the singer's formant (1). The common goal among these schools was the production of a voice that would rise above the musical instruments because electrical amplification had not yet been developed.

In folk music, these performers did well as long as they kept their performance venues small. However, with the birth of the recording industry in the early to middle portion of the 20th century and continued urbanization, the performance venues for this type of music grew. In addition, electrical amplification was developed. These amplification devices were built into the musical instruments but not into the vocal instrument. Therefore, performers had to learn how to amplify their voices or to produce a loud voice to be heard over the accompaniment. Successful performers learned how to do this efficiently by controlling the volume of voice use and applying appropriate electrical amplification to preserve their voices.

Performance Style—Classical

Opera, art song, and legitimate musical theater are generally considered within the classical styles of vocal production. These performers have usually had significant amounts of vocal training and attempt to take advantage of the singer's formant resonatory characteristics to have their voices heard above the accompanying musical instruments. Within these styles, however, are many different schools of training techniques, each of which is probably

best suited for different anatomic vocal tract characteristics. Successful performers will have found a style of training that is relatively atraumatic for their vocal mechanisms. In addition, within each of their styles, they will have identified a particular number of vocal roles that they can learn and perform well. They become known for performing these roles and are sought out to appear in each one. The unsuccessful performer will often attempt to perform a role for which he or she is not anatomically or physiologically well suited. This will often lead to inefficient vocal behaviors and excess vocal trauma.

Performance Style—Commercial

Commercial singing styles are those that do not use the singer's formant to be heard above the accompanying instrumentation. Gospel, rhythm and blues, country, bluegrass, pop, rock, and musical theater belting are usually considered the commercial styles of singing voice production. Often these performers have had little vocal training and may not even be aware of their absolute voice range. They sing as they talk, with the purpose of telling a story. Communication of the message through word and song is therefore critically important to their performance and to the legitimacy of their style. The shape of the pharynx is not configured to produce a "singer's formant," and they use volume with or without amplification to be heard above the instrumental accompaniment. The performer's style is dependent on the region in which he or she learned to sing and is influenced by the type of message he or she wishes to convey.

PATHOPHYSIOLOGY

Changes in vocal effort and quality are secondary to excess/inefficient use of the vocal mechanism and repeated trauma to the vocal fold mucosa. All laryngeal vibratory patterns carried to excess result in vocal fold trauma. Vibration is associated with mucosal stress and strain. The mucosa is specifically defined as the epithelium plus the superficial supporting submucosa or superficial lamina propria. Prolonged vibration leads to sloughing of the superficial layers of the epithelium plus breakdown of the anchoring filaments in the basement membrane zone, which bonds the epithelium to the underlying superficial submucosa (12).

Repeated or prolonged trauma creates injury, which the body attempts to heal. Injury induces inflammation to start the healing process. The injury and subsequent inflammation can be compounded by repeated trauma before adequate healing or by superinfection with bacteria, which may occur more readily secondary to the loss of the protective epithelial layer. It is widely believed that reflux of gastric contents also can irritate this region and impair healing. One small-animal study, however, did not show any significant alteration in the acute-phase healing after surgically injured vocal folds were coated repeatedly with gastric contents at various pH and normal saline (13).

Loss of Pliability

Inflammatory mediators induce angiogenesis (14). Therefore, these vocal fold lesions are often vascular in nature and may have associated telangiectatic vessels (Fig. 72.9). The healing process also results in excess collagen deposition and the formation of excessive cross-linkages. The regenerated submucosa is of a different nature and viscosity than the native mucosa. The vocal fold vibratory patterns are altered as the submucosa is less pliable than before injury. Early in the process, this loss of pliability is difficult to visualize. It may result in early vocal fatigue or vocal changes that are problematic only for the vocal performer. In relatively severe forms, these differences in pliability may be visualized as vibratory asymmetry on laryngeal stroboscopic examination and cause dysphonia in both the speaking and singing voice.

Benign Vocal Fold Lesions

Severe and repeated forms of vocal trauma result in a benign pathologic response (15). Because vibration is traumatic in itself, too much vibration and vibration

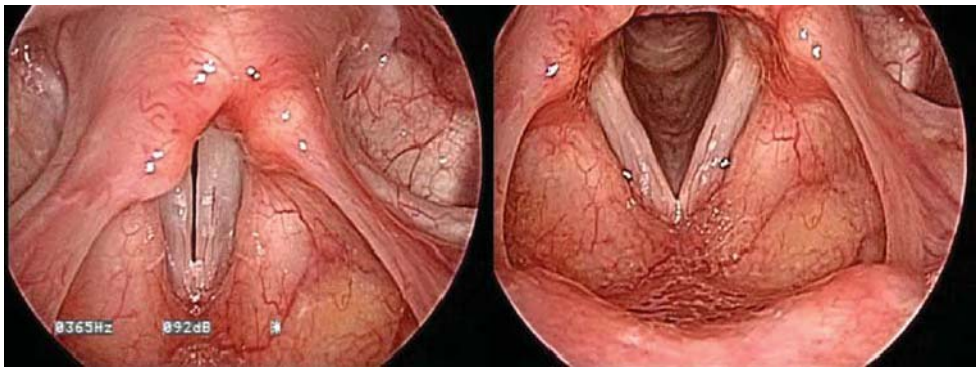


Figure 72.9 A telangiectatic vessel and vibratory asymmetry in a professional singer.

produced with inefficient application of the physiologic principle of laryngeal adduction, tension, and respiratory support are probably even more traumatic to the vocal fold epithelium. On a long-term basis, as the body responds to the trauma, the vocal folds heal in patterns that produce characteristic changes in the underlying submucosa or superficial lamina propria. These patterns are clinically referred to as benign vocal fold lesions of the lamina propria (nodules, polyps, fibrous mass). They represent a chronic response to trauma. In general, this response is acellular. It is probably regulated by vocal fold fibroblast activity that is altered by the trauma and the vibratory patterns. The epithelium, which is initially damaged in the region of each lesion, usually regenerates with minimal alteration other than slight thickening or keratosis. The basilar layers are well formed, and maturation of the epithelial layers occurs as expected. Within the superficial portion of the lamina propria, the extracellular matrix proteins are disorganized. Collagen and fibronectin concentrations are increased, and the normal laminar appearance of the lamina propria is disrupted.

Laryngeal Vibration

Laryngeal vibration is affected because of either the change in mucosal viscosity or interruption of the aerodynamic configuration of the larynx by the lesion or both. As stated, the lesion itself is made of a different arrangement and concentration of the extracellular matrix proteins than the normal lamina propria. This difference results in a change in viscosity of the lamina propria and loss of freedom for the tissue to vibrate. It also causes a change in vocal fold mass (Fig. 72.10). The lesion may be so large that the normal nearly closed laryngeal configuration cannot be achieved. In this instance, vibration is obtained only if the airflow is increased. The required increase may not be physiologically possible, and therefore laryngeal vibration will not be initiated or easily sustained. In these instances, the vibratory mechanism does not generate a harmonic sound source adequate for resonation through the vocal tract.

THE PEDIATRIC PATIENT

Special consideration must be given to the pediatric voice patient. The immature larynx differs from the adult in several different ways. Placement of the larynx is higher in the neck, the cartilages are softer and more elastic, and the ratio of membranous to cartilaginous vocal fold is lower. Most importantly the layers of the lamina propria differ significantly.

Development of the Lamina Propria

At birth, the neonate has paired vocal fold structures covered with respiratory epithelium. The trilaminar organization of the lamina propria, which is present in adults, is not yet developed (16). In the neonate, the subepithelial tissue of the vocal fold is composed of relatively densely arranged fibroblasts and extracellular matrix proteins. As the neonate produces sounds, the vocal folds vibrate. It is believed that this vibration influences the genetic expression of the fibroblasts to produce the mature components of the extracellular matrix (17). Through growth and maturation, the subepithelial tissues in the region of the vocal folds organize into various layers based on the concentrations of the major extracellular proteins. This specialized arrangement is identified by age 14 years. This theory of development is supported through histologic evaluation of the lamina propria from patients of various ages (18). Alterations in the passive movement of laryngeal fibroblasts in cell culture have been demonstrated to influence genetic expression of these cells (19). Because activity influences genetic expression, it is possible that vocal activity during the formative years will ultimately affect overall lamina propria development. Therefore, childhood voice use or vocal abuse may affect the potential development of these structures.

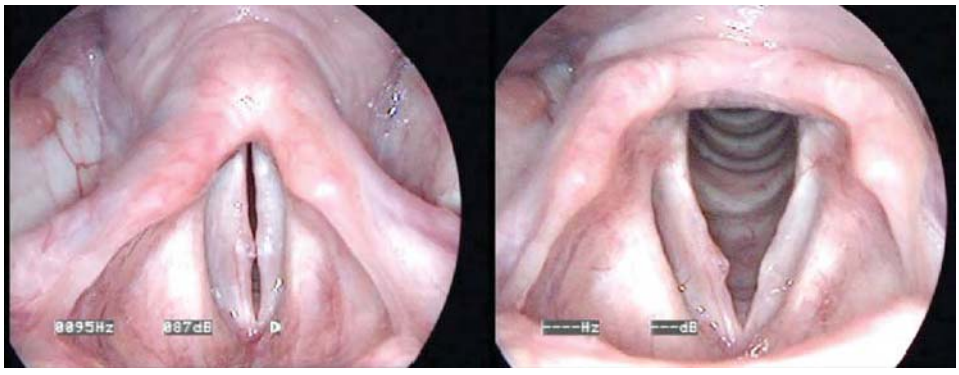


Figure 72.10 Bilateral vocal fold lesions secondary to voice overuse in a professional singer impeding vocal fold closure.

EVALUATION OF THE PATIENT WITH VOCAL DIFFICULTIES

It is nice to have the luxury of time to care for patients with vocal problems. However, patients often do not appear until their vocal difficulties have created, to them at least, a near-crisis situation. The otolaryngologist must be sensitive that what is a small vocal change could have significantly negative effects on the patient's vocal performance. The physician must counsel the patient regarding the difficulty in determining the exact cause of the voice problem. Diagnosis will require a thorough history of the vocal complaint as well as a focused physical examination of the head and neck and careful evaluation of the voice-production technique by a clinician interested in and knowledgeable about the previously discussed principles.

When speakers/performers use their voices to the maximum, abuse their voices, or use the mechanisms of voice production inefficiently, difficulties develop. Often vocal professionals will appear for evaluation when they first notice a change in their voices. If they are thoughtful about their voices, this will usually occur before others around them notice a vocal change. Therefore, their speaking and possibly their singing voice may still be normal in quality.

Complaints

The most common complaint from the singer is often a noticeable increase in effort required to produce voice or early vocal fatigue. They also may notice that this occurs more frequently in their mixed voice, in which they are attempting to adjust tension and airflow finely to regulate sound. Finally, they may also complain of a loss of the high range of their voice (especially when singing softly) when vibration is confined to the most superficial portion of the lamina propria. This may even have resulted in the loss of one or two of the top notes of their vocal range.

Singers/performers who are not so in touch with their voices may not appear until an obvious roughness or loss of occurs in their voices. However, this may have developed over years, and now the roughness is considered an integral part of their style. Often they are sought by their fans for this rough or breathy voice. The problem is frequently that they can no longer maintain stability in their voices.

History

A careful history with regard to the exact nature of the problem is critical. The physician must determine when and how the problem began. Was the onset associated with another event such as an illness, or did it occur coincident with a period of stress or a difficult performance? Once inciting events have been discussed, the physician should determine what makes the voice better and what makes it worse. Often patients will state that voice rest makes the problem better and that voice use makes the problem worse, or vice versa. The former is a fairly strong indication that the problem is secondary to abusive or inefficient vocal techniques. The latter suggests that the acute edema from voice use can help with underlying glottal insufficiency-related pathology (lesion, scar, etc.). The patient may not actually state that the voice is worse after use, but rather that voice is better on first waking and then deteriorates through the course of the day. By the end of the day or the performance, the patient may complain of neck pain or a tired sensation.

Next the physician must have the patient describe the vocal change. It is not sufficient to say that the patient is "hoarse." Rather, the physician should ask the patient about sensations of fatigue in the larynx (neck, throat), changes in quality with regard to roughness or breathiness, and last, what part of the vocal range is most affected. Often the performer is seen before obvious changes have occurred in all parts of the performing voice. The speaking voice may still be normal. Thus, some idea of vocal range and style requirements is imperative to direct the accuracy of the vocal complaint history.

Finally, with regard to history, the physician should determine what the patients have attempted to do to correct the situation. Are they taking over-the-counter, prescription, and/or a friend's medications? Have they sought counsel from friends or another physician? Have they begun treating themselves for reflux diseases? Do they have symptoms of reflux, and if they are taking medication, are they taking it properly? If so, has the medication use made a difference in the complaint? (Table 72.4).

Perceptual evaluation of the speaking voice should occur as the patient relates his or her history. The GRBAS (grade, roughness, breathiness, asthenia, strain) scale can be used to describe the voice. This is a 4-point scale wherein 0 = normal, 1 = mild, 2 = moderate, 3 = severe. In addition, the 30-question Singing Voice Handicap Index or can be used to quantify the impact of the patient's complaint on his or her quality of life (20) (Fig. 72.11). Alternatively, the

TABLE 72.4 HISTORY

Was the onset associated with illness?
Was there a period of stress or a difficult performance?
Does voice rest make the problem better or worse?
Does voice use make the problem better or worse?
How does the voice change throughout the day?
Is there any neck pain?
Does your throat feel tired or fatigued?
Have you noticed a change in voice quality?
What part of the vocal range is most affected?
Do you have symptoms of reflux?
Have you taken over-the-counter, prescription, and/or a friend's medications?
Are you taking the medications properly?
Has the medication use made a difference?

These are statements that many people have used to describe their voices and the effects of their voices on their lives. Circle the response that indicates how frequently you have the same experience in the last month.

1) It takes a lot of effort to sing.	never	almost never	sometimes	almost always	always
2) My voice cracks and breaks.	never	almost never	sometimes	almost always	always
3) I am frustrated by my singing.	never	almost never	sometimes	almost always	always
4) People ask "What is wrong with your voice?" when I sing.	never	almost never	sometimes	almost always	always
5) My ability to sing varies day to day.	never	almost never	sometimes	almost always	always
6) My voice "gives out" on me while I am singing.	never	almost never	sometimes	almost always	always
7) My singing voice upsets me.	never	almost never	sometimes	almost always	always
8) My singing problems make me not want to sing/perform.	never	almost never	sometimes	almost always	always
9) I am embarrassed by my singing.	never	almost never	sometimes	almost always	always
10) I am unable to use my "high voice."	never	almost never	sometimes	almost always	always
11) I get nervous before I sing because of my singing problems.	never	almost never	sometimes	almost always	always
12) My speaking voice is not normal	never	almost never	sometimes	almost always	always
13) My throat is dry when I sing.	never	almost never	sometimes	almost always	always
14) I've had to eliminate certain songs from my singing/performances.	never	almost never	sometimes	almost always	always
15) I have no confidence in my singing voice.	never	almost never	sometimes	almost always	always
16) My singing voice is never normal.	never	almost never	sometimes	almost always	always
17) I have trouble making my voice do what I want itto.	never	almost never	sometimes	almost always	always
18) I have to "push it" to produce my voice when singing.	never	almost never	sometimes	almost always	always
19) I have trouble controlling the breathiness in my voice.	never	almost never	sometimes	almost always	always
20) I have trouble controlling the raspiness in my voice.	never	almost never	sometimes	almost always	always
21) I have trouble singing loudly.	never	almost never	sometimes	almost always	always
22) I have difficulty staying on pitch when I sing.	never	almost never	sometimes	almost always	always
23) I feel anxious about my singing.	never	almost never	sometimes	almost always	always
24) My singing sounds forced.	never	almost never	sometimes	almost always	always
25) My speaking voice is hoarse after I sing.	never	almost never	sometimes	almost always	always
26) My voice quality is inconsistent.	never	almost never	sometimes	almost always	always
27) My singing voice makes it difficult for the audience to hear me.	never	almost never	sometimes	almost always	always
28) My singing makes me feel handicapped.	never	almost never	sometimes	almost always	always
29) My singing voice tires easily.	never	almost never	sometimes	almost always	always
30) I feel pain, tickling, or choking when I sing.	never	almost never	sometimes	almost always	always
31) I am unsure of what will come out when I sing.	never	almost never	sometimes	almost always	always
32) I feel something is missing in my life because of my inability to sing.	never	almost never	sometimes	almost always	always
33) I am worried my singing problems will cause me to lose money.	never	almost never	sometimes	almost always	always
34) I feel left out of the music scene because of my voice.	never	almost never	sometimes	almost always	always
35) My singing makes me feel incompetent.	never	almost never	sometimes	almost always	always
36) I have to cancel performances, singing engagements, rehearsals, or practices.	never	almost never	sometimes	almost always	always

Cohen, S. M., Jacobson, B. H., Garrett, C. G., Noordzij, J. P., Stewart, M. G., Attia, A., Ossoff, R. H., & Cleveland, T. F. (2007). Creation and validation of the singing voice handicap index. *Annals of Otology, Rhinology, & Laryngology*, 116, 402-406.

Figure 72.11 Singing Voice Handicap Index.

These are statements that many people have used to describe their singing and the effects of their singing on their lives. Circle the response that indicates how frequently you have the same experience in the last 4 weeks.

	0 = Never	1 = Almost Never	2 = Sometime	3 = Almost Always	4 = Always
1. It takes a lot of effort to sing.	0	1	2	3	4
2. I am unsure of what will come out when I sing.	0	1	2	3	4
3. My voice "gives out" on me while I am singing.	0	1	2	3	4
4. My singing voice upsets me.	0	1	2	3	4
5. I have no confidence in my singing voice.	0	1	2	3	4
6. I have trouble making my voice do what I want it to.	0	1	2	3	4
7. I have to "push it" to produce my voice when singing.	0	1	2	3	4
8. My singing voice tires easily.	0	1	2	3	4
9. I feel something is missing in my life because of my inability to sing.	0	1	2	3	4
10. I am unable to use my "high voice."	0	1	2	3	4

Figure 72.12 Singing Voice Handicap Index-10.

Singing Voice Handicap Index-10 has been developed as a shorter, less burdensome questionnaire with high test-retest reliability (21) (Fig. 72.12).

Physical Examination

Palpation of the external neck structures at rest and during phonation is frequently helpful in identifying unnecessary tension in these structures. At rest, the extrinsic laryngeal muscles in the neck, the tongue base above the hyoid bone, and the membranous components of the laryngeal framework should be soft and nontender. With phonation, they may tense minimally, but the patient should be able to talk with little if any difficulty while these structures are being lightly palpated. If light palpation results in significant pain, if the thyrohyoid space contracts during phonation, or if the structures are tense or become tense, then this may indicate inefficient use of the laryngeal mechanism (22). Palpation of the strap muscle attachments to the hyoid is particularly helpful to assess excessive external laryngeal muscle tension (Fig. 72.13). During palpation, the patient's neck/throat pain can often be reproduced.

The condition of the oral cavity, oropharynx, nasal cavity, and nasopharynx should be assessed for erythema, edema, inflammation, or other signs of infection. Muscular function of the pharynx should be evaluated, looking both for adequacy of palatal elevation and for lateral pharyngeal wall contraction.

Laryngoscopy

The laryngeal examination should pay close attention to vocal fold adduction and abduction. This is assessed with a constant light source and may be videotaped by attaching a camera to either a flexible or a rigid indirect laryngoscope. Mirror examination is probably no longer adequate because newer technologies such as the Hopkins rod endoscope, flexible fiberoptic scopes, or distal chip flexible endoscopes are readily available. In the majority of patients, these endoscopes allow a more prolonged visualization over the mirror examination. Depending on the clinician's techniques, patients are more comfortable with either rigid transoral telescopic examination or flexible transnasal examination. Proponents of each technique will cite advantages of their favored technique over the other. However, no adequate scientific studies have been carried out to support one technique over the other. They are probably best used as complementary techniques, and the laryngologist should become familiar with both.

Stroboscopy

After assessment of vocal fold abduction and adduction, a stroboscopic light source can be used to assess the vibratory parameters of the vocal folds. These parameters have been discussed in detail elsewhere. The otolaryngologist must understand the physiologic requirements for vocal fold vibration and what the absence of vibration may indicate. When the vocal folds are not vibrating in a relatively periodic manner, stroboscopy is of little use because the



Figure 72.13 Laryngeal palpation.

stroboscope light source flashing in a periodic manner relative to the aperiodic vibratory patterns will not produce a useful image.

Acoustic Analysis

Voice measures can be performed by a speech language pathologist to quantify the perceptual assessment of voice. There are several commercial software programs available to aid in acoustic analysis. A multitude of parameters can be evaluated including voice pitch, range, loudness, maximum phonation time, and aerodynamic measures (Fig. 72.14).

Discussion of Findings

When an obvious vocal fold lesion, impairment in glottic closure, or asymmetrical vibratory pattern is identified, the physician can point these out to the patient and begin to discuss the influence the findings may have on the function of the sound source. Caution should be used when discussing an apparent lesion(s) in the face of possible acute inflammation from recent heavy voice use or an upper respiratory infection. Before discussing the diagnosis and treatment of vocal fold lesions(s) with a professional voice performer, all attempts should be made to differentiate localized vocal fold edema versus a vocal fold lesion(s). Just because the abnormality is present, however, the physician should not always assume it is the cause of the problem unless a preexisting examination took place when the patient did not have the complaint and the lesion or change was not present. In addition, even if an obvious lesion(s) is present, the patient's behaviors most likely contributed to the formation of the lesion. If the behaviors are altered, then the lesion(s) may resolve. The patient must be asked to undergo evaluation of the vocal technique. Serial examination of the larynx during this period of altered behavior should be undertaken to assess the effect that the change in behavior will have on the lesion(s). If a significant change in the appearance occurs relatively surgical intervention is unlikely.

REFLUX

Frequently, patients have been told that reflux is the cause of their vocal difficulty and that they need antireflux medication. However, for voice problems not associated with classic reflux symptoms, this type of treatment has not been shown to be particularly successful (23). Randomized medication-versus-placebo studies for the use of proton-pump inhibitors (PPIs) for these types of patients have involved limited numbers of patients. Although these studies have not shown a particular benefit of medication over placebo for the management of nonspecific voice complaints, both studies had significant methodologic flaws that preclude definitive conclusions regarding the use of PPIs for nonspecific voice complaints (24,25). What is known about extraesophageal reflux is that it is not harmful to treat a patient for reflux disease with PPIs; that when questioned, most patients with atypical symptoms of reflux will have more typical symptoms of gastroesophageal reflux (GER);

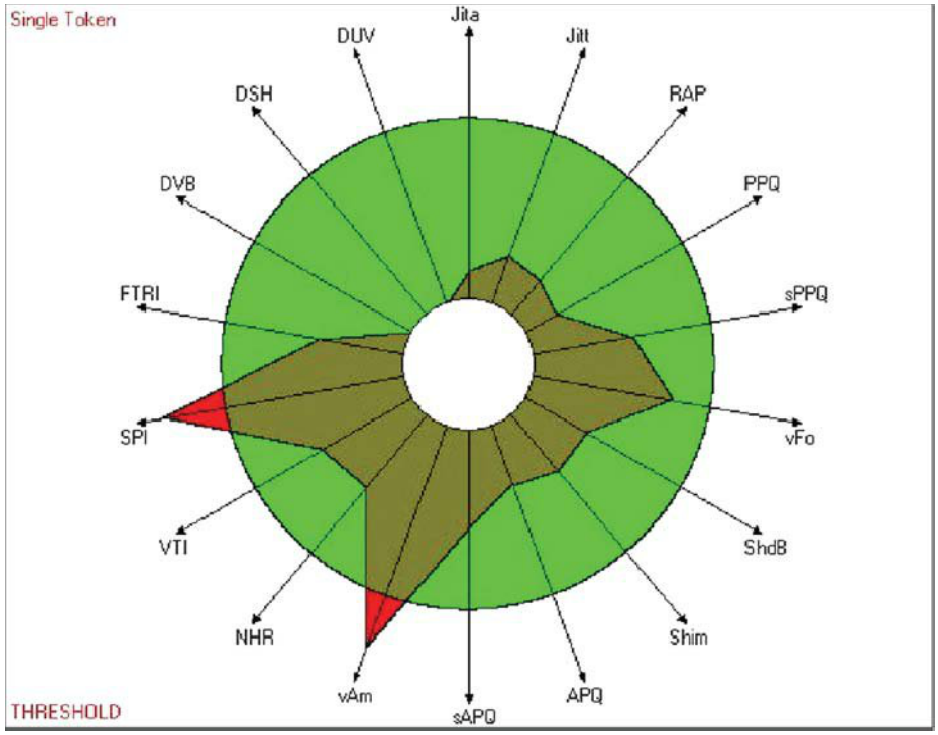


Figure 72.14 Multidimensional voice program.

and most patients with primary GER will actually have coexisting atypical symptoms. In clinical practice, therefore, if patients have typical symptoms of GER, then their voice complaints are more likely to respond, at least in part, to antireflux therapy (26,27).

MANAGEMENT

Multidisciplinary Evaluation

In most instances, vocal problems are secondary to inefficient voice-use patterns or voice abuse and overuse. Although the physician must identify and address secondary medical problems that may affect voice production, such as chronic lung disease, gastrointestinal disturbances, and systemic neurologic illnesses, treatment is primarily directed at eliminating the source of the trauma and improving the efficiency of the vocal mechanism.

The primary step in management, therefore, is patient education on the particular effects of voice production on the vocal mechanism and the potential harmful effects of irritants to the vocal fold mucosa such as smoke, nonhumidified air, and reflux (28). This education process is best undertaken by a team of clinicians. An otolaryngologist manages the medical issues and addresses the elimination of irritants. A speech–language pathologist addresses misuse and abuse of the speaking voice, and a vocal pedagogue addresses efficiency issues in the singing voice. All three clinicians must evaluate and discuss all aspects of clinical care so that a unified treatment plan can be presented to and carried out with the patient. If the evaluation by the otolaryngologist, speech pathologist, and vocal pedagogue cannot occur simultaneously, then the first clinician examining the patient, frequently the otolaryngologist, should discuss these physiologic changes and institute laryngeal hygiene interventions until the patient's vocal techniques for singing and speaking can be fully evaluated.

Laryngeal Hygiene Measures

Behavioral changes begin with lifestyle modifications such as smoking cessation, avoidance of excessively dry environments, and the elimination of extraneous and loud voice use not required for the professional career. Patients are also asked to alter their diets by changing the timing of food consumption. They are instructed to avoid foods high in fat content and foods containing natural diuretics. In addition, the patient is instructed to increase free water intake. These measures are designed to promote healing of the laryngeal mucosa by providing rest from vibration, reduction of irritation, and a healthier, thinner mucus coating to act as a lubricant for the vocal folds. These interventions are often labeled "laryngeal hygiene measures" and are a form of speech therapy (Table 72.5). Their application must be monitored, and they are most successfully used if patients are provided with a scheme for positive reinforcements. Frequently, the vocal improvements in themselves are the strongest form of positive reinforcements.

TABLE 72.5 LARYNGEAL HYGIENE MEASURES

Smoking cessation
Avoid excessively dry environments
Eliminate extraneous and loud voice use
Avoid eating prior to bed
Avoid foods high in fat content
Avoid foods containing natural diuretics
Increase free water intake

Hygiene measures in themselves usually provide some degree of relief and may eliminate the problem altogether (29). This phenomenon is particularly true in established performers as they continue to take on more obligations in both their personal and professional lives. One example is the female performer, avocational choral singer or otherwise, who finds herself experiencing vocal difficulties shortly after her children begin to speak. In addition to her previous vocal uses, she now finds herself reading or singing to her child when she would have normally rested her voice.

Performance

The performance schedule and style also should be addressed at the initial presentation. Performance schedules often require over-use/abuse of the vocal mechanism. Interestingly, most opera companies ask their singers to perform only every other day. Typically, larger companies will run two shows, with one performed on Thursday and Saturday and the other on Friday and Sunday. Opera companies must have recognized early that even classical styles of voice production are traumatic and performers benefit from rest between performances. Opera companies also expect to lose money on each performance and survive only through investment of their endowment and charitable contributions. Commercial singers on the other hand, perform four to seven nights consecutively. This habit reduces the financial costs with each performance and allows the group to survive and cover their expenses. It does not allow significant rest between performances. Patients frequently need to be counseled on the avoidance of too many consecutive shows and the need to rest their voice between performances. The reminder that they are being paid to sing and not to speak with their friends or fans is often helpful.

Voice Therapy

Laryngeal hygiene measures take away harmful behaviors. Psychological reconditioning for the elimination of behaviors is a difficult task for the patient and

clinician to accomplish. Positive reinforcement is provided through easing and improvements in vocal production; however, this may not be enough to improve the voice significantly (28). Under these circumstances, patients should undergo vocal instruction on healthier/more efficient methods of vocal production. These interventions introduce new behaviors that are more easily rewarded in a positive manner when they are completed successfully. This type of voice therapy should be directed by a clinician experienced in methods of voice production.

Speech–language pathologists completing a master's degree clinical clerkship or apprentice year are certified by the American Speech and Hearing Association. This certification does not imply that the clinician is interested or experienced in methods of voice production. Speech–language pathology is a broad field, and the clinician may have a stronger interest in language or speech rather than voice. Usually, the clinician interested in voice has had to seek out individual experiences in education in this field as only the minimum of voice instruction is required for graduation. Just as the otolaryngologist may be more interested in other areas of their specialty than laryngology, so too may be the speech–language pathologist. The otolaryngologist interested in practicing laryngology must seek out similar interested speech pathologists in their community.

Some of these techniques of vocal retraining include laryngeal manipulation techniques to allow the patient to eliminate excess cervical and laryngeal tensions through massage and repositioning. Others address reduction in cervical or laryngeal muscular hyperactivity through relaxation techniques generalized for the entire body. Still others address aspects of vocal production, such as flow phonation or resonant voice therapy, which attempt to have the patients learn new physical sensations during voice production.

With regard to retaining singing voice techniques, many performers are often fearful that someone will attempt to change their style or sound that has made them successful. The classical singers have years of study and a complicated emotional relationship with their previous teachers invested in their voices. Often they will respond only to someone who shows empathy for their experiences. The commercial performer is often a person who does not want to appear reliant on others. They may feel that their technique or lifestyle gave them what they have and could not be the cause of the vocal problem. The successful pedagogue must be aware of these feelings. Patients need to express a readiness level to change before therapy can be instituted. The otolaryngologist must identify a vocal-pedagogue colleague who has an understanding of the physiologic methods of voice production and the maturity to work with this group of patients.

ACUTE CARE FOR THE EMERGENT VOCAL PROBLEM

When patients appear for evaluation, they usually expect to have their problem fixed rapidly. They want a pill or a surgery to correct the difficulty. The physician must explain to them that most vocal problems are created through inefficient behaviors. The physician must also explain the patient's roles in creating the vocal problems and attempt to abolish the "quick fix" mentality. This can be aided by explaining the complexity of vocal production. Attempts to relate the complaints to previous voice-use pattern also can help establish the concept that the patients behaviors have contributed to the difficulty. Finally, in the resistant patient, voice rest to eliminate all inefficient behaviors can be used.

Voice Rest

For 1 week, the patient is asked to comply with absolute voice rest. He or she then returns for repeated evaluation and examination with stroboscopy. If the patient notices that the voice complaint is significantly reduced or that the stroboscopic appearance of the larynx is significantly improved, then the patient will more likely accept the fact that his or her behavior is responsible for at least a portion of the problem. Voice rest is a diagnostic tool that should not be used lightly. It is emotionally difficult to comply with voice rest, and it can have significant financial implications. Prolonged periods are not beneficial and are unnecessarily stressful. Voice rest is like a crash diet. Once the behaviors return, the lesion will enlarge. The disease-free period may allow the patient to get through a difficult or important performance, and it may improve the readiness level to accept behavioral-based intervention therapy.

Steroids

Systemic steroids also may be used to speed the temporary reversal of laryngeal inflammation induced by poor behaviors or an upper respiratory infection. Once again, these may help the patient through a difficult performance, but they are not an option for long-term management. In addition, patients need to be warned about the potential that the steroid dose, either oral, intramuscular, or intravenous, may not significantly alter the larynx and voice production and that steroids can be associated with adverse side effects. These include changes in mental status, temporary weight gain, insomnia, acne, hyperactivity, and aseptic necrosis of the hip. First-time steroid use should be avoided before a major performance. Finally, if a vascular lesion is present, steroids may be relatively contraindicated, as they can result in an increase in capillary membrane permeability and may predispose to vocal fold hemorrhage.

Topically inhaled steroids are contraindicated in the management of voice problems. These steroids are meant to reduce inflammation in the lungs. On the vocal folds, they are irritating, predispose to fungal overgrowth, and increase the likelihood of fungal laryngitis. The medications and the vehicles with which they are aerosolized dry the vocal fold mucosa; thus they alter the viscosity and create a disturbance in the vibratory abilities of the vocal folds. In addition, it has been suggested that prolonged use can lead to vocal fold atrophy. The latter, however, has not been proven scientifically.

Performance Cancellation

Occasionally, the vocal professional presents to the physician with an acute vocal problem immediately before a vocal performance. The physician will be asked to determine if the patient can perform. Accepted contraindications to performance include vocal fold hemorrhage, vocal fold ulceration, acute inflammation from presumed viral or bacterial causes, and the feeling of the patient that performance at that time will be difficult, not productive of an adequate voice quality, and damaging for the patient's image and career. The physician must document the vocal history, the laryngeal appearance, and the conversation with the patient or the patient's managerial assistant or both. This becomes a legal part of the medical record. It is shared only once the patient has signed a medical release for dissemination to the designated parties. This should not be taken lightly, as the act of canceling a performance may in itself be damaging to the performer's reputation.

The patient–doctor relationship dynamics can be strained or altered by the involvement of the institution (employer) who has employed the sick singer. The otolaryngologist must treat the issues associated with this "triangle" very carefully. Sometimes a vocal performer will seek the assistance of an otolaryngologist to obtain help in getting out of a pending singing obligation (usually in favor for a more lucrative role elsewhere). This situation must be handled with great delicacy, and documented permission must be obtained from the patient before communication with the employer is attempted. It is best to review, in detail, the medical "report" that will be given to the employer (once patient approval is obtained) before providing your opinion to the singer's employer.

SURGICAL MANAGEMENT

Indications

The mere presence of a vocal fold lesion is not an indication for surgical intervention. Because of voice overuse and abuse, performers are at increased risks of developing lesions on the vibrating portions of their vocal folds. Because these lesions develop as a histologic response to injury, the source of the injury must be eliminated. This can be done through vocal hygiene measures, which reduce the absolute activity, or the patients can be reeducated to use their vocal mechanisms more efficiently so that they can perform for longer periods with less laryngeal stress. Not every patient will want to or be able to make the required changes. For this reason, some patients never become surgical candidates. In others, the voice improves, and the lesion may or may not reduce in size. As long as the patient is able to perform to the level needed, then no reason exists to remove the lesion.

When the patient attempts to comply with behavioral recommendations, three outcomes are possible. First, the behavioral changes can result in enough resolution to allow the patient to perform to the desired level. Second, the patient may not be able to make the changes. Third, the patient may appear to make the changes, but the lesion may not become small enough to allow the patient to function properly. In the second and third conditions, surgery may be indicated. In the second situation, the hope is that by improving the laryngeal configuration, the patient will be able to function more efficiently so that the lesion does not reoccur. In the third situation, the hope is that the lesion is not persistent because of continued unrecognized harmful behaviors. In both of these instances, the surgeon must trust the opinions of his speech–language pathology and vocal pedagogy colleagues.

The patient must be counseled about the risks of surgery, including undesirable healing with stiffening of the vocal fold and further impairment of laryngeal vibratory function. The patient must be aware that a risk exists that the postoperative voice or function could be worse secondary to poor healing. The patient also must be aware that postoperative behavioral changes will be necessary to lessen the likelihood of recurrence of the lesion, and this period of healing and reeducation will take 2 to 6 months before the patient is ready to perform at the optimal level. Finally, the patient must be aware that if he or she is unable to make the required behavioral changes, then the lesion or a similar lesion may reoccur.

If a patient is noncompliant with the recommendations of the voice care team, then even if the lesion is enlarging, the patient should not undergo surgery as long as the surgeon is certain that the lesion is not of neoplastic origin. In this instance, if the vocal fold lesion(s) is removed and the abusive phonation style continued, the patient's voice will not improve or will even deteriorate. This poor outcome will be blamed on the surgeon. This patient has not expressed a readiness level for surgery. These conversations must be documented with the patient and become part of the medical record. The discussion does not excuse poor surgical techniques but documents that these potential outcomes and alternative therapies have been considered. In this manner, the patient is fully informed of all options.

Surgical Techniques

In professional voice patients, as in most patients with vocal difficulties not due to neurologic impairment, dysphonia results from traumatically induced acellular changes in the vocal fold as a response to repeated injury. These lesions disrupt the normal laryngeal vibratory patterns and lead to a disordered sound-source signal. These lesions usually develop within the superficial portion of the submucosa. Surgery is designed to restore the normal laryngeal configuration with minimal involvement of the unaffected regions. Techniques using high magnification and microinstrumentation have been developed to aid in the accomplishment of these goals. These techniques, termed microflap surgeries, have been used for more than a decade. They have been used by multiple surgeons and are associated with reliable outcomes (30–32).

CONCLUSIONS

The techniques used to care for professional voice patients are based on an understanding of laryngeal anatomy and human physiology for voice production. The laryngologist must have an understanding of the vocal demands of the voice patient. These concepts are important for both professional and nonprofessional voice patients and should be generalized from one group to the other. The difference between the groups of patients is that, because of performance requirements, professional voice patients may place their laryngeal mechanism at greater risk of damage than do nonprofessional patients. The otolaryngologist is best able to treat the patient when he or she has taken the time to learn these special demands or partners with someone who has.

HIGHLIGHTS

- The vocal fold lamina propria develops into an organized trilaminar structure by age 14 years. The genetic expression of the fibroblasts that direct this organization are likely affected by use.
- Human voice production requires that power derived from air from the lungs drives the vocal folds passively into vibration. This vibration creates a sound source that is modulated through the supraglottic vocal tract.
- During voice production, the speaker controls the sound output through fine regulation of subglottic pressure, laryngeal closure, and vocal fold tension.
- The harmonic sound source from the larynx is modulated by changes in the shape, length, and distal opening of the supraglottic vocal tract. These physical changes in the supraglottic vocal tract are created by muscular contraction and movements of the tongue, pharynx, and lips.
- The harmonic regions that are amplified by the vocal tract are termed formants. The first two formants are responsible for vowel differentiation, whereas the third, fourth, and fifth formants provide the sound timbre. The singer's formant is created by changing the shape of the supraglottic vocal tract to boost the higher formants.
- Many vocal problems are secondary to inefficient use of the mechanisms of voice production.
- Most vocal fold lesions of the lamina propria result from prolonged or repeated trauma due to inefficient laryngeal vibratory patterns. The lesions form as a response to injury.
- Evaluating patients with voice complaints requires a thorough history specific to voice, a complete head and neck examination, probably including laryngeal stroboscopy, and knowledge regarding the vocal requirements and the physiologic principles used for voice production.
- Laryngeal stroboscopy is used to evaluate vocal fold vibratory activity.
- Laryngoscopy is used to evaluate cricoarytenoid-joint motion.
- Voice rest is a diagnostic tool. Prolonged voice rest can be emotionally difficult and financially damaging and is rarely indicated.
- Systemic steroids may be beneficial in reducing vocal fold edema. Topical steroids are irritating to the vocal folds, are associated with increased incidence of fungal laryngitis, and are contraindicated in the management of voice problems of patients.

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73 Office-Based Procedures in Laryngology

Manish D. Shah *Michael M. Johns III*

Laryngologic procedures were originally developed over 100 years ago to be done under local anesthetic in the office setting. Medical and surgical advances—such as general anesthesia, endotracheal intubation, and the operating microscope—led to a movement of procedures to the operating room. These advances provided surgeons with the advantages of bimanual dexterity, binocular vision, and high-power magnification and, thus, increased precision. Recently, there has been a resurgence in the popularity of awake office-based laryngeal procedures (1–3).

Several technologic advances have facilitated the revival of awake office-based laryngeal procedures. Distal-chip flexible endoscopes, ultrathin esophagoscopes, a variety of injection materials, and fiber-based lasers have all contributed to this trend (1,4).

Conducting laryngeal procedures in an awake patient has numerous advantages. First, awake procedures are substantially more convenient for patients when compared to procedures under general anesthesia or sedation. They may leave the hospital on their own and even return to work the same day. Patient safety is increased by avoiding the risks associated with general anesthesia, which is especially important for patients with significant medical comorbidities.

Second, there are significant advantages for the surgeon. The ability for the patient to phonate allows the surgeon to monitor voice quality before, during, and after the procedure. Furthermore, diseases that were once observed until severe enough to warrant exposing the patients to the inconveniences and risks of general anesthesia, such as glottal leukoplakia/dysplasia or papillomatosis, can be treated as frequently as indicated by clinician concern and patient symptoms.

Finally, there is a cost savings by avoiding expensive operating room resources (5,6), and patients and their families can minimize or avoid lost work days.

LARYNGEAL VISUALIZATION

The development of endoscopic technology and illumination has led to improved visualization of the larynx, which is essential to the diagnosis and treatment of laryngeal pathology. Laryngeal videostroboscopy, kymography, and high-speed cinematography are all techniques that allow for detailed examination of vocal fold vibration that cannot be appreciated with standard mirror or fiberoptic laryngeal examination. These topics are covered in more detail elsewhere in this book (see Chapter 65).

For awake office-based procedures, both rigid and flexible endoscopes can be used, as is described in this chapter. Rod-lens endoscopes generally provide superior image quality when compared to flexible fiberoptic endoscopes due to larger and more stable light-carrying fibers. However, the development of flexible endoscopes with a chip-based camera at the end of the scope ("distal-chip") has led to image quality that is near equivalent in quality to rigid rod-lens scopes (7).

PATIENT SELECTION AND PREPARATION

For the purposes of this chapter, "office-based" implies that the patient is awake, with no or minimal sedation, sitting upright, and able to provide phonatory feedback. Procedures may actually be done in a hospital-based procedure room such as an endoscopy suite, but the advantages of these procedures are realized as long as there is adherence to these principles.

The vast majority of patients will tolerate an awake laryngeal procedure; however, patient preparation is essential. The surgeon must clearly explain the procedure, including the application of topical anesthesia, and gauge the patient's level of comfort and anxiety. It is essential to explain the abnormal sensations produced by topical

anesthesia of the pharynx and larynx as well as the mild discomfort the patient may feel during the procedure itself. Procedures should not be attempted on patients who seem too anxious to proceed; however, even very anxious patients will tolerate an awake procedure if they are adequately informed ahead of time and coached throughout.

Patients must have a patent nasal airway for passage of a flexible laryngoscope and must be able to tolerate such an examination without an intense gag reflex. Patients who are not able to remain still for the duration of the procedure, such as patients with cervical dystonias or severe head tremor, may be difficult to treat (8). Those on anticoagulants should stop taking these medications prior to injections or biopsies. However, the experience of the authors and of others (3,8) suggests that complication rates are not higher in these patients even if they are unable to stop these medications.

ANESTHESIA

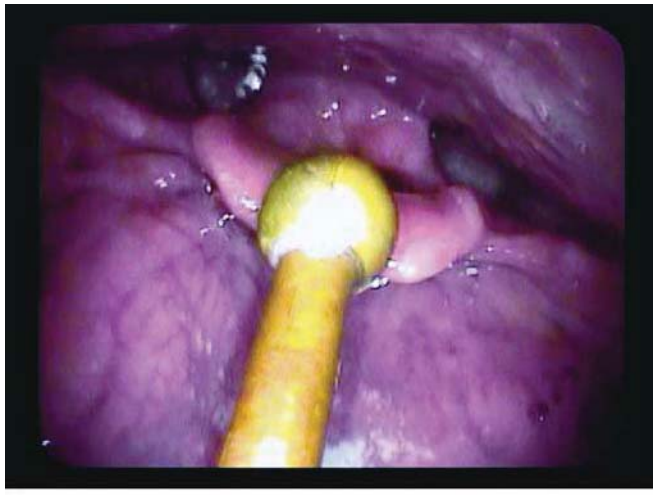
Adequate anesthesia of the laryngopharynx is of utmost importance to the success of any awake laryngeal procedure. This can be achieved by either topical application of anesthetic medication or superior laryngeal nerve (SLN) blocks (Fig. 73.1A). Almost always, the former will suffice; however, the latter can be useful in certain patients. Whichever method is used, patients must be instructed to remain NPO for 30 to 45 minutes after the procedure due to the risk of aspiration secondary to laryngopharyngeal anesthesia.



A



B



C

Figure 73.1 **A:** Equipment and medications required for laryngopharyngeal topical anesthesia. Shown in the photograph are topical 4% lidocaine solution, oxymetazoline, spray bottle to aerosolize medications for nasal anesthesia, Abraham cannula, and syringe with needle for transtracheal injection of anesthetic. **B:** Transtracheal injection of anesthetic for topical laryngotracheal anesthesia. **C:** An Abraham cannula is used to drip topical anesthetic onto the larynx.

Topical

The nasal cavity should be anesthetized and decongested if a flexible scope is to be used for the procedure. Our preference is to use oxymetazoline and 4% topical lidocaine. The laryngopharynx can then be anesthetized by one of four methods:

1. Transtracheal injection of 2 to 4 mL of 4% lidocaine into the lumen of the trachea (Fig. 73.1B). This will elicit a strong cough reflex, delivering the lidocaine to the subglottic, glottic, and supraglottic levels. The airway should be entered below the cricoid cartilage as opposed to through the cricothyroid membrane. This avoids the plexus of blood vessels found at the cricothyroid membrane and minimizes bleeding in the larynx, which can obscure structures during the procedure itself. If the patient has a tracheostomy, instillation of the anesthetic through the tracheostomy tube with subsequent occlusion of the tube during the cough will produce a similar effect.
2. With a flexible or rigid scope used to visualize the larynx, an Abraham cannula (Pilling; Teleflex Medical, Research Triangle Park, NC) can be used to deliver 2 to 4 mL of 4% lidocaine to the base of tongue, epiglottis, and larynx (Fig. 73.1C). A "laryngeal gargle" is performed by having the patient phonate during the delivery of the anesthesia in order to maximize contact time with the laryngeal mucosa (9).
3. The anesthetic can be delivered via a syringe attached to the working channel of a flexible laryngoscope. As above, a "laryngeal gargle" will maximize effectiveness of anesthesia.
4. Lidocaine can also be nebulized for anesthesia; however, further topical anesthesia is often required for patients to tolerate the procedure (1,4).

Lidocaine will result in 45 to 60 minutes of anesthesia within 90 seconds of application. However, most patients will only tolerate the procedure for approximately 20 to 30 minutes (1,8). Various topical anesthetic medications may be used as long as the maximum dose guidelines are strictly followed (1,8).

Superior Laryngeal Nerve Block

The site of injection for an SLN block is halfway between the hyoid bone superiorly and the superior border of the thyroid cartilage inferiorly, and halfway between the anterior midline and the superior cornu of the hyoid bone (10). This corresponds to the point where the internal branch of the SLN pierces the thyrohyoid membrane to enter the larynx. One to two milliliters of anesthetic is injected in this area, superficial to the thyrohyoid membrane, to provide a nerve block. The duration of anesthesia will depend upon the agent(s) used. The procedure should be done on both sides of the larynx.

Complications of Topical Anesthesia

Significant complications of topical anesthesia are very infrequent (10). Vasovagal reactions can rarely occur (10), but actual syncope can often be prevented if the prodromal symptoms are recognized. The procedure should be aborted and the patient placed in a reclined position.

Systemic toxicity may result from inappropriately high doses of topical anesthetic agents. Early symptoms can include perioral and tongue paresthesias, visual disturbance, lightheadedness, dysarthria, muscle twitching, and tinnitus. These symptoms must be recognized very early as cardiovascular collapse, convulsions, and cardiorespiratory arrest are possible. This highlights the importance of strict adherence to recommended maximum doses for each anesthetic agent. Dose adjustments may be required in patients with hepatic compromise, renal insufficiency, or heart block.

Allergic reactions are also possible but are usually mild, and anaphylaxis is rare (8). Even more rare is methemoglobinemia, which results in impaired oxygen delivery to tissues and is most commonly seen with the use of benzocaine or prilocaine. Early signs include "chocolate cyanosis"—a brown or gray discoloration of the lips and mucous membranes. It can progress to involve dysrhythmias, seizures, myocardial infarction, coma, and death.

MONITORING DURING AWAKE LARYNGEAL PROCEDURES

Patients do experience significant changes in hemodynamic parameters during awake laryngeal procedures. In a study of 31 patients who had monitoring of their vital signs during their procedure, 23% of patients developed severe hypertension and 29% significant tachycardia (11). Furthermore, none of these patients reported or showed signs of abnormal amounts of discomfort (11). Despite the fact that others have found that the vast majority of patients tolerate procedures and report minimal pain or discomfort (12,13), these findings suggest that patients are experiencing significant hemodynamic changes that do not correlate to subjective comfort levels. Given the low complication rates of awake procedures, these changes likely do not pose a significant danger to patients. Thus, in general, it is the opinion of the authors that monitoring is not indicated in patients who do not receive sedation. However, patients with significant comorbidity such a severe cardiac or pulmonary disease may benefit from pulse oximetry and/or blood pressure monitoring.

AIRWAY EVALUATION AND ASSESSMENT

With adequate anesthesia, the airway can be examined fully in the office. It allows for evaluation of both dynamic and fixed obstruction, which cannot be done under general

anesthesia with rigid endoscopy. This can yield important information to help plan and guide any potential operative intervention, as well as to monitor operative results during follow-up. Concern of laryngospasm and lack of patient tolerance often prevent clinicians from employing these techniques. However, it is a very safe technique (9) that can provide immediate and valuable information.

Cricoarytenoid Joint Fixation and Posterior Glottic Stenosis

When a patient presents with an immobile vocal fold, one must distinguish between cricoarytenoid (CA) joint fixation and nerve paresis or paralysis if their history is suggestive of the former as a potential etiology. This determination is important to guide therapy and determine prognosis. CA joint mobility can be assessed by looking for the "jostle sign." An immobile arytenoid due to nerve paresis or paralysis will be "jostled" by the mobile arytenoid with phonation, whereas the arytenoid of a fixed CA will not jostle. However, this can be a very subtle sign to diagnose.

CA joint mobility can be more reliably assessed via palpation, which has classically been done via direct laryngoscopy under general anesthetic. Palpation can, however, be done awake if the larynx has been adequately anesthetized (14,15). A flexible or rigid endoscope is used to visualize the larynx while the surgeon or patient holds the tongue, and a curved forceps or Abraham cannula can be used to provide gentle pressure at the vocal process of the arytenoid cartilage in a lateral and posterior direction.

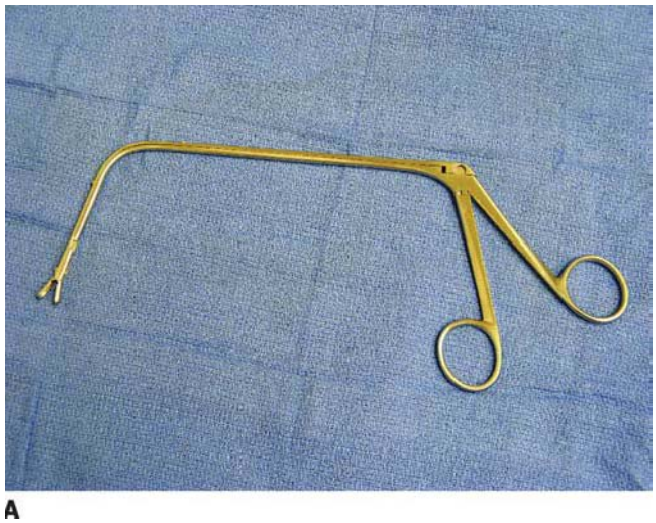
Similarly, it is often important to distinguish between bilateral vocal fold immobility due to a neurologic cause and posterior glottic stenosis. A similar maneuver to that described above can be done with two instruments simultaneously to assess for CA joint mobility as well as posterior glottic stenosis (15).

Subglottic and Tracheal Stenosis

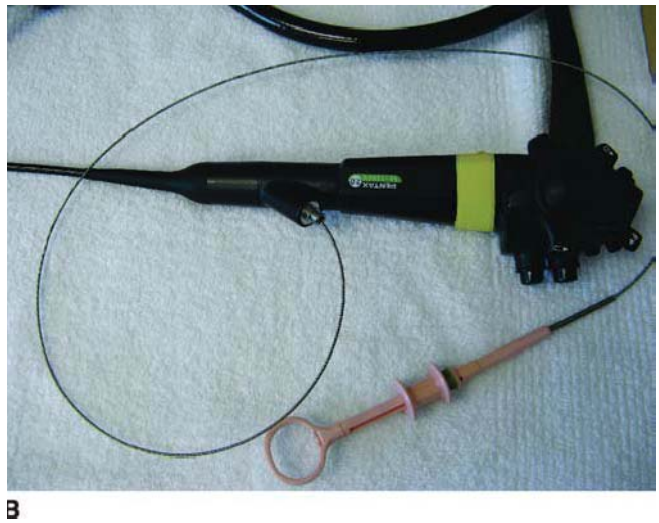
The complete tracheobronchial tree can be evaluated with adequate topical anesthesia. With the anesthesia techniques described above, examination to the level of the carina is possible. Further examination of the bronchi usually requires application of topical anesthesia to the bronchi via the working channel of the scope. A flexible endoscope can easily be passed distal to the vocal folds with no significant risk of laryngospasm and is well tolerated by the majority of patients (9). Subglottic and tracheal stenosis, laryngeal and upper airway tumors, and tracheomalacia can be evaluated closely. The latter is easier to examine awake as opposed to under general anesthesia due to its dynamic nature. The length and degree of stenosis can be assessed, although length may be difficult or impossible to assess in severe stenoses if the scope will not pass through easily or if the patient has the sensation of airway obstruction.

LARYNGOPHARYNGEAL BIOPSY, PANENDOSCOPY, AND TUMOR STAGING

Biopsies may be done peroral with a rigid scope and a long curved biopsy forceps (Fig. 73.2A) after appropriate topical anesthesia of the larynx. The patient holds on to their tongue while the surgeon holds the scope and directs the biopsy forceps. However, this technique can be difficult to perform and is not well tolerated by all patients. The development of flexible endoscopes with working channels that pass easily through the nasal cavity has facilitated biopsies to be done in this manner. Generally, this technique is better tolerated by most patients. The scope is advanced to a position with the lesion of interest in view, and a 1.8-mm flexible cup biopsy forceps (Fig. 73.2B and C) is passed through

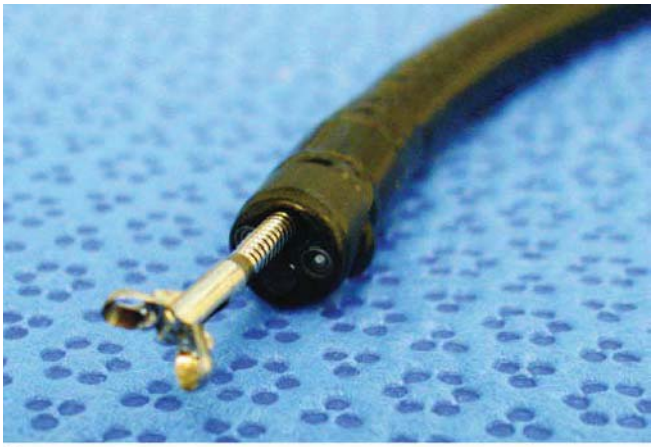


A



B

Figure 73.2 **A:** Curved biopsy forceps for peroral laryngeal biopsies. **B:** Flexible biopsy forceps passing through working channel of flexible endoscope.



C



D

Figure 73.2 *(Continued)* **C:** Biopsy forceps tips visible beyond the end of a flexible endoscope. **D:** Biopsy of vocal fold lesion using a flexible 1.8-mm biopsy forceps.

the working channel by an assistant until visible beyond the tip of the scope. The forceps are then opened and the scope is advanced until the forceps come into contact with the lesion (Fig. 73.2D). The forceps are then closed and removed from the scope. The scope can be left in place and multiple biopsies can be taken, which is advisable as the small size of the biopsy forceps can result in false-negative results.

The ability to conduct biopsies, along with transnasal esophagoscopy (TNE) and awake bronchoscopy, allows for awake panendoscopy and tumor staging to be done in the office setting. This has been demonstrated to be as effective as operative staging under general anesthesia (16).

VOCAL FOLD INJECTION

Like many procedures in laryngology, vocal fold injection began as an office-based procedure but became a well-established technique under general anesthesia. Awake injections are certainly more convenient for patients and also avoid the risks of general anesthesia. This is significant for patients with significant medical comorbidity or who are recovering from a recent operation. The latter situation can pose a dilemma in patients with operative injury causing vocal fold immobility (17), and an awake injection offers a safe alternative.

The majority of awake office-based vocal fold injections are done for injection laryngoplasty. Indications for injection augmentation include vocal fold paralysis or paresis, vocal fold atrophy, scar, sulcus vocalis, and postsurgical defects. This chapter focuses on these indications. Other indications for injection include more superficial injection of steroid, cidofovir, or bevacizumab (1,18,19).

Numerous studies have shown awake injection laryngoplasty to provide excellent results in treating glottal insufficiency (17,20), even when compared to traditional injection laryngoplasty done under general anesthetic (5,21). Furthermore, there is a substantial cost savings associated with awake injection over traditional injection under general anesthetic (5).

Injection augmentation provides almost immediate relief of symptoms. Using a temporary material in the setting of a vocal fold paralysis or paresis alleviates symptoms while waiting for potential recovery of nerve function. It also can serve as a trial to determine if a more long-lasting injection or procedure would be of clinical benefit to the patient (22). Furthermore, early injection laryngoplasty in patients with potentially recoverable vocal fold paralysis seems to reduce the need for permanent medialization in the form of laryngeal framework surgery in the future, possibly by creating a more favorable vocal fold position that can be maintained by synkinetic reinnervation (23,24).

The treatment of vocal fold scar, sulcus vocalis, and vocal fold atrophy can be complicated and is covered elsewhere (see Chapter 68). Injection augmentation may be beneficial in these patients to help correct glottic insufficiency that may be contributing to their vocal handicap. Again, using a temporary injectable material provides a trial for both the clinician and patient with regard to potential benefit (22).

Techniques for Awake Vocal Fold Injection

Adequate visualization and anesthesia of the larynx are essential for a safe, precise, and effective injection. In addition to the application of topical anesthesia as described above, the skin overlying the injection site for the percutaneous approaches should be anesthetized appropriately. Apart from the peroral technique described below, all injections will require an assistant to hold the scope in position during the procedure.

The location and amount of material to be injected is similar irrespective of the approach used for the injection (see Chapter 69). The injection should be placed within the vocal fold muscle, lateral to the superior arcuate line. Injection of material into the superficial layers of the vocal fold will disrupt normal vocal fold vibratory patterns. Placing the injection too far lateral is not harmful but will not result in significant medialization as the injectable will fill the paraglottic space. In terms of the anteroposterior dimension, the injection should be placed lateral to the vocal process of the arytenoid and at the midpoint of the membranous vocal fold. Anterior injections should be avoided as they will result in abnormal mucosal wave propagation and a "pressed" voice.

The amount to be injected to correct glottal insufficiency depends on each individual case, but most vocal folds are adequately medialized with 0.5 mL or less of material. Overcorrection is required such that there is a slight convexity to the margin of the vocal fold to account for the aqueous component of most injectable materials that will resorb. The patient's voice can be tested through the procedure to determine the most appropriate amount and location of material to be injected—a distinct advantage of awake injections.

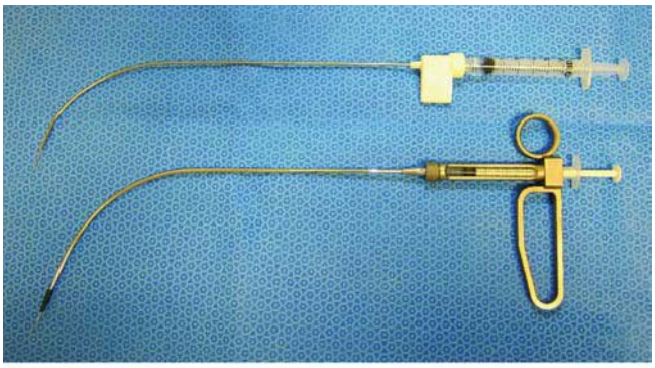
Peroral Approach

After appropriate laryngopharyngeal anesthesia, the patient's tongue is held by the patient or the surgeon, and the larynx is visualized with either a flexible or rigid scope. The latter offers the advantage of eliminating the need for an assistant as the patient holds their own tongue while the surgeon holds the scope in one hand and the needle for injection in the other. Use of the flexible scope held by an assistant, however, is generally better tolerated by the patient and allows the surgeon to have bimanual control of the needle.

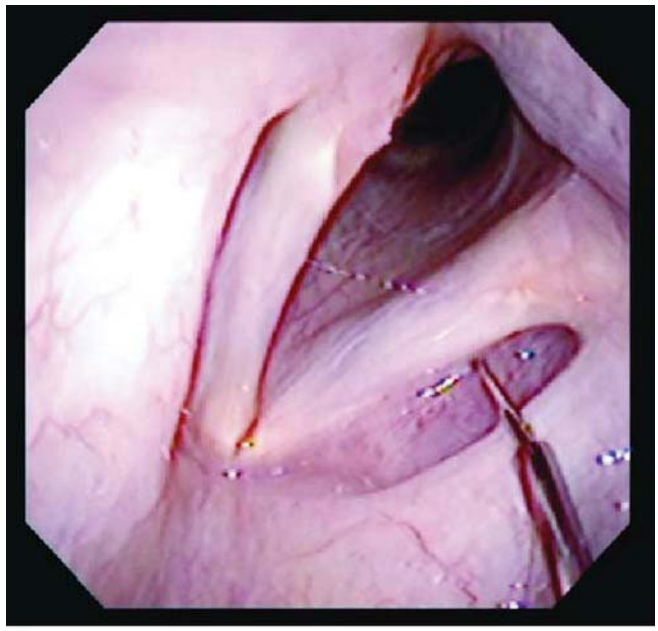
A long curved needle is required. The curved orotracheal injector (Medtronic Xomed, Jacksonville, FL) is designed for peroral injections (Fig. 73.3A). This device allows for injection of materials and liquids with low viscosity such as hyaluronic acid and collagen-based materials. Other long needles designed for injection during direct laryngoscopy in the operating room can often be bent to the required shape for peroral injection, such as the needle shown in Figure 73.3A (24-gauge rigid injection needle, Merz Aesthetics, Franksville, WI). The needle is advanced to the injection site through the oral cavity and past the oropharyngeal structures. Needle placement can be easily controlled and visualized, allowing for a precise injection (Fig. 73.3B).

Thyrohyoid Approach

The thyroid notch must be readily palpable in order to employ this approach (Fig. 73.4A). In addition to topical laryngeal anesthesia, the skin overlying the thyroid



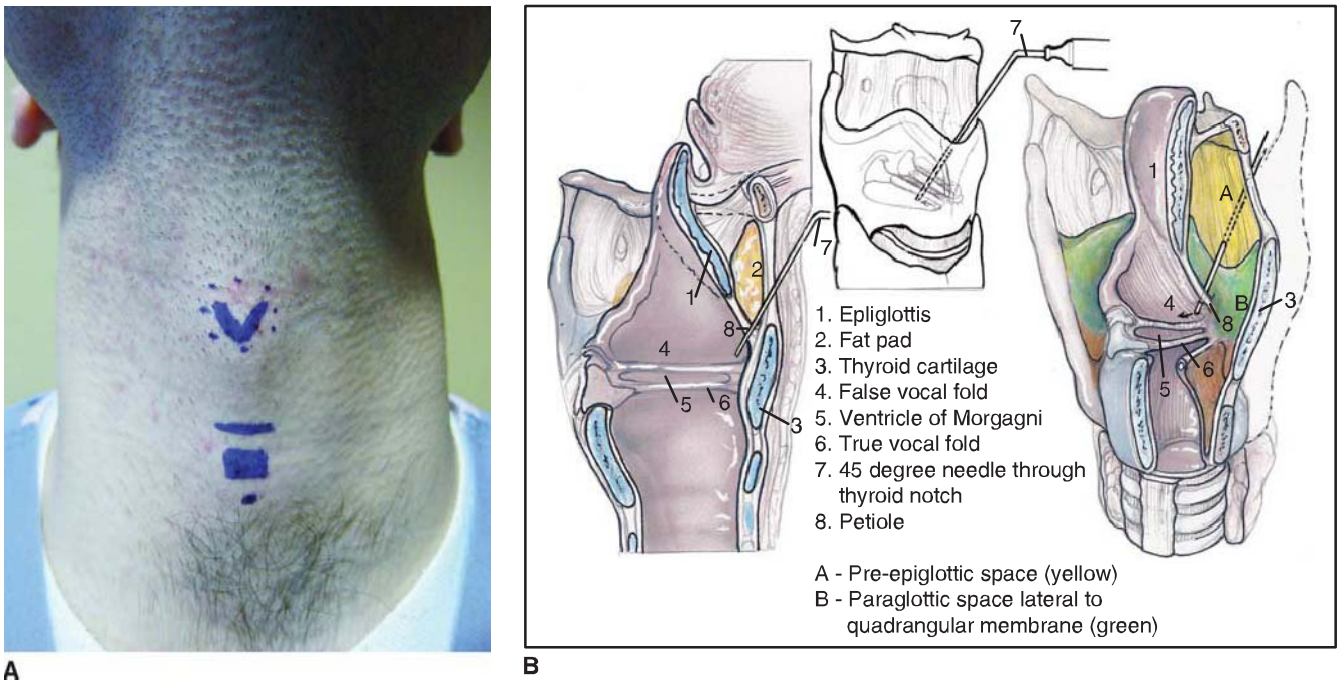
A



B

Figure 73.3 **A:** Equipment for peroral vocal fold injection. A bent needle from Merz Aesthetics (**top**: Franksville, WI) and the orotracheal injection instrument (**bottom**: Medtronic Xomed, Jacksonville, FL) are shown. **B:** Peroral vocal fold injection.

notch should be anesthetized. A flexible scope is used to visualize the larynx. A 1.5-inch 23- or 25-gauge needle is then inserted at the notch and guided acutely downward, through the pre-epiglottic space (Fig. 73.4B and C), aiming to pierce the laryngeal mucosa at the petiole of the epiglottis in the midline. The needle can then be guided to either vocal fold for injection (Fig. 73.4D). Similar to the peroral approach, there is clear visualization of needle



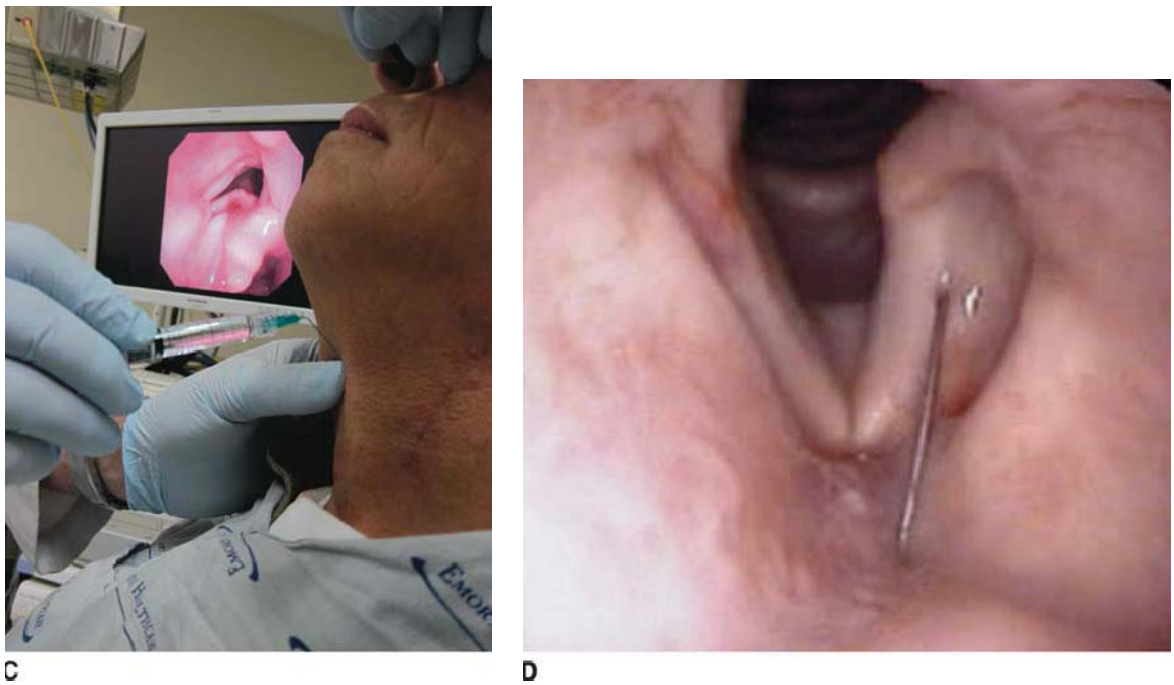


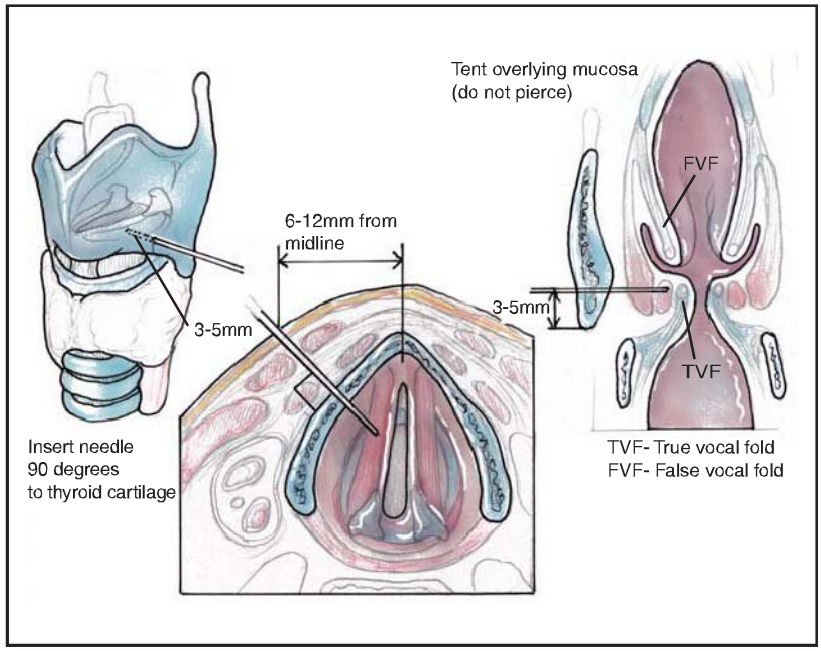
Figure 73.4 **A:** Landmarks for thyrohyoid approach to vocal fold injection. Shown are the thyroid notch ("V"), inferior border of the thyroid cartilage (*thin line*), and the cricothyroid space (*thick line*). The *dotted circle* shows the area of skin that should be anesthetized. **B:** Thyrohyoid approach for vocal fold injection. The needle enters just above the level of the thyroid notch and is directed acutely downward through the pre-epiglottic space to pierce the laryngeal mucosa approximately at the level of the petiole of the epiglottis. **C:** Thyrohyoid approach for vocal fold injection. **D:** Needle pierces laryngeal mucosa near the petiole of the epiglottis for the thyrohyoid approach for vocal fold injection.

placement, allowing for a very precise injection (25). We prefer to bend the needle to approximately a 45-degree angle, which allows one to achieve the acute downward vector required for injection without the syringe hitting the patient's chin.

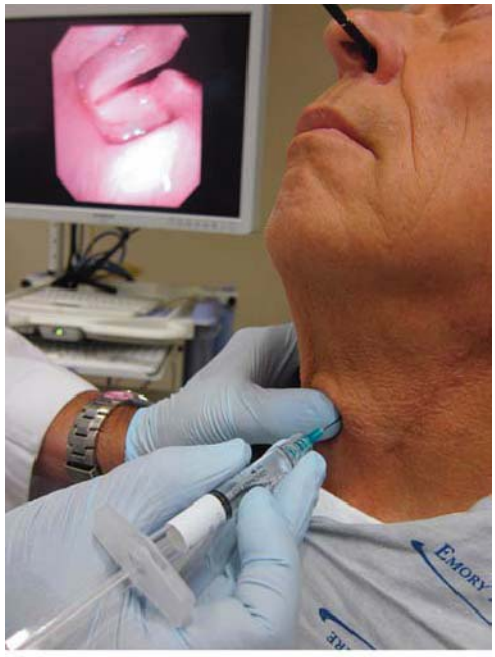
Transthyroid Cartilage or Transcricothyroid Membrane Approach

The skin and soft tissue overlying the thyroid cartilage, down to the level of the perichondrium, should be anesthetized (Fig. 73.5A). The goal of these two approaches


A



B


C


D

Figure 73.5 **A:** Landmarks for transthyroid cartilage and transcricothyroid approaches for vocal fold injection. Shown are the thyroid notch ("V") that marks the midline, inferior border of the thyroid cartilage (*thin line*), and the cricothyroid space (*thick line*). The *dotted circle* shows the area of skin that should be anesthetized. **B:** Transthyroid cartilage approach for vocal fold injection. The needle is inserted through the thyroid cartilage at a point approximately 6 to 12 mm lateral to the midline and 3 to 5 mm above its inferior border. The angle of the needle insertion is exactly perpendicular to the lamina of the thyroid cartilage. **C:** Transthyroid cartilage approach for vocal fold injection. **D:** The needle is seen "tenting" the mucosa from within the right vocal fold to confirm needle position during the transthyroid cartilage and transcricothyroid approaches.

is to conduct the injection without entering the lumen of the larynx; that is, the path of the needle is entirely submucosal. In theory, these procedures can be done without topical laryngeal anesthesia. However, we prefer to use topical anesthesia in case the laryngeal mucosa is breached—this prevents patient discomfort and allows for the procedure to continue uninterrupted.

For the transthyroid cartilage approach, a 23-gauge needle is inserted through the thyroid cartilage at a point approximately 6 to 12 mm lateral to the midline and 3 to 5 mm above its inferior border. The angle of the needle insertion is exactly perpendicular to the lamina of the thyroid cartilage (Fig. 73.5B and C). Once through, the tip of the needle can be used to "tent" the overlying mucosa without piercing it to confirm needle position prior to injection (Fig. 73.5D). Significant calcification of the thyroid cartilage in older patients may make this approach impossible. The Casiano transcervical laryngeal injection medialization needle (Medtronic Xomed, Jacksonville, FL) may help overcome this limitation.

The transcricothyroid membrane approach is similar to that used for botulinum toxin injection into the vocal fold. A 23-gauge needle is inserted approximately 5 mm lateral to the midline of the thyroid cartilage just below its inferior border. Once past the inferior border, the needle tip is aimed cephalad and laterally. As with the transthyroid cartilage approach, once in the vocal fold, the tip of the needle can be used to "tent" the overlying mucosa without piercing it to confirm needle position prior to injection. If the surgeon has difficulty locating the tip of the needle, the airway can be entered in the midline and the needle tip visualized prior to insertion into the vocal fold. For this reason we prefer using topical anesthesia in all patients.

The disadvantage of both of these techniques is that they are partially blind—apart from "tenting" the mucosa, the tip of the needle is not seen. Thus, it is more difficult to determine the exact depth of injection into the vocal fold.

Injection Materials

Awake office-based injections have been facilitated by the development of a variety of safe injectable materials. Any material that can be injected under general anesthetic can be injected in the office, except autologous fat. Experience with injection techniques is recommended prior to using long-lasting injectable materials. The types of materials available to be injected are covered in more detail elsewhere (see Chapter 69).

Postprocedure Care

Patients are advised to expect a poor voice immediately postprocedure due to edema and overcorrection. This will slowly improve over the subsequent 1 to 2 weeks. Postprocedure pain is usually minimal, and acetaminophen will typically suffice.

Potential Complications

Overall, it has been shown that awake vocal fold injections are safe with a very low complication rate (17,20,21,26,27). The most serious potential complication is airway obstruction, from overinjection, edema, or development of a hematoma. Patients who are unable to stop their anticoagulant medications are theoretically at a higher risk of bleeding; however, it is still a rare occurrence. Infraglottic submucosal collections of injectable are possible, most likely due to improper needle placement during injection (27). It has also been hypothesized that migration of material postinjection may lead to undesirable results.

Injection into the superficial lamina propria of the vocal fold is likely the most common significant complication. This will cause impairment of the normal vibratory function of the vocal fold, resulting in prolonged dysphonia. A superficial injection may necessitate removal under general anesthetic, especially if a long-lasting injectable such as calcium hydroxylapatite was used (28). Mathison et al. (21) did find that this complication occurred more frequently with awake injections compared to those done under general anesthetic.

LASER PROCEDURES

Awake laser procedures have revolutionized the management of certain laryngeal pathologies. As with all awake procedures, the risks of general anesthesia can be avoided in those with significant medical comorbidity. Furthermore, they allow certain laryngeal pathologies, such as recurrent respiratory papillomas and glottal dysplasia, to be treated at the earliest sign of recurrence as opposed to the traditional approach of waiting for more significant disease in an attempt to minimize exposure to repeated general anesthesia. This allows for a lower patient and surgeon threshold for conducting a therapeutic procedure.

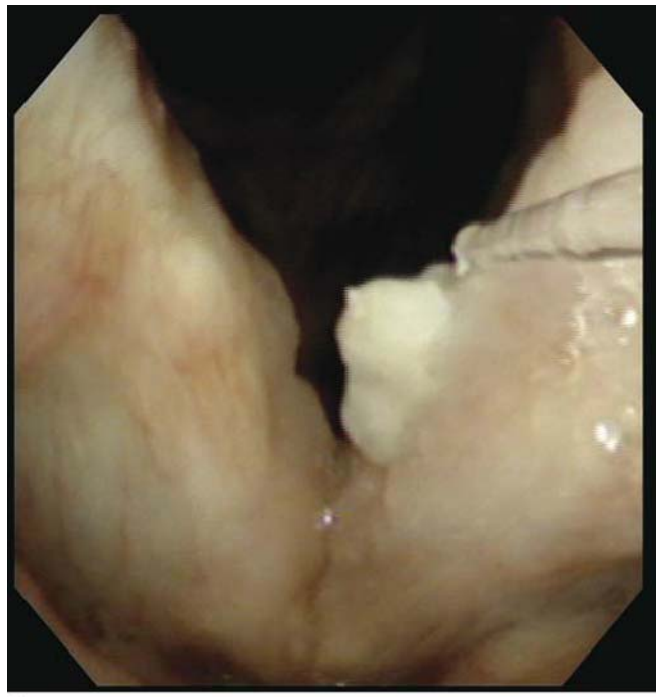
Awake laser procedures are well tolerated in patients who have received adequate topical anesthesia (29–31). Most patients experience minimal pain, typically do not require any postoperative analgesia, and prefer the awake procedures to procedures done under general anesthetic (12). Studies have shown that awake laser treatment of a variety of laryngeal pathologies is effective and safe. Complication rates are very low, with patient mild discomfort during the procedure being the most common complication (29–32). It should be emphasized that appropriate laser safety precautions by the surgeon, patient, and other staff involved are essential.

Laser Selection

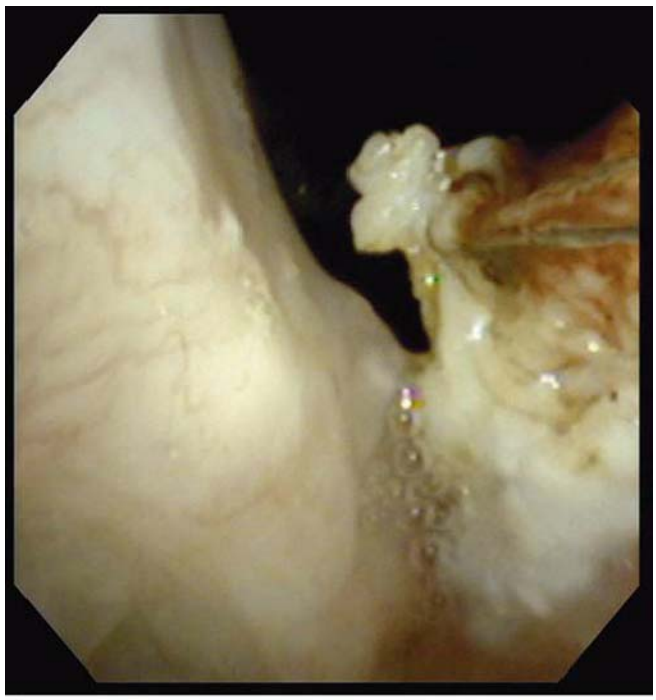
The ideal laser for laryngeal surgery should have superficial penetration, produce minimal collateral thermal injury, and be able to cut and coagulate (1). For awake office-based laser procedures, the laser must be deliverable through a fiber that can be passed through the working channel of a flexible



A



B



C

Figure 73.6 **A:** Patient and surgeon positioning for awake office-based laser procedure. **B:** Recurrent respiratory papillomas of the true vocal folds being treated with the pulsed KTP laser. Noncontact mode is being used to ablate the superficial papilloma while avoiding any bleeding. Notice the blanched color of the treated papilloma. **C:** Treatment of papillomas on the true vocal folds with pulsed KTP laser in contact mode. This allows for removal of the treated superficial papilloma and further treatment of deeper papilloma.

endoscope (2 mm) (Fig. 73.6A). Each laser has a specific energy absorption spectrum, thus targeting a distinct chromophore. This is what determines the effect of a particular laser on each tissue type. This effect is further determined by the laser power, pulse width and interval, and spot size. The tissue characteristics further influence the interaction, such as the distribution of the chromophore and the heat dissipation ability of the tissue. The commonly described lasers for awake laryngeal surgery are discussed here.

CO_2 (Wavelength 10,600 nm; Chromophore Water)

The CO_2 laser was the first laser used for laryngeal surgery and has remained popular as it fulfilled almost all of the above properties of an ideal laser. Until recently, the CO_2 laser was not able to be delivered via flexible fiber and was limited to mirror reflected line-of-sight surgery, typically with an operating microscope.

However, with the development of the photonic bandgap fiber assembly (OmniGuide, Cambridge, MA), the

CO_2 laser can now be delivered through a fiber that can be passed through the working channel of a flexible endoscope (33–36).

Due to the fact that there is a high concentration of water in laryngeal tissue, CO_2 laser energy is dissipated quickly without deeper penetration (35). It cuts through tissue with minimal collateral thermal injury—one of the major reasons for its popularity for laryngeal surgery.

Thulium (Wavelength 2,013 nm; Chromophore Water)

The thulium laser has similar properties to the CO_2 laser due to having water as its target chromophore. It has similar cutting capabilities; however, its coagulation capabilities are superior providing excellent hemostasis (37). It can be delivered through a small flexible glass fiber, not requiring the expensive fiber required for flexible CO_2 laser delivery. It does seem to have a greater thermal effect on tissues; however, postoperative healing is clinically similar to that observed with CO_2 laser (37). The thulium laser can be used in contact and noncontact modes, a distinct advantage in awake laser surgery.

Pulse Dye Laser (Wavelength 585 nm; Chromophore Oxyhemoglobin)

The mechanism of action of the pulse dye laser (PDL) is presumed to be ablation of the blood supply of a lesion, leading to involution. Due to its selectivity for oxyhemoglobin, it is thought that tissue damage is confined to the walls of microvessels and the surrounding perivascular tissue ("photoangiolysis"). However, it has also been shown to be effective for nonvascular lesions, suggesting that another mechanism of action is also at play. This laser can also be used in contact or noncontact mode (29).

Potassium Titanyl Phosphate Laser (Wavelength 532 nm; Chromophore Oxyhemoglobin)

Similar to the PDL, it is theorized that the potassium titanyl phosphate (KTP) laser ablates the blood supply of a lesion due to its chromophore being oxyhemoglobin. However, its wavelength is more strongly absorbed by oxyhemoglobin, and it has a longer pulse width when compared to the PDL. It is thought that this results in more efficient intravascular coagulation and avoidance of vessel rupture and bleeding that can be encountered with the PDL (30,38). Furthermore, the KTP laser can be used in both contact and noncontact modes, as well as either pulsed or continuous, the latter being useful for hemostatic cutting. However, when used in this setting it has the potential to create more thermal injury when compared to the CO_2 or thulium lasers (1).

Clinical Indications

Papilloma

Microsurgical CO_2 laser excision and ablation or cold steel excision has classically been the standard surgical management for recurrent respiratory papillomatosis (RRP). However, due to the selectivity of the PDL and KTP lasers for oxyhemoglobin, and the abundant vascular supply to papillomas, these lasers have become popular in treating RRP in the office setting (Fig. 73.6B and C). Several studies have shown that these lasers provide effective and safe treatment for papillomas (29,31,32,39,40). Thulium and flexible CO_2 lasers have also been used for awake treatment of papillomas (32,37).

Patients presenting with a new diagnosis of RRP should likely be treated for the first time under general anesthetic for appropriate disease mapping and biopsies. Subsequent procedures can be done with the patient awake as long as the amount of disease is not too bulky. The amount of disease that can be treated awake will depend on each patient's tolerance of the procedure as well as surgeon experience. Bulky disease can be treated superficially (Fig. 73.6B) and then removed with a combination of contact with the fiber and suctioning with the flexible scope (Fig. 73.6C). This will expose untreated disease below, which can be treated further.

Awake procedures allow disease to be treated at the earliest sign of recurrence as opposed to the traditional approach of waiting for more significant disease in an attempt to minimize exposure to general anesthesia. Both the patient and surgeon can have a lower threshold for conducting a procedure.

Glottal Leukoplakia/Dysplasia

There are a variety of management options for patients with glottal leukoplakia or dysplasia that include biopsy and observation, laser resection or ablation, and phonomicrosurgical excision. Patients with recurrent or persistent glottal disease, however, often pose a dilemma as the surgeon will want to avoid the negative consequences of repeated general anesthesia and vocal fold surgery. Thus, patients are often observed until their symptoms become quite problematic or the surgeon becomes concerned about the clinical behavior of their glottal disease. Awake laser treatment offers the surgeon and patient a low-morbidity and low-cost option for treatment of these problems (29,30). Given the importance of the microcirculatory supply to the pathogenesis of these lesions, the PDL and KTP lasers have gained popularity for their presumed photoangiolytic properties and have been shown to be effective and safe (29–32,40).

Vascular Lesions

Vascular ectasias and varices often require surgical treatment as they can rupture, causing vocal fold hemorrhage, and they can impair the normal vibratory pattern of the vocal fold. Due to the presumed photoangiolytic properties of the PDL and KTP laser, these have been successful in treating such lesions (31,40,41).

Other Laryngeal Pathology

A variety other lesions have been treated with mixed success using awake laser procedures, including vocal fold polyps, granulomas, Reinke edema, and laryngeal amyloidosis (31,32,42–45).

TRANSNASAL ESOPHAGOSCOPY

TNE has become an essential tool in the evaluation and management of patients with dysphagia, head and neck cancer, and gastroesophageal or laryngopharyngeal reflux disease. Studies have shown that TNE is equivalent to conventional esophagoscopy in terms of diagnostic capabilities (46). Furthermore, it is safe and well tolerated with topical anesthesia and no sedation (13). TNE is covered in more detail in Chapter 57.

MISCELLANEOUS PROCEDURES

Secondary Tracheoesophageal Puncture

Traditionally, secondary tracheoesophageal puncture (TEP) is done under general anesthesia using a rigid esophagoscope. However, with the development of TNE, it is possible to safely conduct this procedure with local anesthetic in the office setting (47,48). The TNE scope is used to visualize the upper esophagus, and air insufflation is used to provide distension. As the light of the TNE scope transilluminates at the tracheostoma, an appropriate site for the puncture can be chosen. Local anesthetic should be injected into the site and a puncture made with an 18-guage needle. The TNE scope should be used to insufflate the esophagus to provide maximal anteroposterior distension to prevent injury to the posterior esophageal wall. The puncture site can then be widened with standard TEP dilators over a guide wire passed through the needle or with an 11-blade and a hemostat, all under direct vision of the TNE scope. Once adequately dilated, a 14-French red rubber or Foley catheter is passed through the puncture into the esophagus.

Airway and Esophageal Dilation

Dilation of airway and esophageal stenosis has long been performed under general anesthesia using rigid or flexible endoscopes and a variety of dilators, including hydrostatic balloon dilators.

Balloon tracheal or subglottic dilation can be performed awake with adequate topical anesthesia. It avoids the risks of general anesthesia and provides an option in patients with a difficult or impossible to expose larynx with standard rigid endoscopy. There is a risk of tracheal laceration with balloon dilation—in a large series of patients, approximately 50% experienced a laceration (49). However, none of the lacerations were transmural. The vast majority were superficial and of no clinical significance.

A guide wire is passed through the working channel of a flexible scope that has been introduced through the nasal cavity. The guide wire is then advanced through the area of stenosis. The scope is removed while leaving the guide wire in place. The scope is reintroduced beside the guide wire such that the entire procedure is visualized. An appropriate-sized balloon catheter is then passed over the guide wire, into the area of stenosis, and inflated for 30 seconds or until the patient requires a breath. This procedure has been reported to be safe and effective (50); however, formal data in the literature are lacking. The use of lasers to make radial incisions in an area of stenosis prior to balloon dilation has also been described (50,51), but further research is required to determine if these techniques are safe and effective in the awake setting.

A similar technique has been described for esophageal dilation and seems to be safe and well tolerated with only topical anesthesia (52). However, it is unknown if the awake procedure provides similar efficacy to balloon dilations performed under sedation or general anesthetic.

CONCLUSIONS

Awake office-based laryngeal procedures offer both the patient and surgeon numerous advantages and benefits. In many cases, when carefully selected, awake procedures allow the surgeon to achieve equivalent and sometimes superior results to those that can be achieved in the operating room. However, there are still certain instances where the advantages of the operating room setting and general anesthesia allow for a superior outcome. Insight, prudence, and sensible clinical judgment must be used when determining which treatment will provide the patient with the best possible outcome.

HIGHLIGHTS

- Awake office-based laryngeal procedures have experienced a resurgence in popularity secondary to numerous technologic advancements that permit precise, safe, and effective procedures.
- Use of only topical anesthesia avoids the risks associated with general anesthesia and maximizes patient convenience.
- Awake laryngeal procedures have been shown to be safe and effective for the treatment of a wide variety of laryngeal pathologies.
- Sensible clinical judgment is required when determining which patients and clinical problems can be dealt with effectively in an awake office-based setting.

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V

Trauma

Grant S. Gillman *Jonathan M. Sykes* *Stephen S. Park*

Principles of Trauma

74

Peter J. Koltai *James Chan*

Trauma is the leading cause of death and disability of Americans younger than 40 years (1). In the United States, more than 150,000 violent deaths occur each year, and more than 500,000 trauma victims are left with permanent disabilities. Annually, approximately 30 to 40 million visits are made to emergency departments for injury treatment (2). The cost to our society is significant. In 2000, $117 billion was spent by Americans, which accounts for 10% of all medical expenditures (3). This is comparable to the percentages attributable to other public health issues such as obesity (9.1%) and smoking (14.4%) (4).

Deaths from trauma fall into three categories—immediate, early, and late. Immediate death occurs within minutes of injury and is caused by acute airway obstruction or major vessel disruptions of the brain, heart, or other internal organs. Early death occurs in the first few hours after injury and is associated with excessive hemorrhage, blood accumulation around the brain, or respiratory failure. Late death occurs days to weeks after trauma and is caused by sepsis and multiple organ failure.

More than half the deaths due to trauma occur within several minutes of the accident. Because immediate treatment is rarely available, accident prevention is the most logical way to decrease this number. Many public health injury prevention strategies have been successfully implemented including use of seat belts (5) and bicycle helmets (6), implementation of blood alcohol limits (7), and fire safety education including widespread smoke alarm use (8). Early deaths account for about one-third of all trauma deaths. Although not all of these patients can be saved, many can be treated effectively with rapid and definitive response. This requires a parallel system of coordinated prehospital care and hospital care at dedicated trauma centers.

Death at an accident scene is usually related to head injury with associated hypoventilation due to loss of consciousness. Intubation in the field can thus be lifesaving. Massive hemorrhage is another common cause of prehospital death. When intravenous catheters are inserted at the scene, circulatory volume can be maintained until the hemorrhage can be surgically controlled. Rapid transport to a hospital with an organized team of surgeons, anesthesiologists, and trauma professionals is vital for the effective treatment of trauma patients. In urban areas, ambulances usually provide efficient transportation to the hospital. In rural areas, distance becomes a critical factor and helicopters or airplanes can be lifesaving.

Trauma patients undergo rapid and severe changes in normal body function, including hemorrhage, tissue hypoxia, cellular damage, and disrupted function of vital organs. The physiologic response to massive injury is dramatic and occurs both systemically and locally. Systemic responses include activation of the clotting sequence, shifts of extravascular fluid into the circulatory system, redistribution of blood flow to the heart and brain, and alterations in renal and pulmonary function to maintain acid–base balance. Metabolic changes include skeletal muscle and fat breakdown to provide substrate for the body's fuel-intensive response to trauma. Local responses include immunologic activation with leukocytes mobilization, acute-phase protein synthesis, inflammatory cell migration into the injured area, and onset of fibroblast proliferation and blood vessel ingrowth to begin the wound repair process. Understanding the restorative mechanisms that occur in an acutely injured patient is necessary for the complex task of treating these patients with regard to fluid maintenance, nutritional requirements, wound healing, and susceptibility to infection (9,10).

NEUROENDOCRINE RESPONSE

Hemostatic adjustments to trauma are mediated by the neuroendocrine system. Stimuli such as hemorrhage, hypoxia, and tissue damage stimulate a graded response that increases to a peak level, after which additional response is no longer possible. Pain is the first signal from

the central nervous system (CNS) to reestablish homeostasis. The hypothalamic response to pain stimulates the pituitary gland to release corticotropin, which stimulates adrenal secretion of cortisol. Pain causes elaboration of antidiuretic hormone for fluid conservation. Pain activates the sympathetic nervous system and stimulates direct adrenal secretion of epinephrine.

Blood loss stimulates vascular pressure and volume receptors and precipitates a CNS-mediated decrease in cardiac output, an increase in peripheral vascular resistance, and redistribution of blood flow to vital organs. Hypoxia and hypercapnia cause chemoreceptor stimulation, vasomotor activation, and increased respiratory drive. At later stages, stimulation of the hypothalamus by interleukin 1 initiates the hypermetabolic response to injury manifested by the elevated temperatures experienced by injured patients (11,12).

The hormonal response to trauma is marked by a rise in the catabolic hormones, corticotropin, cortisol, growth hormone, glucagon, epinephrine, and norepinephrine. In contrast, plasma concentrations of the primary anabolic hormone, insulin, are decreased due to CNS-mediated sympathetic inhibition of the pancreas. Posttraumatic hyperglycemia provides non–insulin-mediated tissues such as the brain with a preferential supply of glucose.

Glucagon, cortisol, and catecholamines maintain blood glucose levels and prevent hypoglycemia. The primary function of glucagon, which is produced in the pancreas, is to promote gluconeogenesis in the liver. After trauma, direct sympathetic stimulation of the pancreas enhances glucagon secretion. Corticotropin release by the anterior pituitary gland causes adrenal production of cortisol, which promotes the breakdown of skeletal muscle into amino acids and facilitates gluconeogenesis in the liver. The hypoglycemic effect of cortisol counteracts insulin.

Release of catecholamines is the most fundamental hormonal reaction to trauma. Epinephrine, released by the adrenal medulla in response to direct neurostimulation, is a potent regulator of the circulatory system and systemic metabolism. Epinephrine's hemodynamic effects include vasoconstriction, increased cardiac rate, and increased myocardial contractility and conductivity. Epinephrine also promotes glucose production by enhancing hepatic gluconeogenesis and inhibiting insulin release. Norepinephrine, the primary sympathetic nervous system neurotransmitter, exerts a direct effect on the circulatory system and vital organs. With massive and prolonged sympathetic discharge, norepinephrine can enter the bloodstream and exerts a direct vasoconstrictive effect on the vascular system similar to that of epinephrine (9,10).

METABOLIC RESPONSE

The postinjury period is characterized by catabolism. Negative nitrogen balance, hyperglycemia, and heat production reflect the increased energy requirements for ongoing reparative and inflammatory processes. Increased energy expenditure is due to sustained release of circulating catecholamines and increased activity of the sympathetic nervous system. The primary energy source during this period comes from oxidation of lipids promoted by the elaboration of the catabolic hormones (9,10).

Although fat is the primary energy source after injury, protein is also broken down to produce energy. In a fasting catabolic patient, glucose can be generated only from the breakdown of protein. Lipid breakdown to triglycerides and glycerol contributes minimally to form precursors for the synthesis for new glucose. As a result, protein is rapidly broken down to form precursors for new glucose synthesis in a trauma patient in the catabolic state. The result is rapid loss of muscle mass. The depth and the length of the catabolic state are related to trauma severity. Although it represents an adaptive mechanism, a persistently prolonged and severe catabolic state leads to severe malnutrition, multiple organ failure, and death (9,10,13–15).

TREATMENT OF A PATIENT WHO HAS SUSTAINED TRAUMA

The key to improving survival and managing disability in the trauma patient are the initial evaluation and resuscitation performed at a dedicated trauma center. The American College of Surgeons has developed a protocol taught in advanced trauma life support courses to improve the care of injured patients during the early hospital phase. It is based on a primary and secondary survey approach that allows physicians to handle the complex, multisystem problems of trauma patients. This treatment algorithm can be divided into four categories—primary survey, resuscitation, secondary survey, and definitive care.

The primary survey involves hierarchical assessment of airway, breathing, and circulation. The purpose is to identify extreme, life-threatening injuries and institute immediate life-sustaining maneuvers. Resuscitation is performed simultaneously with the primary survey. The secondary survey consists of a rapid but systematic head-to-toe physical examination with the patient completely disrobed. This global assessment is done to identify all potentially life-threatening and occult injures. An important part of the primary and secondary survey are radiographic studies including the use of ultrasonography. Samples are drawn for baseline blood studies, typing, and cross-matching. Once these priorities have been addressed, vital signs are rechecked. When the patient's condition is stable, a detailed management plan is established.

Primary Survey

Airway

The foremost emergency measure is establishing the airway, which may be lost to a variety of causes. The oropharynx, larynx, and trachea can be obstructed by secretions,

blood, and foreign bodies. Oropharyngeal airway collapse can occur with loss of consciousness and from facial fractures (Chapter 78). Direct trauma to the larynx and trachea may cause airway obstruction below the oropharynx (see Chapter 77). Manuevers to secure an adequate airway range from the simple to the complex and begins with manual cleaning of the oropharynx followed by suctioning of secretions (Chapter 63).

The primary risk during early airway management is neck movement when there is an occult cervical spinal fracture. The airway must be controlled with the assumption that such a fracture exists. The neck must be completely immobilized in a neutral position. One member of the trauma team must be assigned to kneel at the head of the stretcher to maintain inline manual head stabilization and avoid hyperextension by holding the cervical spine with the hands while immobilizing the head with the forearms (Fig. 74.1). Traction on the head is avoided, because distraction with further injury to the spinal cord can occur if the patient has an unstable cervical spinal injury. Once the neck of an unconscious patient has been secured, forward traction of the mandible is performed to overcome pharyngeal collapse (Fig. 74.2). The next step is oropharyngeal airway placement in the unconscious patient. If the patient is conscious, a nasopharyngeal airway is used. Once the airway has been established and the patient is spontaneously breathing, supplemental oxygen can be provided through nasal prongs or a face mask.

When these simple measures are unsuccessful, more aggressive airway management is needed. Nasotracheal intubation is the preferred technique for establishing an airway in a conscious patient who may have a cervical spinal injury because it can be done without excessive neck mobility. Nasotracheal intubation is better tolerated by an awake patient than is orotracheal intubation and does not necessitate sedation or muscle relaxation. Nasotracheal intubation is precluded if the patient has extensive maxillofacial injuries.

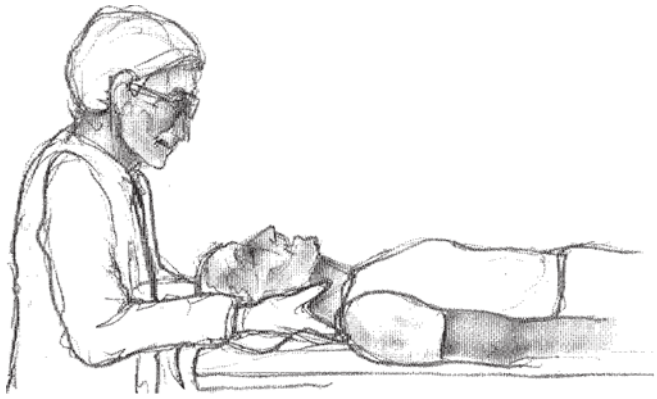


Figure 74.1 Stabilization of the cervical spine during primary survey of an injured patient.

If the nasotracheal route cannot be used, orotracheal intubation is the next step. In ideal circumstances, a cross-table lateral cervical spine radiograph is obtained before orotracheal intubation to evaluate for a possible cervical spinal fracture. It is nevertheless important to remember that even a normal cross-table lateral radiograph of the cervical spine does not definitively exclude the presence of cervical spinal fracture or instability (16). When emergency airway control with orotracheal intubation is indicated, intubation proceeds with inline stabilization whether or not radiographs have been obtained. Bag-mask intubation can be an effective method of maintaining the airway until radiographs are obtained. If the patient is unconscious and cervical spinal injury has been ruled

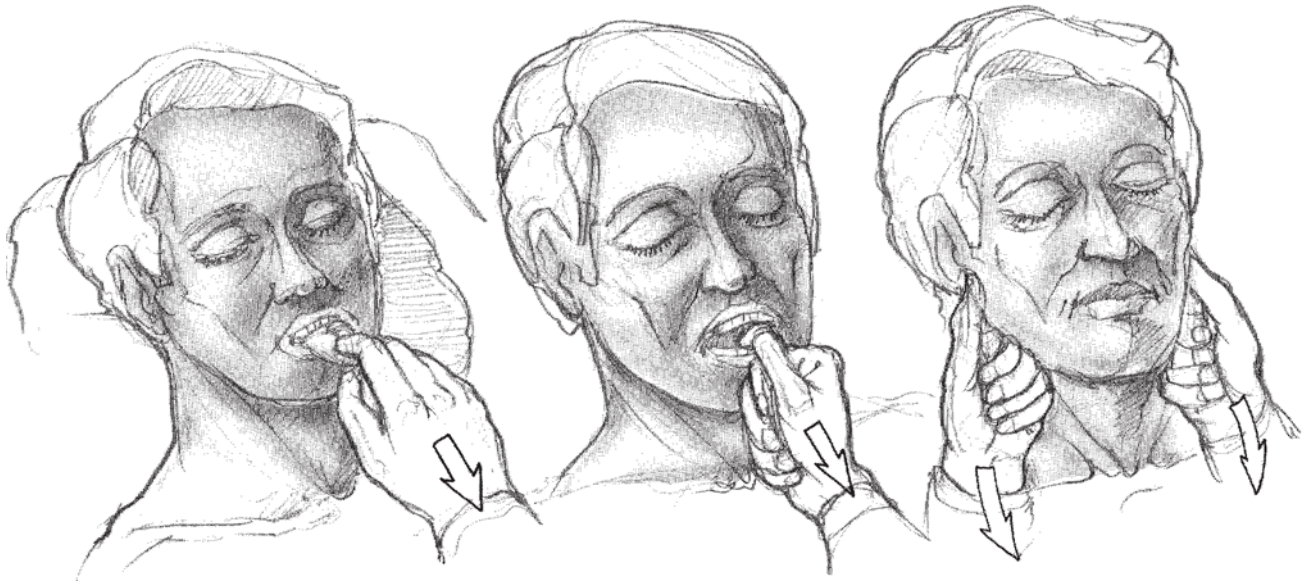


Figure 74.2 Once the neck of an unconscious patient has been secured, forward traction of the tongue and mandible is performed.

out, orotracheal intubation can be readily accomplished. A patient who is awake must be paralyzed with succinylcholine for successful orotracheal intubation.

After intubation, the chest is auscultated to ensure that the tube is in the trachea and not in the esophagus or in one of the mainstem bronchi. Correct endotracheal tube positioning can be confirmed reliably by the presence of end-tidal carbon dioxide. Carbon dioxide from the lungs can be detected rapidly by observing a color change on a disk that can be connected rapidly to the endotracheal tube. If no carbon dioxide is detected, the endotracheal tube is in the esophagus, and a new airway is attempted. If the patient is in cardiac arrest, end-tidal carbon dioxide is unreliable in confirming the positioning of an endotracheal tube. A follow-up chest radiograph to confirm the position of the tube must be obtained expeditiously.

If an endotracheal tube cannot be inserted, as when a patient has major facial fractures or has sustained laryngotracheal trauma, surgical airway intervention may be needed. There are four surgical methods of obtaining an airway—needle cricothyrotomy, conventional cricothyrotomy, tracheotomy, and percutaneous transtracheal ventilation.

For children, needle cricothyrotomy is the best procedure. The procedure is performed by placing a number 12 or number 14 intravenous cannula with a plastic sheath through the cricothyroid membrane into the tracheal lumen. Once in the airway, the needle is withdrawn and the plastic sheath is advanced. When properly positioned, the sheath is connected with intravenous tubing to wall or bottled oxygen at 50 pounds per inch of pressure (about 15 L oxygen per minute). Ventilation is accomplished by means of 1-second intermittent injections of oxygen followed by 4-second exhalations. Patients can be maintained for up to 30 minutes with this technique, after which hypercapnia becomes a problem.

Surgical cricothyrotomy is the preferred approach for adult patients who need surgical airway intervention (Fig. 74.3). It consists of a small vertical skin incision over the area of the cricothyroid membrane followed by a horizontal incision through the cricothyroid membrane itself. The blunt end of the scalpel is inserted between the cricoid and the thyroid cartilages and rotated 90 degrees to make an opening through which an endotracheal tube or tracheostomy tube can be inserted.

For patients with laryngeal trauma, tracheal trauma, or tracheal disruption, cricothyrotomy is inadvisable, and emergency tracheotomy is performed. Percutaneous transtracheal ventilation, a technique similar to needle cricothyrotomy, is an acceptable alternative in the treatment of these patients. In the trauma patient, continuous pulse oximetry monitoring is extremely helpful in determining the adequacy of oxygenation and is used in the care of all critically injured patients to allow early detection of arterial oxygen desaturation.

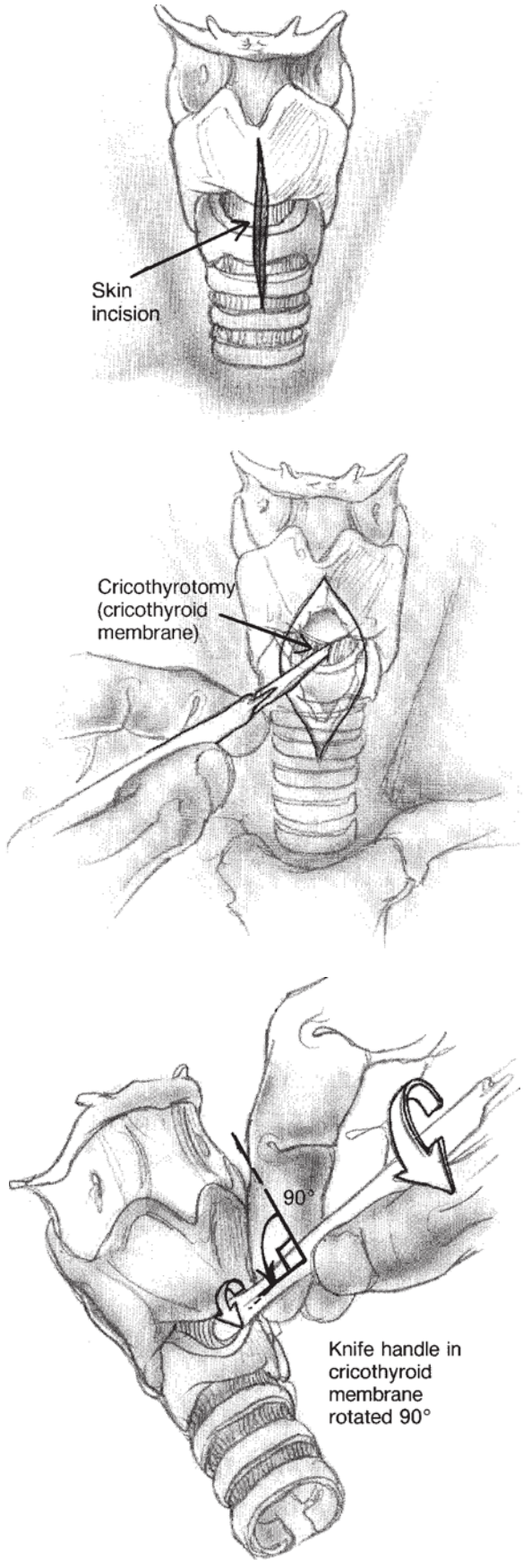


Figure 74.3 Cricothyrotomy.

Breathing

Loss of respiratory drive among trauma patients is most commonly caused by severe head trauma. Ventilation is provided with a bag-mask until cervical spinal injury is ruled out. An endotracheal tube is then inserted, and mechanical ventilation begun. As part of the primary survey, injuries to the chest wall and structures within the thoracic cavity that can cause hypoventilation must be recognized and rapidly managed. These injuries include sucking pneumothorax, massive pneumothorax, and tension pneumothorax.

Sucking pneumothorax occurs when there is a defect in the chest wall larger than the tracheal diameter. Because of reduced resistance through this opening, inspiratory and expiratory efforts result in movement of air through the opening in the chest wall into the pleural space rather than through the trachea. Occluding the chest wall defect and chest tube placement followed by intubation with positive pressure ventilation is the best management of this injury.

Massive hemothorax is vented promptly. Although blood loss of 1,000 to 1,500 mL into the thoracic cavity almost always necessitates emergency thoracotomy, initial management is aimed at decompressing the chest cavity so that adequate ventilation can proceed. Tube thoracotomy is performed by means of making an incision at the fourth or fifth intercostal space in the midaxillary line (Fig. 74.4). A short subcutaneous tunnel is developed by means of finger dissection, and the tube is passed posterosuperiorly along an intrapleural tract toward the pleural apex. Continued hemorrhage at a rate of greater than 200 mL/h is an indication for thoracotomy.

Tension pneumothorax develops when a pleural, bronchial, or tracheal tear allows air to be forced into the pleural space without a means of egress. The result is collapse of the ipsilateral lung. As pleural pressure increases, the mediastinum and trachea shift to the opposite side, compress the contralateral lung, and compromise oxygenation. The mediastinal shift kinks the inferior and the superior vena cava; the kink impairs venous return, and hypotension develops. Signs and symptoms of tension pneumothorax are acute shortness of breath, tracheal deviation away from the injury, increased resonance to percussion, distention of the neck veins, and decreased breath sounds over the injured hemithorax. Tension pneumothorax is a clinical diagnosis made on these clinical grounds. Diagnostic chest radiographs should not delay chest decompression as this may lead to the patient's death. Tension pneumothorax is managed by means of allowing air to escape through needle thoracocentesis with a large-bore, 12-gauge intravenous cannula inserted into the second intercostal space in the midclavicular line (Fig. 74.5), followed by definitive treatment with chest tube insertion. Pneumothorax also can cause hypotension owing to its effect on myocardial performance. Any patient who remains in shock after chest trauma needs empirical chest ventilation.

Circulation and Shock

Once the airway and breathing have been reestablished, the next step is to assess the adequacy of the circulatory system. Shock is the clinical manifestation of the inability of the heart to maintain adequate circulation to vital organs. This low-flow state can be caused by cardiac dysfunction,

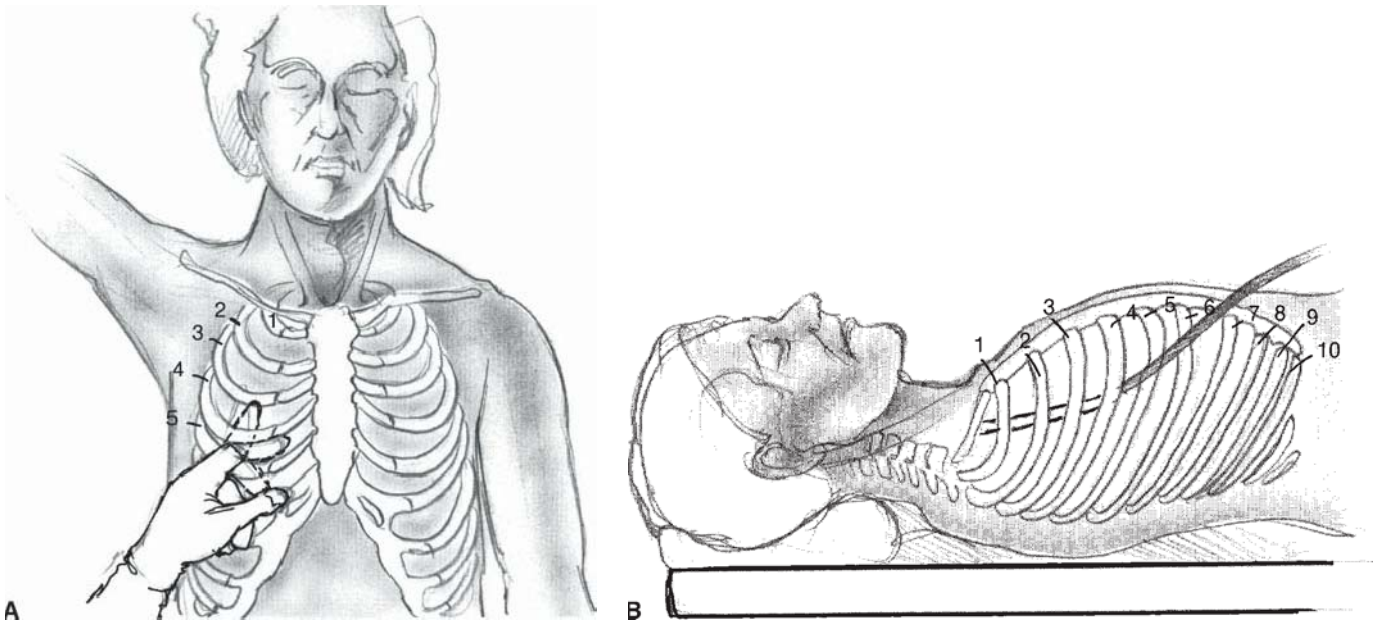


Figure 74.4 Tube thoracostomy. An incision is made in the fourth or fifth intercostal space in the midaxillary line. **A:** A short subcutaneous intrapleural track is developed by means of finger dissection. **B:** The tube is passed posteriorly and superiorly toward the pleural apex.

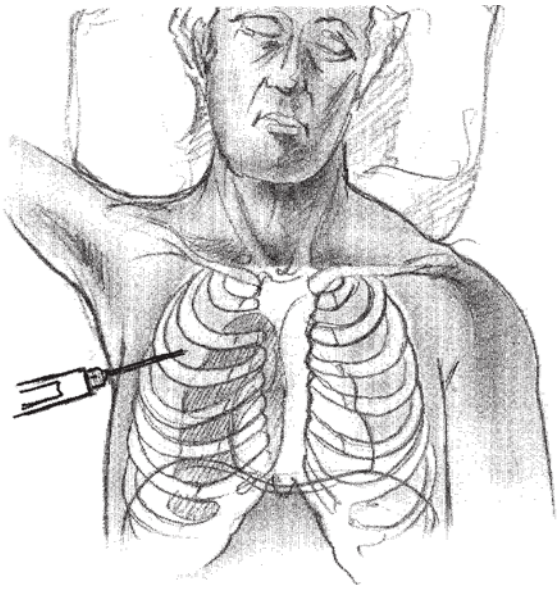


Figure 74.5 Needle thoracentesis for management of pneumothorax. The needle is inserted into the second intercostal space in the clavicular line.

loss of blood volume, loss of vascular resistance, and an increase in venous capacity (13). The cellular response to shock is a shift from aerobic to anaerobic metabolism in nonvital organ systems. The result is lactic acidosis. If hypoperfusion persists, oxygen delivery to vital organs becomes inadequate, and acidosis deepens. Unless oxygenation and perfusion are restored, organ failure progresses, and the patient dies.

The clinical presentation of shock depends on the severity. A patient with mild shock may be anxious and restless; if shock is severe, the patient appears listless or exhausted. The skin is cool and sallow with decreased capillary filling in the nail beds. Thirst, nausea, and vomiting are common. Blood pressure is low, and the pulse is fast and weak. Poor filling of peripheral veins makes it difficult to place intravenous catheters. There are four categories of shock—hypovolemic shock, neurogenic shock, cardiogenic shock, and septic shock. The first three are associated with the acute phase of trauma.

Hypovolemic Shock

Hypovolemia is the most common cause of shock after trauma. Hemorrhage is assumed to be the cause unless proved otherwise. Attempts have been made to classify the severity of hemorrhagic shock as follows to give better guidelines for resuscitation:

Class I hemorrhage is the loss of about 15% of blood volume. The primary manifestation is mild anxiety.

Class II hemorrhage is the loss of 15% to 30% of blood volume. The result is tachycardia and tachypnea, anxiety, decreased capillary refill, and decreased urine output. Supine blood pressure remains normal.

Class III hemorrhage is the loss of 30% to 40% of blood volume. Patients often are extremely anxious or combative and have marked tachycardia and tachypnea, prolonged capillary refill time, and a marked decrease in urine output. Only at this stage of severe hypovolemia does supine hypotension occur.

Class IV hemorrhage is the loss of more than 40% of blood volume. The result is marked hypotension and tachycardia. Urine output is almost completely shut off, and mental status can range from anxiety to coma. Blood loss of this magnitude is often fatal.

Hypovolemia should be managed with rapid volume replacement. Patients needing acute fluid resuscitation are usually those in whom venous access is most difficult. For most patients, 14-gauge intravenous catheters can be inserted into the antecubital veins with little difficulty. If the systolic blood pressure is so low that percutaneous access in the antecubital spaces is precluded, greater saphenous vein cutdown can be performed. Percutaneous femoral vein or subclavian catheterization is another alternative, but the surgeon must be familiar with the anatomic features of the area (1–7,10,12).

Crystalloids, such as lactated Ringer solution or normal saline solution, are the preferred fluids for resuscitation. In adults, blood volume is about 7% of total body weight (about 5 L for a normal-sized man). In children, blood volume is 8% or 9% of total body weight; in infants, 10%. The requirements for crystalloid resuscitation can be based on the results of clinical assessment of the percentage of blood loss and the knowledge of the approximate blood volume of the patient. Circulating volume can be restored by infusing 3 mL crystalloid solution for each milliliter of estimated blood loss. This ratio can be much greater in massive hemorrhage. The crystalloid solution is infused as rapidly as possible until blood pressure and heart rate return to acceptable levels. Further fluid replacement can be monitored according to the adequacy of the urine output (1–7,10,12).

When crystalloid replacement is inadequate, blood replacement becomes necessary. As a rule, trauma patients who arrive in the emergency department with supine hypotension likely need transfusion. Blood is added to resuscitation when the crystalloid infusion exceeds 50 mL/kg. Cross-matched, type-specific blood rarely is available to acutely injured patients, but un-cross-matched type-specific whole blood can be obtained rapidly in most hospitals and rarely causes serious complications. If type-specific blood is unavailable, type O-negative (universal donor) blood can be given safely to a trauma patient in need of emergency blood transfusion. The risk of transfusion reactions with O-negative blood in this situation is minimal.

Substantial clotting problems can occur with massive crystalloid and blood replacement therapy for hemorrhagic shock. Although blood components are not used

in early resuscitation, dilutional coagulopathy can develop after substantial transfusion. This dilutional coagulopathy is managed with fresh-frozen plasma and platelet transfusion, depending on the degree of ongoing bleeding. Platelets and fresh-frozen plasma are administered according to the degree of coagulopathy, not the specific number of units of blood administered. As a rule, using fresh-frozen plasma can be considered after the tenth unit of banked blood and then after every fourth unit. Use of platelets can be considered after the fifteenth unit of blood, and then after every fifth unit. Coagulation profiles can be monitored.

Adjunctive steps can be helpful in the care of patients sustaining hemorrhagic trauma. In cases of external hemorrhage, the bleeding often can be controlled with minimal pressure. Tourniquets usually are not helpful, because direct compression can control blood loss. Blind clamping must be avoided to prevent injury to adjacent nerves. The scalp may be the source of profuse bleeding, and rapid temporary suturing may be needed.

Military antishock trousers (MAST), which are inflatable pants, can be placed around the patient's legs and pelvis to decrease circulation to the extremities and thereby improve central circulation. They are not meant to replace adequate fluid therapy but can be useful in the prehospital phase of the trauma delivery system. Caution must be exercised in using MAST because abdominal compartment inflation can impair respiration, and leg compartment overinflation for long periods can cause compartment syndrome.

Neurogenic Shock

The purpose of fluid restoration is to reestablish adequate perfusion to vital organs. Measurements such as blood pressure, heart rate, urinary output, and level of consciousness help measure the success of fluid resuscitation. When these signs do not change in response to adequate resuscitation, other causes must be suspected. One such cause can be neurogenic shock, which is caused by brainstem dysfunction or spinal cord injury that denervates the sympathetic nervous system. The result is vasodilatation and decreased peripheral vascular resistance and consequent loss of blood pressure. Neurogenic shock is characterized by the absence of tachycardia, warm extremities, and lack of anxiety in the presence of hypotension. No patient should be presumed to have neurogenic shock, despite evidence of neurologic injury, until all other causes of shock have been systematically evaluated and eliminated. Once this has been done, neurogenic shock management is fluid resuscitation to replete intravascular volume, vasopressors to restore lost vascular tone, and appropriate neurosurgical intervention (13).

Cardiogenic Shock

Cardiogenic shock is loss of circulatory perfusion because the myocardium cannot produce sufficient flow to maintain tissue oxygenation. Among trauma patients, cardiogenic shock is generally associated with three injuries: tension pneumothorax, cardiac tamponade, and myocardial contusion. Cardiogenic shock is suspected when hypotension persists despite appropriate resuscitation. The most common features of cardiogenic shock are distended jugular veins and elevated central venous pressure in the presence of hypotension. These signs may not occur until the patient has undergone adequate fluid replacement. Cardiogenic shock may coexist with hypovolemic shock.

A common feature of tension pneumothorax is impaired myocardial function due to decreased venous return. Increasing intrathoracic pressure distends the jugular veins and causes hypotension. In an emergency, tension pneumothorax can be confused with cardiac tamponade because both conditions are associated with hypotension and neck vein distention. In some instances, it is impossible to differentiate these two conditions, and empiric thoracocentesis is necessary on the side most likely to be affected. If there is a rush of air with restoration of hemodynamic status, the diagnosis of tension pneumothorax is confirmed. If not, the procedure is repeated on the opposite side of the chest. If the patient's condition does not improve, cardiac tamponade is considered, and the patient is empirically treated.

Cardiac tamponade in a trauma patient is caused by blood accumulation between the myocardium and its pericardial covering. Because the pericardium is nondistensible, small volumes of blood can accumulate in the acute setting resulting in marked myocardial impairment. The pathophysiologic changes leading to cardiogenic shock are caused by a decrease in ventricular filling during diastole and myocardial contractility impairment due to ischemia from coronary circulation impairment. The classic cardiac tamponade signs are hypotension, jugular venous distention, and distant heart sounds. The jugular veins may not become distended if the patient has hypovolemia; thus diagnosis often is made as the result of suspicion based on an injury such as a penetrating chest wound.

Emergency department treatment of a patient with cardiac tamponade is pericardiocentesis (Fig. 74.6). The procedure is performed by inserting a 14- or a 16-gauge catheter in the left subxyphoid position with the needle aimed toward the posterior portion of the left shoulder. Aspirating as little as 10 to 20 mL of blood can bring about dramatic improvement in myocardial function; however, frequent false-negative and false-positive results under extreme circumstances may prompt a left anterior thoracotomy with direct pericardial decompression.

Emergency thoracotomy is an option when a trauma patient does not respond to resuscitation and is in cardiac arrest. Other considerations for emergency thoracotomy include initiating direct cardiac massage and controlling massive hemothorax due to cardiac puncture or tears in the thoracic aorta.

Myocardial contusion, another cause of cardiogenic shock after trauma, is caused by blunt injury, typically

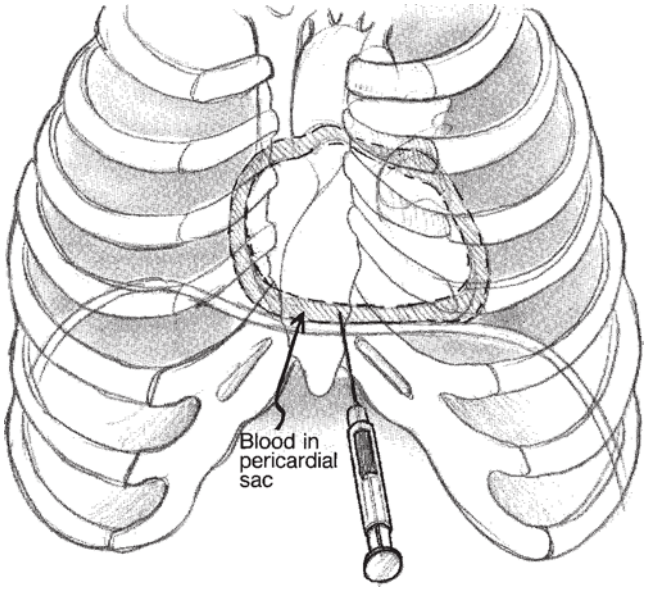


Figure 74.6 Pericardiocentesis for acute cardiac tamponade performed through the left subxyphoid approach.

when the chest hits a steering wheel. Physical signs include ecchymotic discoloration of the anterior chest wall and flail chest. Severe myocardial contusion is unusual, whereas blunt chest trauma is common. Marked myocardial contusion can be confirmed with transthoracic or transesophageal electrocardiography. Wall motion, valvular dysfunction, and the presence of pericardial fluid or tamponade can be seen with echocardiography. Management is aimed at preventing fluid overload while maintaining cardiac output and medically suppressing ventricular arrhythmia. With the increasing frequency of trauma among elderly patients, the possibility of an acute myocardial infarction, arrhythmia, or congestive heart failure precipitating an accident must be strongly considered (13).

Secondary Survey

The secondary survey consists of a detailed physical examination with the patient fully exposed. It is undertaken once the lifesaving priorities of the primary survey have been addressed. The breadth and speed of this examination depend in large measure on the patient's injuries and the need for definitive surgical intervention. Valuable information regarding the patient's history must be collected, including the mechanism of injury, preexisting medical problems, current medications, known drug allergies, and when the patient last ate. Routine objective studies also can be performed at this time, including a complete blood cell count, chest radiography, and urinalysis. If drug overdose or alcohol consumption is suspected, appropriate toxicologic studies can be performed. Hypotension warrants blood typing and cross-matching.

Head and Spine Injuries

Altered mentation is the most frequent sign of injury to the CNS and is presumed to be caused by injury until proved otherwise. Cervical spinal and spinal cord injuries are common among patients with multiple injuries, and the greatest concern is to avoid further injury to vital neurologic structures. Rigid immobilization of the cervical spine is imperative until a complete set of spinal radiographs, including cervical, thoracic, and lumbar spine radiographs, has been obtained. The entire spine is palpated for tenderness and altered contour. For patients with definitive cervical spinal injuries, use of a rigid collar reinforced with sandbags on either side and wide tape across the forehead is mandatory (Fig. 74.7).

Altered mental status can be caused by direct injury to the cortex and brainstem, by increased intracranial pressure (ICP), or by decreased cerebral perfusion. Whereas the first two conditions necessitate formal neurosurgical intervention, the changes in pressure and perfusion can be managed in the emergency department. The tool used to assess mental status is an abbreviated neurologic examination to define the Glasgow Coma Scale score (Table 74.1). This graded evaluation is performed to assess the functions of eye opening, verbal response, and motor response. A Glasgow score less than 8 indicates serious head injury, although the score can be artificially low if an endotracheal tube is in place. Further neurologic assessment includes evaluation of pupillary reflexes, deep tendon reflexes, and rectal sphincter tone. A serious head injury can have nonneurologic signs such as hypoventilation and hypertension.

Emergency department treatment of a patient with a head injury is aimed at minimizing cerebral edema and reducing ICP. These goals are met by means of controlling the airway

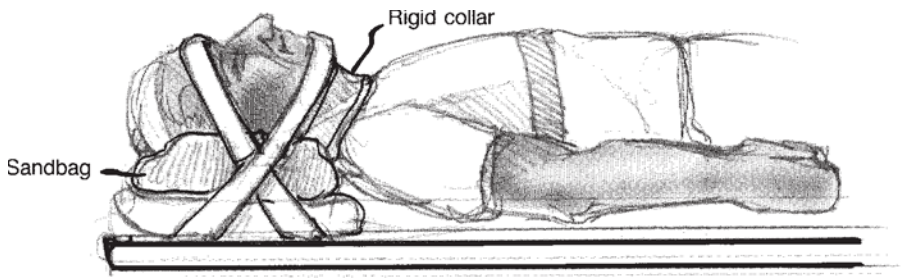


Figure 74.7 For patients with definitive cervical spinal injuries, use of a rigid collar reinforced with sandbags on either side and wide tape across the forehead is mandatory.

TABLE 74.1 GLASGOW COMA SCALE

Function	Score
Eye Opening	
Spontaneous	4
Verbal stimulus	3
Painful stimulus	2
None	1
Verbal Response	
Oriented	5
Confused	4
Inappropriate	3
Incomprehensible sounds	2
No response	1
Intubated 1T	
Best Motor Response	
Obeys commands	6
Localizes painful stimulus	5
Withdraws from painful stimulus	4
Flexion response	3
Extensor response	2
No response	1
Score Range	
Extubated	3–15
Intubated	3T–11T

to maintain acceptable oxygenation. Ventilation is adjusted to maintain a carbon dioxide level of about 35 mm Hg. Patients with suspected cerebral trauma and a Glasgow Coma Scale score less than 8 need continuous monitoring of ICP. ICP is maintained at less than 20 mm Hg. Elevations in ICP are managed by means of administering mannitol, an osmotic diuretic, to reduce the amount of intracellular water in the brain. Ventriculostomy can be used to monitor ICP and can be therapeutic in that it allows cerebrospinal fluid removal to control ICP. Maintenance of cerebral blood flow, measured as a cerebral perfusion pressure (mean arterial pressure minus ICP) of 70 mm Hg with the use of fluids and vasopressors, is gaining increasing acceptance. There is no role for the administration of steroids for the control of cerebral trauma. Any patient who has changes in mental status after injury needs cranial computed tomography (CT) as part of the secondary survey (17).

The management of spinal cord injury with distal deficits has changed over the last several years. Emphasis remains on maintaining spinal immobilization to prevent additional spinal cord injury. Recent research (18) has found that administering steroids can play a role in minimizing neurologic deficits for patients with spinal cord injuries. Administering methylprednisolone as a bolus of 30 mg/kg followed by a drip at 5.4 mg/kg each hour for 23 hours led to small improvement in neurologic function among these patients when administered within 8 hours of the injury.

Once the neurologic system has been evaluated, the secondary survey continues with assessment of the rest of the head. The scalp can be a source of considerable blood loss, and immediate suturing may be needed. Basilar skull fractures can manifest as mobility of the facial bones, hemotympanum, cerebral spinal fluid otorrhea and rhinorrhea, and periorbital and mastoid ecchymosis.

Neck Injuries

All injuries to the neck are potentially life threatening because numerous vital structures traverse this area. Neck injuries are classified as blunt or penetrating. Blunt trauma to the neck can cause cervical spinal injury, pharyngeal and tracheal injuries, and carotid artery injury. Penetrating neck wounds are classified according to location (see Chapter 76). Zone I injuries are below the level of the clavicles, Zone II injuries are between the clavicles and the angle of the jaw, and Zone III injuries are above the angle of the jaw (Fig. 74.8). Posterior injuries can damage the cervical spine. Anterior and lateral wounds can injure the great vessels of the neck, the larynx, the trachea, and the esophagus as well as important nerves such as the vagus, phrenic, hypoglossal, spinal accessory, and branchial plexus. High

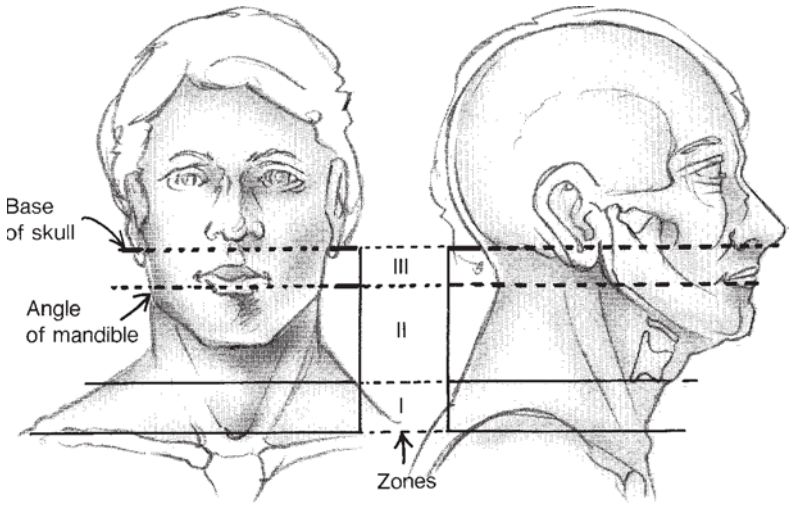


Figure 74.8 Penetrating neck wounds are classified according to location. Zone I injures are below the level of the clavicles. Zone II injures are between the clavicles and the angle of the jaw. Zone III injures are above the angle of the jaw.

penetrating injuries (Zone III) threaten the great vessels and cranial nerves at the base of the skull; penetrating injuries at the base of the neck (Zone I) threaten the great vessels exiting the thorax.

Clinical examination of an injured neck involves careful airway assessment, including evaluation for hoarseness, stridor, dyspnea, and hemoptysis. Subcutaneous emphysema, crepitus, and distorted laryngeal landmarks indicate laryngotracheal injury. Dysphagia and chest pain are characteristic of esophageal injuries. Flexible laryngoscopy is an excellent tool for examining the hypopharynx and larynx after neck injuries. It is rapid and easy to use and provides an excellent way to evaluate the patency of the airway and the function of the larynx. Flexible laryngoscopy also can aid in diagnosing laryngeal fractures and vagal injuries. CT of the neck also can help to delineate laryngeal fractures.

When laryngeal or tracheal injury is apparent and airway compromise is imminent, tracheotomy is performed. Cricothyrotomy is not used under such circumstances because of the risk of further injury to the larynx and upper trachea. Although it may be necessary to perform tracheotomy in the emergency department, this procedure is best done in the operating room, where proper instrumentation, optimal lighting, and appropriate personnel are available, especially when the patient has sustained blunt laryngotracheal disruption. This injury usually is caused by severe compression of the laryngotracheal complex between the steering wheel and the vertebral column or from "clothesline" injury, such as catching the neck on a barbed-wire fence while riding a snowmobile or a motorcycle. Under these circumstances, active airway management can be fraught with danger. Intubation may not be feasible, and tracheotomy can cause retraction of the distal trachea into the mediastinum.

Patients with penetrating neck injuries are at risk of airway obstruction, hemorrhage, and injury to the cervical spine. Important clinical signs include stridor, hoarseness, subcutaneous emphysema, expanding hematoma, external hemorrhage, hemoptysis, dysphagia, cranial nerve dysfunction, and branchial plexus injury. Active airway intervention is important when there is evidence of airway distress. It is best accomplished with nasotracheal or orotracheal intubation. Bleeding in the oropharyngeal area may preclude intubation and necessitate emergency surgical airway intervention, which can cause great difficulty if there is bleeding in the deeper layers of the neck. External hemorrhage is controlled with compression, and no effort is made to gain hemostasis by means of blind clamping.

There has been much controversy with regard to routine exploration of penetrating neck injuries, not only as definitive treatment but also as a diagnostic technique. Some authors advocate routine exploration of all injuries penetrating the platysma. Others advocate selective exploration and observation based on preoperative arteriographic findings and on the presence or absence of symptoms that suggest vascular, airway, and neurologic injury.

Most patients in stable condition with penetrating injuries to the base of the neck (Zone I) are best examined by means of arteriography, laryngoscopy, and esophagoscopy or a barium swallow radiographic study. Patients in stable condition with penetrating injuries above the angle of the mandible (Zone III) are best examined with arteriography to exclude carotid or vertebral artery injury. Patients with injuries between the angle of the mandible and the base of the neck (Zone II) can be examined by means of routine exploration or combinations of arteriography, laryngoscopy, and esophageal evaluation if the injury has penetrated the platysma. Patients in unstable condition with active hemorrhage need surgical exploration.

When a patient has marked neurologic deficits after blunt neck trauma and the findings of CT of the head are normal, the possibility of blunt carotid injury with carotid occlusion or dissection is considered and excluded with arteriography. Management of these injuries involves anticoagulation with heparin or reconstruction, depending on the nature of the injury.

Thoracic Injuries

Thoracic injuries are classified as blunt or penetrating. Most blunt injuries are caused by motor vehicle accidents. Penetrating injuries typically are from violence with knives or guns. The principal forms of life-threatening blunt chest trauma are flail chest, pulmonary contusion, tracheobronchial disruption, and torn thoracic aorta.

Flail chest occurs when part of the chest wall becomes isolated owing to multiple fractures of the ribs or sternum (Fig. 74.9). The severity is determined by the size of the flail

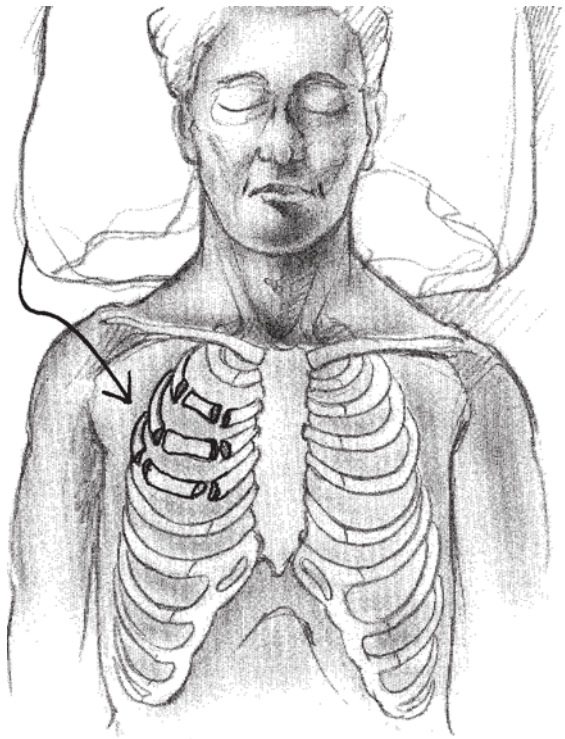


Figure 74.9 Flail chest.

segment, which moves paradoxically with inspiration and thus reduces ventilatory efficiency. Ventilation is further compromised by the size of the underlying pulmonary contusion that invariably accompanies a severe flail chest. If ventilation becomes inadequate, hypoxia and hypercapnia occur and the patient needs intubation and ventilatory assistance.

Pulmonary contusion is a common finding in blunt chest trauma. It often is associated with flail chest and hemopneumothorax and is common in multisystem trauma. Pulmonary contusion causes alveolar edema and impairs gas exchange. The primary sign of pulmonary contusion is hypoxia. Initial management is adequate oxygenation and avoidance of fluid overload, which can promote pulmonary edema. If a patient has hypovolemia and pulmonary contusion, aggressive fluid resuscitation is indicated, regardless if lung injury is present. Intubation and mechanical ventilation often are needed to support respiration.

Most intrathoracic blunt tracheobronchial injuries are caused by compression of the trachea and bronchi between the sternum and the vertebral column in motor vehicle accidents. The areas most commonly involved are the proximal mainstem bronchi and the distal trachea. Common features of this injury include pneumothorax, subcutaneous emphysema, and hemoptysis. Initial therapy often entails venting the pneumothorax. Bronchoscopy is indicated for diagnosis.

Traumatic rupture of the thoracic aorta is the most common cause of immediate death after motor vehicle accidents. In 90% of cases, the aortic injury occurs beyond the origin of the left subclavian artery at the level of the ligamentum arteriosum, where the descending aorta is relatively fixed. Motion between the more mobile aortic arch and fixed descending aorta can cause aortic injury when rapid deceleration is the mechanism. In about 10% to 20% of cases, thoracic aorta rupture does not cause immediate death because intrathoracic hemorrhage is contained by the aortic adventitia, and the patients can be saved if the injury is rapidly recognized. Although arteriography is the only definitive study for diagnosing this injury, the first indication of an aortic tear usually is evidence of superior mediastinal widening on routine chest radiographs. Clinical features, such as retrosternal or interscapular pain from mediastinal blood dissection and hypertension from sympathetic stimulation of the nerves around the aorta, can provide clues to the presence of aortic rupture. Early recognition and definitive surgical repair are crucial because the rupture becomes complete in a high percentage of patients within the first 24 to 48 hours after injury. The decision to perform thoracic arteriography to exclude aortic disruption is made early in the resuscitation and is based on findings of mediastinal widening on the initial supine chest radiograph obtained in the emergency department.

The injuries associated with penetrating thoracic trauma—hemopneumothorax, tension pneumothorax, and cardiac tamponade—are discussed earlier. After immediate management, a decision must be made regarding surgical thoracotomy when there is persistent bleeding from a chest wound. Considerations include the volume of the initial chest tube drainage, the rate of ongoing hemorrhage once the lung has been reexpanded, and the patient's hemodynamic status.

Abdominal Injuries

Abdominal injuries are life threatening because the peritoneal cavity can harbor occult blood loss and fecal contamination. Unrecognized abdominal injury is a common cause of death after trauma, and prompt recognition is of primary importance in its prevention. Diagnosis can be delayed by the silent nature of the injury, other life-threatening problems, or an altered state of consciousness.

Examination of the abdomen begins at the level of the nipples and extends to the pubic symphysis. The examination includes inspection, auscultation, percussion, and palpation. Rectal examination is mandatory for assessment of sphincter tone, pelvic crepitus, prostate position, and hemorrhage. Although the absence or presence of bowel sounds may not correlate well with the presence of injury, other signs, such as abdominal tenderness, are highly suggestive of peritoneal inflammation and can indicate the need for laparotomy.

Abdominal injuries are classified as blunt or penetrating. Blunt abdominal injuries usually are associated with injury to solid organs, such as the liver, spleen, pancreas, and kidneys. The most common finding among patients with blunt abdominal trauma and solid organ injuries is hemoperitoneum with shock. Trauma patients with persistent hypotension and possible blunt abdominal trauma require a search for occult bleeding. This can be done expeditiously with focussed assessment for the sonographic evaluation of the trauma patient (FAST) or diagnostic peritoneal lavage (DPL). These studies can be done rapidly in the trauma bay. FAST is an ultrasonographic examination performed by the trauma surgeon or emergency room physician and can detect fluid in the peritoneal cavity (19). In addition, the pericardial sac can be evaluated. In hospitals without the expertise or equipment to perform FAST, a DPL can be performed. Initial peritoneal aspiration of more than 10 mL of blood is an indication for laparotomy.

Lavage is performed by means of instilling 15 mg/kg normal saline solution into the peritoneal cavity and letting the fluid drain out by means of gravity. When the total erythrocyte count in the lavage effluent exceeds 100,000/mL, most patients have abnormal findings at laparotomy.

Abdominal CT is an excellent diagnostic study to exclude intraperitoneal or retroperitoneal injury if the patient is in hemodynamically stable condition. As experience with abdominal CT has increased, it has become clear that many patients with minor liver and spleen injuries with hemoperitoneum stop bleeding spontaneously and never need abdominal exploration.

Patients with penetrating abdominal trauma and overt signs of peritonitis or hypovolemia need surgical exploration; however, therapy is less clear-cut when the patient's

condition is hemodynamically stable or when signs of peritonitis have yet to evolve. The common mechanisms of penetrating trauma are gunshot wounds and stab wounds. With gunshot wounds, laparotomy is indicated when the missile penetrates the peritoneum. Plain abdominal radiographs are obtained to outline the missile trajectory. Broad-spectrum antibiotics are administered in anticipation of definitive surgical therapy.

Stab wounds of the abdomen can be managed selectively because the likelihood of visceral injury, even with peritoneal violation, is inconsistent. The first diagnostic steps are to ascertain the depth of the injury and to assess the integrity of the peritoneum. These steps are best done by means of exploring the wound in the emergency department with the patient under local anesthesia. Peritoneal lavage follows local exploration if there is an indication that the anterior muscular fascia has been penetrated. Criteria for a positive peritoneal lavage result differ in blunt injuries from stab wounds. Although 100,000 erythrocytes per milliliter is the accepted positive result for blunt injuries, an erythrocyte count of 5,000 to 10,000/mL is accepted as a positive result in a stab wound and indicates that laparotomy is needed. Patients with positive peritoneal lavage results need exploratory laparotomy. Those with negative peritoneal lavage results can be admitted for observation.

Extremity Injuries

During the secondary survey, the arms and legs are examined carefully to assess perfusion, neurologic function, deformity, and range of motion. Serious injuries include fractures, dislocations, amputations, and compartment syndromes. Life-threatening injuries involve massive blood loss due to pelvic fractures, traumatic amputations, and open femoral fractures. Pelvic fractures associated with hypovolemia are stabilized with application of MAST. An expanding hematoma or pulsatile, bright red bleeding indicates acute arterial injury and is controlled with manual pressure.

Before it is assumed that bleeding is coming from a pelvic fracture when the patient's condition is unstable, it is necessary to exclude ongoing intrathoracic or intra-abdominal hemorrhage. Supraumbilical DPL may be indicated to exclude an intra-abdominal source of hemorrhage in these patients. In the care of patients with persistent pelvic hemorrhage, angiography is indicated for diagnosis and definitive management by means of embolization of the bleeding vessels by interventional radiologists. A direct surgical approach to the bleeding pelvis rarely is indicated.

Rectal and vaginal examinations are an important part of the management of pelvic fractures. Patients with severe pelvic fractures may have associated injuries to the vagina, rectum, and urethra. A high-riding prostate or a positive result of a heme test of stool can alert the clinician to this possibility. Bladder rupture also is considered if a patient has a pelvic fracture and hematuria. An abnormal result of a prostate examination or blood at the urethral meatus indicates urethral injury and is a contraindication to insertion of a Foley catheter. Under this circumstance, retrograde urethrography is performed before a Foley catheter is placed.

Vascular injuries can be associated with penetrating wounds, fractures, and joint dislocation. Signs are typically those of ischemia, and the patient has pain, pallor, paralysis, paresthesia, and pulselessness. Recognition is important to preserve the extremity, and the diagnosis is confirmed with arteriography. Knee dislocation is often associated with popliteal artery injury and distal ischemia. Popliteal artery angiography is usually recommended to exclude injury if a patient has a knee dislocation.

Crush injuries to the lower leg and forearm can cause compartment syndrome due to hemorrhage and edema within recognized fascial planes. The patient typically has a painful, pale extremity with decreased sensation and pulse. The earliest sign of compartment syndrome is the patient's report of paresthesia or sensory deficit in the limb. Loss of peripheral pulses is a relatively late finding and often implies irreversible damage to the limb. Compartment syndrome occurs most often with closed fractures of the tibia and fibula. Emergency fasciotomy is the appropriate therapy.

Traumatic amputation necessitates microsurgical reimplantation when possible. Bleeding from the proximal limb is controlled with manual pressure. The amputated parts must be kept in a moistened sterile towel and placed in crushed ice until definitive therapy can be provided (11,12).

Inhalation Injuries

Thermal injuries must be managed in an orderly way, similar to that of all serious traumatic injuries. Inhalation injuries occur in 3% to 20% of all burn patients. Most inhalation injuries are caused by fires in closed spaces, but the possibility of blunt injuries to the throat or abdomen, as in blast injures or car accidents with fires, must be considered. An otolaryngologist may be asked to facilitate airway management for patients with inhalation injuries.

Although all types of trauma are suspect, specific types, such as explosive burns and burns sustained in a confined building, are associated with inhalation injury. Physical signs of inhalation include a decreased level of consciousness, singed nasal hairs, carbon deposits in the oral cavity, carbonaceous sputum, and the finding of inflammatory changes in the supraglottic larynx at flexible laryngoscopy.

The glottic and supraglottic airway can sustain marked edema from routine thermal trauma. The result is immediate or delayed airway obstruction. Patients with clear signs of supraglottic inhalation injuries need early endotracheal intubation with mechanical ventilation. The subglottic airway often is protected from burns unless the patient is exposed to superheated gas or steam. The vocal folds form

an anatomic barrier. In addition, reflex closure of the glottis also serves to protect the subglottis and trachea. Carbon monoxide levels in the blood should be measured and oxygen therapy should be given immediately. Hyperbaric oxygen therapy is considered when a patient has marked carbon monoxide poisoning (12).

Definitive Management

Once the primary and secondary surveys have been completed, the patient has been adequately resuscitated, and the patient's condition is judged to be stable, a plan for definitive care is formulated. This plan begins with a ranking of the injuries in the order in which they are to be managed. If at any point the vital signs become unstable, the primary and secondary surveys are repeated. If the instability is from an injury that warrants definitive surgical intervention, the patient is transferred to the operating room. Patients who do not need further surgical intervention are transferred to the intensive care unit or to a surgical floor for further observation. Transfer errors include inadequate management of the airway, poorly secured intravenous lines and drainage tubes, and inadequate patient monitoring. It is a tragedy to resuscitate a patient in the emergency department successfully only to lose the patient on transfer to the operating room.

ROLE OF THE OTOLARYNGOLOGIST

Since the early 1970s, the responsibility of otolaryngologists as members of the trauma team has continued to expand. In most institutions, otolaryngologists are viewed as experts in managing the airway and are expected to perform difficult intubations and provide emergency surgical airways. They are also being recognized for expertise in the management of maxillofacial trauma and penetrating injuries to the neck. Otolaryngologists often are called on to assist in the immediate care of trauma victims in the emergency department.

As valued members of the trauma team, otolaryngologists must continue to refine management skills for injuries associated with the specialty but also need to be knowledgeable about the general care of trauma patients. Otolaryngologists need to understand the concepts of the primary and secondary survey and be capable of stabilizing the neck, securing the airway, placing chest tubes, and starting intravenous lines. They also should be able to perform the complete examinations needed in the secondary survey and know how to interpret the diagnostic procedures that must be performed as part of the survey. To be fully integrated and recognized as responsible members of the trauma team, otolaryngologists involved in the care of trauma patients should be certified by the American College of Surgeons advanced trauma life support course.

HIGHLIGHTS

- The most fundamental neuroendocrine reaction to trauma is the release of catecholamines, which cause vasoconstriction, increase cardiac rate, increase myocardial contractility and conductivity, and stimulate gluconeogenesis.
- The postinjury period is characterized by catabolism with negative nitrogen balance, hyperglycemia, and heat production, all of which reflect the reparative processes.
- The most important factor in the successful care of trauma patients is the initial evaluation and resuscitation performed partly in the field and in the emergency department. Primary and secondary surveys allow physicians to manage complex multisystem problems. This treatment algorithm has four steps—primary survey, resuscitation, secondary survey, and definitive care.
- The foremost emergency measure after trauma is airway establishment. The primary risk during early airway management is movement of the neck when there is an occult cervical spinal fracture. When the airway is being controlled, it must be assumed that such a fracture exists.
- Correct positioning of the endotracheal tube can be confirmed reliably by the presence of end-tidal carbon dioxide. If no carbon dioxide is detected, the endotracheal tube is in the esophagus, and a new attempt at intubation is made immediately.
- In the trauma patient, continuous monitoring with pulse oximetry is extremely helpful in determining the adequacy of oxygenation and is used in the care of all critically injured patients.
- Techniques of surgical airway management include needle cricothyrotomy, standard cricothyrotomy, tracheotomy, and percutaneous tracheal ventilation. Needle cricothyrotomy is the best procedure for children; surgical cricothyrotomy is preferred for adults.
- Loss of respiratory drive among trauma patients most commonly is caused by severe head trauma; however, injuries to the chest wall and thoracic structures can cause hypoventilation, which must be recognized and rapidly treated.
- Shock is the clinical manifestation of the inability of the heart to maintain adequate circulation to vital organs. The patient dies unless oxygenation and perfusion are restored. The most common cause of shock after trauma and hemorrhage is hypovolemia. Treatment is rapid volume replacement with crystalloids, such as lactated Ringer solution or normal saline solution through two 14-gauge catheters in the antecubital fossa.

- Cardiogenic shock is loss of circulatory perfusion that occurs when the myocardium does not generate sufficient blood flow for tissue oxygenation. Among trauma patients, cardiogenic shock usually is precipitated by tension pneumothorax, cardiac tamponade, or myocardial contusion. The presence of myocardial contusion is best confirmed with echocardiography. Among elderly trauma patients, the possibility that acute myocardial infarction or arrhythmia has precipitated an accident must be considered.
- In the care of patients with head trauma, ventilation is adjusted to maintain a carbon dioxide level of about 35 mm Hg. Patients with cerebral edema or coma need continuous monitoring of ICP. ICP must be maintained at less than 20 mm Hg. Elevation in ICP is managed with mannitol. Maintenance of cerebral blood flow as measured by cerebral perfusion pressure is best accomplished with the use of fluids and vasopressors.
- In the care of patients with spinal cord injury, administration of methylprednisolone as a bolus of 30 mg/kg followed by a drip at 5.4 mg/kg each hour for 23 hours has been shown to lead to small but important improvements in neurologic function if administered within 8 hours of injury.
- The decision to perform thoracic arteriography to exclude aortic disruption must be made early in resuscitation. The decision is based on findings of mediastinal widening on the initial supine chest radiograph obtained in the emergency department.
- Unrecognized abdominal injury is a common cause of death after trauma. Ultrasonography, when available, is the preferred step in the initial phase of assessment and management. Peritoneal lavage is an acceptable alternative. A total erythrocyte count of 100,000/mL correlates with positive findings at laparotomy after blunt abdominal trauma. For patients with penetrating abdominal trauma, a total erythrocyte count of 5,000 to 10,000/mL correlates with positive findings at laparotomy.
- Abdominal CT is an excellent diagnostic study to exclude intraperineal and retroperineal injury if the patient is in hemodynamically stable condition.
- The extremity injury that poses the greatest risk to life is a pelvic fracture resulting in massive blood loss. The best initial management is application of MAST followed by angiography.
- The earliest sign of compartment syndrome is the patient's report of paresthesia or sensory deficit in the limb. Loss of peripheral pulse is a relatively late finding and often implies irreversible damage to the limb. Compartment syndrome occurs most often with closed fractures of the tibia and fibula. Amputated body parts must be kept in a moist and sterile towel and placed in crushed ice until definitive reimplantation can be provided.
- The physical signs of inhalation injury include a decreased level of consciousness, burned nasal hairs, carbon deposits in the oral cavity, and inflammation of the supraglottic structures. Signs of this type of injury are indications for early endotracheal intubation and mechanical ventilation.
- Definitive management follows the primary and secondary surveys and begins with ranking of the injuries in the order in which they are to be managed. If at any point the vital signs become unstable once again, the primary and secondary surveys are repeated. Transfer out of the emergency department for definitive management can be a period of risk. Transfer errors include inadequate management of the airway, poorly secured intravenous lines and drainage tubes, and inadequate patient monitoring.
- To be fully integrated and recognized as responsible members of the trauma team, otolaryngologists involved in the care of trauma patients should be certified by the American College of Surgeons advanced trauma life support course.

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75 Management of Soft Tissue Injuries of the Face

Scott Shadfar *William W. Shockley*

Soft tissue injuries involving the face, head, and neck are becoming more frequent, and the experienced otolaryngologist is commonly the designated surgeon chosen to make a timely assessment and repair. The management of facial soft tissue injuries present challenges both from a functional and aesthetic perspective. Injuries to the face can affect speech, vision, alimentation, and facial expression. The resulting facial scars and deformities also can be associated with a host of psychosocial issues. This chapter is devoted to the initial evaluation, classification, and early management of facial wounds. We also provide specific anatomical considerations for different anatomic sites with respect to facial soft tissue injury management and care.

ETIOLOGY AND MECHANISM OF INJURY

The leading causes of facial soft tissue injuries are assault, motor vehicle accidents, work-related injuries, sport injuries, animal and human bites, as well as burns. In addition, there has been a surge in the literature highlighting injuries encountered from the battlefield (1). Details into whether protective measures were in place, such as helmets, seat belts, or air bags, can guide the evaluation. Injuries sustained despite these measures calls one's attention to the force behind the injury and need for further workup.

EVALUATION

Patients with serious or life-threatening injuries are first assessed in the emergency room, or trauma bay when available. Advanced Trauma Life Support guidelines are followed where airway, breathing, circulation, disability, and exposure (ABCDE) take precedence. In the critically ill patient, stabilization will proceed in a standard fashion with the insertion of two large-bore intravenous lines. Acute hemorrhage from the head and neck region is addressed at this time. An airway is established if deemed necessary. Any oral or pharyngeal hemorrhage leading to inability to protect the airway calls for airway intervention, all while maintaining cervical spine precautions. In this setting, 3% to 10% of facial injuries with fractures have concomitant c-spine injuries (2,3). Although facial injuries can bleed profusely, they can distract health care providers from other more immediately threatening injuries. Often a moist gauze and pressure dressing can be applied to facial wounds if other injuries, such as chest or abdominal trauma, necessitate urgent treatment.

A thorough history, if obtainable, is necessary when a patient presents with a traumatic injury. Knowledge of the patient's underlying comorbidities and past medical history is especially important in those patients with compromised host defenses as in patients with diabetes, immunosuppression, chronic corticosteroid use, malnutrition, and obesity.

Allergies to medications including local anesthetics, general anesthetics, and antibiotics should be documented. Social history regarding smoking, ethanol, and illicit drug use should also be obtained. In most cases of major trauma, serum alcohol levels and a drug screen should be checked as the presence of cocaine or amphetamines may delay elective operative intervention; these interactions with general anesthesia are known to increase cardiac risks. Tetanus history should also be noted at this time, with appropriate treatment based on the patient's history (see section on "Tetanus").

A complete head and neck examination should be performed with final attention focused on the injured site. A detailed description of the wound in terms of wound classification, location, depth, length, and condition of wound edges should all be assessed and documented. Cranial nerve examination is performed to identify any

deficits. Next, evaluate for deep tissue injury (clear fluids leaking indicative of cerebral spinal fluid [CSF], salivary, or lacrimal injury) (4) as well as presence of fractures or foreign bodies (gravel, wood, broken or loose teeth). When possible, photo documentation should be performed for medical and legal reasons.

Prior to extensive examination and wound preparation, appropriate anesthesia and analgesia should be provided for patient comfort. The authors seldom use sedation, outside of the pediatric population. Imaging studies pertinent to the head and neck region including plain films and computed tomographic (CT) studies should be obtained when there is concern for facial fractures, missing teeth, or foreign bodies. Noncontrast high-resolution CT imaging is the preferred imaging modality to evaluate facial fractures, while contrasted CT angiography is indicated for identification and delineation of a vascular injury as seen in penetrating neck injuries (see Penetrating Head and Neck Injury chapter). Once the patient has been stabilized, the involved physicians should prioritize further workup, management, and surgical repairs. Depending on the nature of the injuries, appropriate consultations should be obtained.

WOUND CLASSIFICATION

Abrasions

Classifying wounds on assessment aids in sorting and developing a treatment algorithm. Wounds are most commonly classified by depth, which is influenced by the mechanism. When the epidermis and partial thickness dermis has been lost, secondary to scraping the skin, this is classified as an abrasion. For these injuries, the critical steps in management include irrigation and cleansing with meticulous removal of any embedded dirt and debris. Once the wound is fully clean, topical ointment is sufficient treatment. The patient is instructed to keep the wound clean and dressed. In most circumstances, a topical antibiotic ointment is both practical and effective. Maintaining a moist environment without crusting helps promote faster reepithelialization from the remaining undisturbed skin appendages. Avoidance of direct sun exposure is recommended as this can cause skin pigmentation at the site of injury, which is most often temporary. Sun avoidance and protection should be mandatory for a minimum of 6 months.

Contusions/Hematomas

Contusions are usually from blunt force trauma without breech of the overlying skin. Disruption of the small capillaries and vessels leads to swelling and ecchymosis. These changes usually resolve over time without intervention. Expectant management is usually sufficient with head elevation and ice packs. Soft tissue hematomas result in marked swelling and can sometimes organize into a localized hematoma. In most cases, all that is needed is supportive care and observation, assuming there are no functional or airway issues. Needle aspiration can be undertaken after liquefaction of the clot, usually around 10 days post injury. If hematomas occur in the tongue, floor of mouth, or neck one must consider the potential for airway compromise. In addition, underlying vascular injuries may be suspected.

Avulsion Injuries

Avulsion injuries result from the shearing or tearing of tissues. This leads to full-thickness cutaneous injury sometimes associated with loss of the involved tissue segment. Avulsion injuries may be associated with subcutaneous, cartilaginous, or bony structures. Avulsion injuries usually arise from high-velocity activities or exposures such as motor vehicle collisions, blasts, and assaults, resulting in shearing of tissues. On occasion, microsurgical techniques will be required for reattachment of avulsed tissues. Conservative trimming of nonviable tissue margins may be necessary; however, tissue-sparing management is preferred with frequent checks to confirm tissue viability. If there are concerns over viability, steps should be taken to optimize tissue vascularity, such as suture removal or wound drainage (5). Specific considerations with respect to management are discussed under each anatomical site.

Lacerations

Lacerations typically occur from impact or sharp objects resulting in a cutting of the skin as opposed to the tearing forces that result in avulsion injuries. Lacerations can be further categorized as linear, tangential, or stellate and are many times jagged with macerated edges. The majority of facial soft tissue injuries fall under this category and the tenants of closure and management are discussed in greater detail throughout the chapter.

Puncture/Penetrating

Wounds that puncture the skin are classified as puncture wounds. Those that enter and exit the skin such as a knife or bullet are known as penetrating wounds. Many times, the underlying damage is more severe than the visible portion of the wound and caution should be exercised in assessing the patient or probing of the wound. The basic principles of acute trauma care apply. Penetrating wounds of the neck can be stratified into a level I to III classification system. Please refer to Chapter 76 for further discussion and management strategies.

Crush Injuries

Prolonged or excessive force placed on any anatomical location can lead to a crush injury. Luckily, the face is seldom the site involved with isolated crush injuries. However when segments of the face, head, and neck are

involved disastrous consequences may occur. Devitalized tissue is frequently present due to small blood vessel injury leading to necrosis and poor wound healing. Management includes conservative trimming of nonviable tissue margins. Hyperbaric oxygen treatments have been shown to be beneficial for hypoxic wounds in limb crush injuries, but no randomized controlled trials have been performed that provide useful guidelines for facial soft tissue injuries (6).

WOUND MANAGEMENT

General Considerations

Regardless of whether the injury is an abrasion, avulsion, or laceration, the initial management is the same. Keeping the wound moist with sterile saline-soaked gauze is recommended. Most wounds can be examined and repaired in the emergency department trauma bay or exam room. Exceptions include those injuries with underlying fractures, nerve, salivary, or lacrimal duct injuries, which will require more complex techniques for repair. Additionally, the pediatric population will often require conscious sedation or a general anesthetic for appropriate examination and closure, depending on the injury, patient's age, and level of cooperation.

Before repair, and many times before a thorough examination, local anesthesia is administered. Once appropriate anesthesia has been achieved, the surgeon can proceed with tissue manipulation and attention should be turned to systematic cleansing of the tissues using sterile normal saline. Various methods can be employed to accomplish removal of foreign debris and bacteria. Whether using a bulb syringe, intravenous catheter on a syringe, or pulsatile irrigator, the goal is to decrease the wound bacterial load. The presence of a wound inoculum of 10^5 bacteria per gram of tissue has been shown to increase the risk of wound infection. Three to five hours are generally needed for bacterial proliferation to reach this inoculum in a clean wound, and after 8 hours the bacterial load increases exponentially (7). Others have described using tap water (8) or forgoing any irrigation in the setting of a clean, noncontaminated, nonbite wound to the face and scalp and did not observe an increased rate of infection (9). The authors still advocate wound irrigation with sterile normal saline, as an inexpensive, effective, and noninvasive measure (4).

All dirt, debris, and foreign material must be carefully and thoroughly removed to avoid the risk of infection or traumatic tattoos. If irrigation techniques are not sufficient, then a scrub or wire brush may be used to remove all material, paying careful attention as to not further damage the delicate tissues or devitalize any partially avulsed flaps. Solvents used to dissolve materials such as tar are only used if absolutely necessary. Wound exploration and dissection may be needed to remove larger pieces of foreign material. Wound debridement of any nonviable soft tissue is performed with removal of necrotic tissue at the initial encounter and subsequent encounters. If there is a question of tissue viability, Futran advocates retaining the tissue and allowing a 24- to 72-hour window for final declaration (10).

For large open wounds, the use of negative pressure wound therapy (NPWT) can be utilized in those patients awaiting definitive therapy. This modality allows promotion of granulation tissue through increased blood flow to the wound, cellular proliferation from mechanical stress placed on the cells at the wound surface, as well as the removal of factors that inhibit wound healing, while avoiding painful dressing changes (11). Contraindications to NPWT related to soft tissue trauma are few, and include fragile skin, ischemic tissue, and the presence of infection (11). Contours of the face, nose, lips, and ears can make this technique difficult to apply in many cases.

Timing of Repair

The proper sequencing and staging of surgical care of facial trauma patients is important in decreasing postoperative complications and obtaining optimal results (5). Based on the wound classification and extent, decisions are made as to whether the injury is amenable to repair in the emergency room versus the operating room. Often patients will be prioritized based on other injuries.

Although the timing of repair has been controversial over the course of the past 20 years, the paradigm has shifted to immediate definitive repair after irrigation and initial meticulous debridement of devitalized tissue. Hochberg et al. argue that the best period for primary repair is within 8 hours of the injury. Tissues are less vulnerable to infection, and wound healing is at its optimum during that time, although this is also dependent on the etiology, the patient's health, and the type of injury (12).

In patients with life-threatening injuries such as intracranial, cervical spine, and severe abdominal or thoracic injuries, surgical closure can be delayed. In those patients with contaminated wounds, delayed repair is preferred due to increased risk of infection. Local wound care and secondary healing can be considered in grossly contaminated wounds as well as those with tissue loss. Allowing wound contracture to occur may minimize the ultimate defect. Delayed closure is reserved for grossly contaminated wounds, selected animal bites, infected wounds, and wounds greater than 24 hours old. Treating with antibiotics and local wound care for approximately 3 to 5 days has been shown to yield the lowest bacterial counts at 96 hours after the injury, optimizing healing following delayed closure (7,13).

Anesthesia

Local Anesthesia

Local anesthesia is usually sufficient to repair most facial lacerations in adults and children. The choice of local anesthetic depends on the length of procedure as well as any known allergies or side effects noted by the patient.

Lidocaine (1%) with 1:100,000 dilution of epinephrine provides a dense block with appropriate time to close most lacerations. The epinephrine acts as a vasoconstrictor, which prolongs the anesthetic effects of lidocaine and provides hemostasis. In the authors' experience, infiltration of lidocaine with epinephrine has been without consequence in end arterial areas such as the nose and ear, and feel there is no literature to substantiate its prohibition. The only exception would be its use in tissues, which appear to have a tenuous blood supply. Dosing limitations should be closely monitored in children and polytrauma patients, especially if multiple teams are using local anesthetics. The maximum recommended dose is 4.5 mg/kg for lidocaine and 7 mg/kg for lidocaine with epinephrine (13,14). The pain associated with the injection of the local anesthetic can be minimized and is influenced by temperature, pH, number of injections, rapidity of injection, and size of needle (15). Warming the anesthetic solution to body temperature, as well as achieving a more alkaline pH with the addition of 1 milliliter (mL) of sodium bicarbonate to 9 mL of lidocaine (1:10 dilution), should attenuate the pain of injection. Additionally, inserting the needle through the wound instead of penetrating the skin, as well as injecting slowly through a 27 or 30 gauge needle, will aid in lessening discomfort.

In the case of children, or those intolerant to local injections, topical anesthetics are available and can be used as an alternative or adjunctive method of local anesthetic administration. Several topical anesthetics are available and are generally a combination of tetracaine, adrenaline, and cocaine (or TAC); a combination of lidocaine, epinephrine, and tetracaine (or LET); or a combination of 2.5% lidocaine and 2.5% prilocaine (16). Application of topical anesthetics as an adjunct prior to needle infiltration may reduce the pain of infiltration and can sometimes be used solely for small superficial lacerations. Bear in mind that these must be applied and left in place with an occlusive dressing for 30 to 60 minutes or more for a pronounced effect.

Regional Anesthetics

Local infiltration of anesthetic suffices for most wounds although regional nerve blocks may also be appropriate in some settings. Nerve blocks of the ophthalmic division of the trigeminal nerve (supraorbital, supratrochlear, infratrochlear) are performed with an injection along the supraorbital rim from lateral to medial, while stretching the eyebrow laterally. This can be used for scalp, upper eyelid, nose, and with the addition of auriculotemporal and zygomatic branch blockade, the temporal region can also be anesthetized. Anesthesia of the lower eyelid, cheek, nose, and upper lip through blockade of the infraorbital nerve aids in closure of lacerations in these areas. Nasal blockade can be more easily performed with appropriate regional blocks and topical anesthetics. Lidocaine or cocaine can be applied to the nasal mucosa by means of cotton tip applicators or pledgets, while the lower lip and chin can be blocked through the use of mental nerve blocks (15).

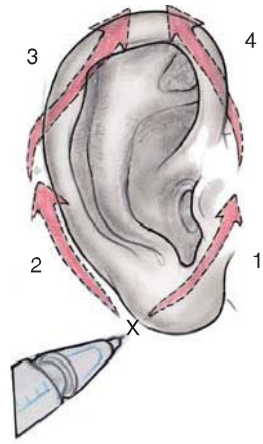


Figure 75.1 Regional block technique providing anesthesia to the entire ear, excluding the concha and EAC. "X" is the point of initial needle insertion. Numbers 1–4 denote the sequence of injections.

Complete regional blockade of the ear is possible with the exception of the concha and medial surface of the tragus which require direct injection if necessary. Prior to injection, a cotton ball should be placed in the external meatus to block any blood from entering the external auditory canal (EAC). Using a circumferential approach, a single inferior injection aimed anterior superior in the auriculotemporal distribution is performed. This is followed by a postauricular injection directed from inferior to superior through the same injection site, without removing the needle below the lobule. Once anesthesia has set in a second pain-free needle stick can be performed superiorly into the posterior auricular area following the postauricular sulcus while avoiding the postauricular artery. The final block is placed superior to the root of the helix, from a posterior to anterior approach (Fig. 75.1).

Tetanus

Tetanus vaccination history is an important feature of any trauma patient. Wounds can be divided into tetanus-prone versus those that are not. Tetanus-prone wounds include those greater than 6 hours old, stellate lacerations, avulsion injuries, wounds deeper than 1 cm, and those with a mechanism of injury from a missile, crush, burn, or frostbite. Those wounds presenting with signs of infection, containing deinnervated or devitalized tissue or contaminants such as dirt, soil, feces, or saliva are also at high risk (7). If both tetanus immune globulin and tetanus–diphtheria toxoid are given, they need to be given in different syringes and at separate sites (7,16). Dosing is beyond the scope of this chapter but recommendations from the Centers for Disease Control and Prevention (CDC) are shown in Table 75.1.

Antibiotics

According to the guidelines distributed by the American Academy of Otolaryngology—Head and Neck Surgery, the use of prophylactic antibiotics are recommended

TABLE 75.1 TETANUS PROPHYLAXIS IN WOUND MANAGEMENT

Recommendations for Tetanus Prophylaxis

	Nontetanus–Prone Wounds		Tetanus-Prone Wounds	
History of tetanus immunization	Td	TIG	Td	TIG
<3 doses or uncertain doses	Yes	No	Yes	Yes
If 3 doses or greater and:				
Last dose within 5 y	No	No	No	No
Last dose within 5–10 y	No	No	Yes	No
Last dose > 10 y	Yes	No	Yes	No

Recommendations are based upon the CDC, Department of Health and Human Services Center for Disease Control and Prevention (www. cdc.gov/vaccines/)
Td, Tetanus diphtheria toxoid; TIG, Tetanus immunoglobulin.

for traumatized or contaminated wounds, incisions or wounds crossing mucosal barriers, patients with prosthetic devices, and patients with compromised host defenses (13). Other factors that must be considered include the mechanism of injury and the time of presentation, with those patients presenting with wounds greater than 24 hours from the incident clearly having a higher bacterial inoculum and likelihood of infection. Other wounds such as compound fractures of the mandible or maxilla with mucosal breech, contaminated wounds, or injuries that occurred under water deserve prophylactic antibiotic treatment as well (17). No literature exists to support routine prophylactic antibiotic usage in soft tissue injuries to the face, so the authors follow the guidelines outlined above.

Oral penicillins are the antibiotics of choice, although in penicillin-allergic patients use of clindamycin or cephalexin should be considered. Fluoroquinolones are suitable for pseudomonal coverage in the case of underwater injury. In general 5 to 7 days is sufficient for prophylactic antibiotics. Grossly infected wounds are given therapeutic treatment with 48 hours of intravenous antibiotics, followed by a total 10 to 14 days of the oral equivalent. The pharmacology and microbiology of bite and burn wounds are discussed separately.

LACERATION REPAIR

When closing facial wounds the inherent bond between function and aesthetics cannot be overemphasized. The surgeon's closure has bearing not only on societal cues, but also in the patient's everyday functions of communication, breathing, alimentation, and display of emotions. This must also be considered when preparing and debriding the wound as distortion of contiguous structures can occur with overaggressive debridement or skin advancement. Complex or stellate wounds can sometimes be excised or converted to simple lacerations which can then be closed primarily. Delicate and atraumatic handling of the tissue edges is of utmost importance. The use of skin hooks is preferred in handling these damaged tissues as to avoid further crushing of the wound edges. Even with meticulous closure of complex lacerations, it is important to communicate to the patient and family that scar revision may be necessary.

Soft Tissue Principles of Closure

The aim of suture techniques in facial injuries is to achieve a tension-free closure with appropriate and accurate tissue approximation. When applicable, closure along the relaxed skin tension lines and abiding by the facial aesthetic units, can aid in making a scar more inconspicuous (Fig. 75.2). The amount of undermining necessary prior to closure varies with the degree of tension anticipated with the closure. A minimum number of nonreactive sutures should be used for the deep layer. Although meticulous closure may provide better tissue alignment, excess deep sutures may lead to a foreign body reaction. Too many skin sutures may compromise blood supply to the wound

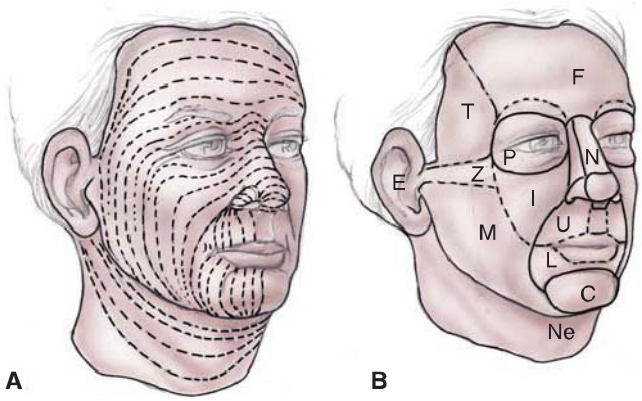


Figure 75.2 **A:** The relaxed skin tension lines (RSTL) should be used in closure design and incision planning. **B:** Depiction of the facial aesthetic units, highlighting the importance of separate reconstruction for each unit. *F*, forehead; *T*, temple; *Z*, zygomatic; *M*, mandibular; C, chin; *L*, lower lip; U, upper lip; N, nasal; I, infraorbital; *P*, periorbital; *Ne*, neck; *E*, ear.

resulting in local necrosis, most notably at the end organ sites of the nose, ear, or avulsed segments with a tenuous blood supply (5).

Suture selection is based on several factors including the depth of the injury, the extent of skin loss, the anatomic structures involved, and surgeon preference (18). Generally, a braided or monofilament deep absorbable suture is used with the knot inverted to take tension off the wound and provide appropriate reapproximation without undue strangulation or tension. Some authors, especially in the setting of contaminated or bite wounds, prefer minimally reactive monofilament sutures (e.g., polydioxanone) over more reactive, braided sutures (e.g., polyglactin) for deep closure. The theoretical increased risk of infection due to bacteria becoming embedded within the braids as well as these sutures eliciting increased tissue inflammation make monofilament absorbable preferred by some authors (19).

The subcuticular or dermal suture provides wound edge eversion and depth equality at the level of the skin for a smooth cosmetic result. The epidermal layer closure has multiple possible techniques (running, interrupted, locking) and options including sutures, staples, tapes, and liquid adhesives. Whether one uses a fine nonabsorbable (e.g., polypropylene) versus an absorbable suture (poliglecaprone 25 or fast absorbing gut) will depend on the surgeon's preference, the likelihood of the patient returning for follow-up, and whether a child will cooperate with suture removal in clinic. Parell and Becker noted no difference in long-term cosmetic results of repairs with permanent versus absorbable sutures and thus preferred absorbable sutures. The advantages were that the sutures do not necessitate removal, thereby saving the surgeon time while lessening patient anxiety and discomfort (20). Others have investigated tissue adhesives as an alternative to suture closure as means of saving time and offering greater convenience and comfort to the patient, especially in the pediatric population. Their usefulness in the management of simple lacerations is well accepted; however, they are less useful in complex lacerations, have low tensile strength, and cannot be used around moist mucous membrane due to premature adhesive dissolution and release (21). Graphic representation of various suturing techniques is depicted in Figures 75.3 and 75.4.

Postoperative Care

The importance of wound care should be stressed to patients and families. The wound should be cleansed twice daily using half strength hydrogen peroxide to prevent crusting. A topical antibiotic ointment should be applied after each cleaning. Since 7% to 13% of patients develop atopic dermatitis associated with neomycin-containing ointments, we recommend avoiding ointments containing neomycin (22). Alternative ointments include bacitracin, mupirocin, or those not containing an antibiotic such as petroleum ointment or water-based ointments such as Aquaphor (Beiersdorf AG, Hamburg, Germany). Sutures on the face are generally removed in 5 to 7 days following repair.

Once the sutures are removed meticulous care should be taken to avoid sun exposure. The use of broad spectrum UV-A and UV-B sun block with an sun protection factor (SPF) greater than 45 is recommended for a minimum of 6 months to 1 year to prevent hyperpigmentation of the scar.

Intraoral and intranasal sutures are usually absorbable and these do not require removal. Antibacterial mouthwash such as chlorhexidine gluconate 0.12% is used three times daily after meals for 1 week for intraoral lacerations. The use of saline nasal rinses can be advised with avoidance of nasal manipulation or nose blowing in the setting of nasal injuries.

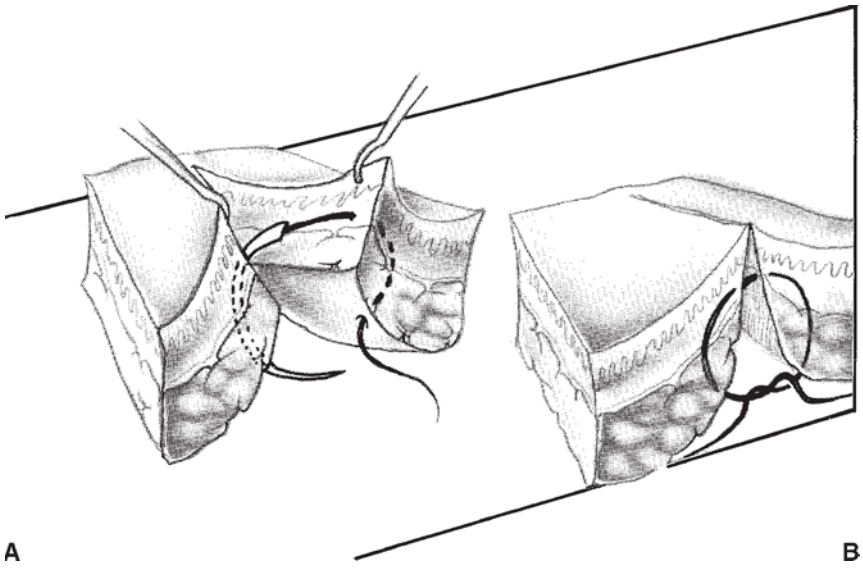


Figure 75.3 Suturing principles for facial wounds. **A:** Inverted deep sutures reapproximate the wound edges, eliminate dead space, and juxtapose similar tissue layers. **B:** Eversion of surface by well-placed sutures.

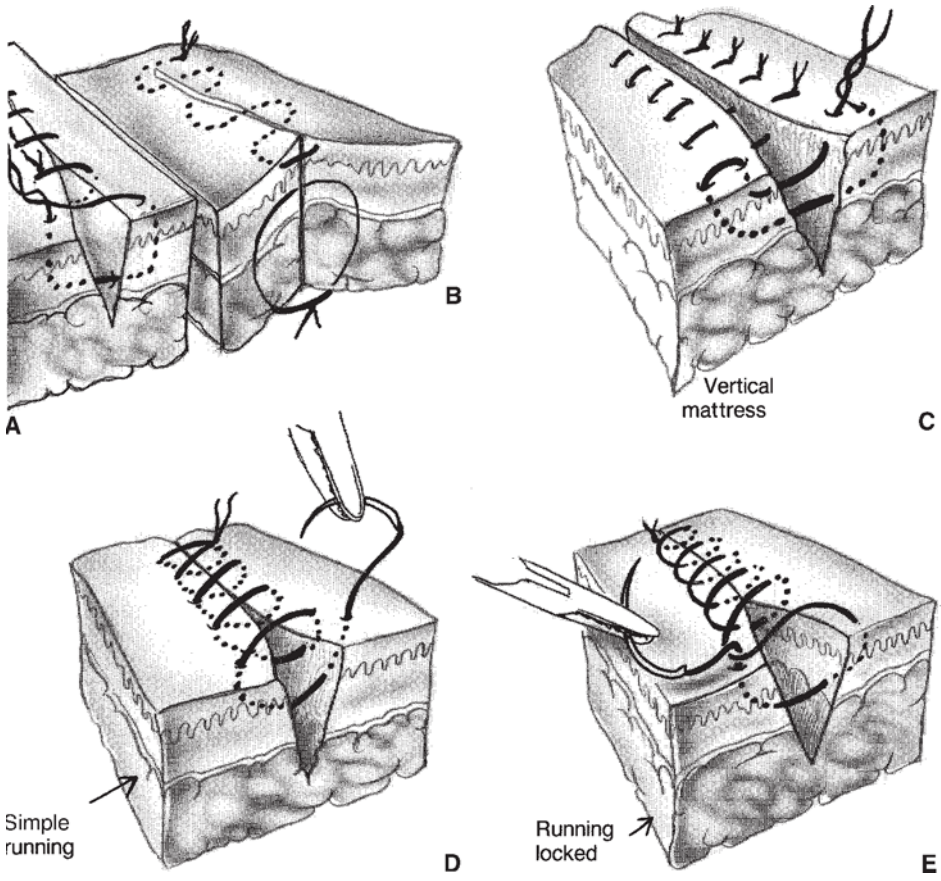


Figure 75.4 Suturing techniques. **A:** Simple interrupted. **B:** Subcuticular running. **C:** Vertical mattress. **D:** Simple running. **E:** Running locked.

Drains

The use of drains in acute facial trauma is not routine but may be advisable in wounds with extensive dead space or following closure after evacuation of a hematoma. A simple latex (e.g., Penrose) drain may be used to facilitate drainage and inhibit reaccumulation. In areas with a large dead space closed suction drains may be more appropriate.

INJURIES BY ANATOMICAL LOCATION

Scalp

Injuries to the scalp are often present as gaping lacerations or avulsions. The scalp is made up of five distinct tissue planes easily remembered by the mnemonic SCALP: S (skin), C (subcutaneous tissue), A (galea aponeurotic layer), L (loose areolar tissue), and P (pericranium) (Fig. 75.5). The layered makeup of the scalp make scalp avulsion injuries more frequent, with each layer providing a plane for dissection (23). The vessels, lymphatics, and nerves course through the subcutaneous layer just superficial to the galea, while the loose areolar tissue or subgaleal plane allows for scalp mobility. As such, scalp avulsions routinely occur through this layer, thereby leaving pericranium intact, which is an important anatomic landmark that must be distinguished at time of closure and reconstruction (23).

The scalp is a highly vascular region. The presence of a rich network of vessels contributes to the profuse bleeding seen in scalp injuries, many times out of proportion to the wound size. Direct pressure is necessary and sufficient

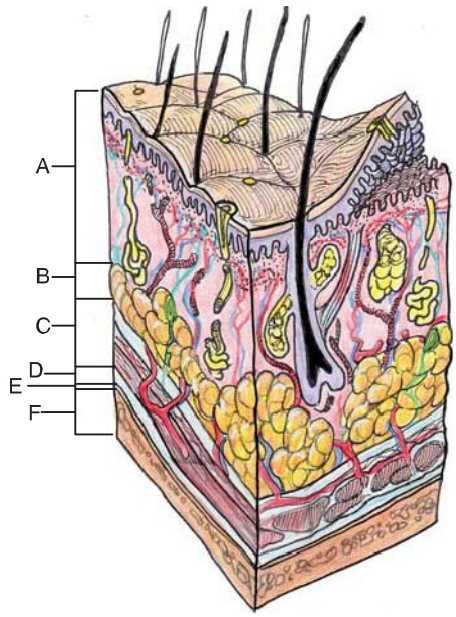


Figure 75.5 Five layers of the scalp: *A*, skin; *B*, subcutaneous tissue; *C*, galea aponeurosis; *D*, loose connective tissue; *E*, pericranium; *F*, calvarium (skull).

to temporize bleeding until further examination can be undertaken. Injection of lidocaine with epinephrine into the wound edges can help in temporizing bleeding as well. When necessary full-thickness sutures can be placed to aid in hemostasis.

Evaluation

Physical examination should proceed in a systematic fashion with specific attention turned to the neurological examination. Underlying skull fractures or associated intracranial processes must be considered. Particular attention should be paid to the present hair distribution and hairline. Wound closure should preserve these landmarks whenever possible. Small areas of alopecia may be managed by wide scar excision or hair transplantation in the future (24).

Closure

Wound preparation should be performed with copious irrigation, and undermining should proceed in the subaponeurotic plane. The scalp is known for its inelasticity, and moving adjacent tissue for wounds greater than 3 cm in size can pose great difficulty. Some authors recommend galeal incisions placed parallel to the laceration in hopes of recruiting an additional 1 to 1.5 cm of tissue and help decrease wound tension during closure. This maneuver requires clinical judgment and experience and is almost never performed by the authors. This strategy is at the expense of tensile strength and vascularity, limiting its use in larger defects (24).

For moderate defects of 2 to 2.5 cm in size, Leedy et al. (23) recommend use of V-Y flaps, V-Y-S flaps, subcutaneous pedicled flaps, or rotation advancement flaps. For large defects with intact pericranium, options include use of split-thickness skin grafts and secondary tissue expanders as well as flap reconstruction (23). If the pericranium is intact, the authors usually allow healing by second intention, thus allowing wound contraction to make the ultimate defect smaller. Reconstructive maneuvers mentioned above are seldom employed at the initial repair.

If the pericranium is not intact, but the surrounding scalp is viable, rotation or other scalp flaps can be used to fill the defect, with skin grafts or primary closure used at the donor-site defect. Large defects without pericranium can be treated with open wound care and complex reconstruction techniques such as rotation-advancement flaps or free tissue transfer can be performed in a delayed fashion.

Total avulsion or near-total avulsion injuries are best managed by microvascular reanastomosis and replantation if the scalp tissue is viable and available. If this option is not available, the authors would typically treat the open wound and then decide upon a strategy that might include a STSG versus flap reconstruction. Leedy et al. (23) feel that free tissue transfer is the best option such as a free latissimus-serratus flap.

The use of 4-0 running locking nonabsorbable suture is advocated for appropriate hemostasis and wound closure at the level of the galea and dermis. Cosmetic results following skin closure have been shown to be equivalent with the use of staples as opposed to sutures, in the pediatric population. Additionally, benefits from time savings, costs, and decreased wound closure times were noted (25). One must consider the restrictions in imaging with the use of stainless steel staples if MRI imaging is anticipated in the immediate perioperative period. If satisfactory primary closure has been obtained the authors allow gentle hair washing after 48 hours with mild baby shampoo. Whether staples or sutures are used, removal is typically at 7 to 10 days.

Complications

Specific to this area, complications include sensory deficits, hematoma formation, scar deformity, and alopecia.

Forehead, Temple, Brow

The area of the forehead, temple, and brow are anatomically linked, with features of significant esthetic importance. Damage to the neuromuscular structures that lie within these regions can leave a patient with significant functional deformities, including forehead paralysis and brow ptosis. Resulting scars may be associated with traction on the eyelid resulting in visual impairment and deformity. The unique layers of the temporal region must be examined closely and are depicted in Figure 75.6, with attention to the neurovascular structures within the various layers. The superficial temporal fascia (STF) is contiguous with the superficial muscular aponeurotic system (SMAS) inferiorly and the galea superiorly. The temporal branch of the facial nerve courses within the STF above the zygomatic arch anterior to the superficial temporal vessels. By connecting a point 0.5 cm inferior to the tragus to a point 1.5 cm lateral to the superior brow, its course can be estimated.

Evaluation

Examination should document any sensory or motor deficits. Palpation of the supraorbital ridges should be performed observing any bony step offs concerning for underlying fracture. It is important to assess for frontal sinus fractures. CSF leak may occur with posterior table involvement and may be visible in the wound. Epidural or subdural hematomas can result from injuries in the temporal region, whereas temporal bone fractures can be associated with hearing loss or facial nerve paralysis.

Closure

Often there is ample adjacent tissue to move; however, the position of important structures must be maintained. Forward or lateral movements of the hairline or eyelid, respectively, should be avoided. The contralateral brow can be used as a guide to align the involved brow. The brow should not be shaved as this is a critical landmark. The brow margins should be identified and the direction of hair growth used for proper alignment. Other considerations are the involvement of the temporal branch of the facial

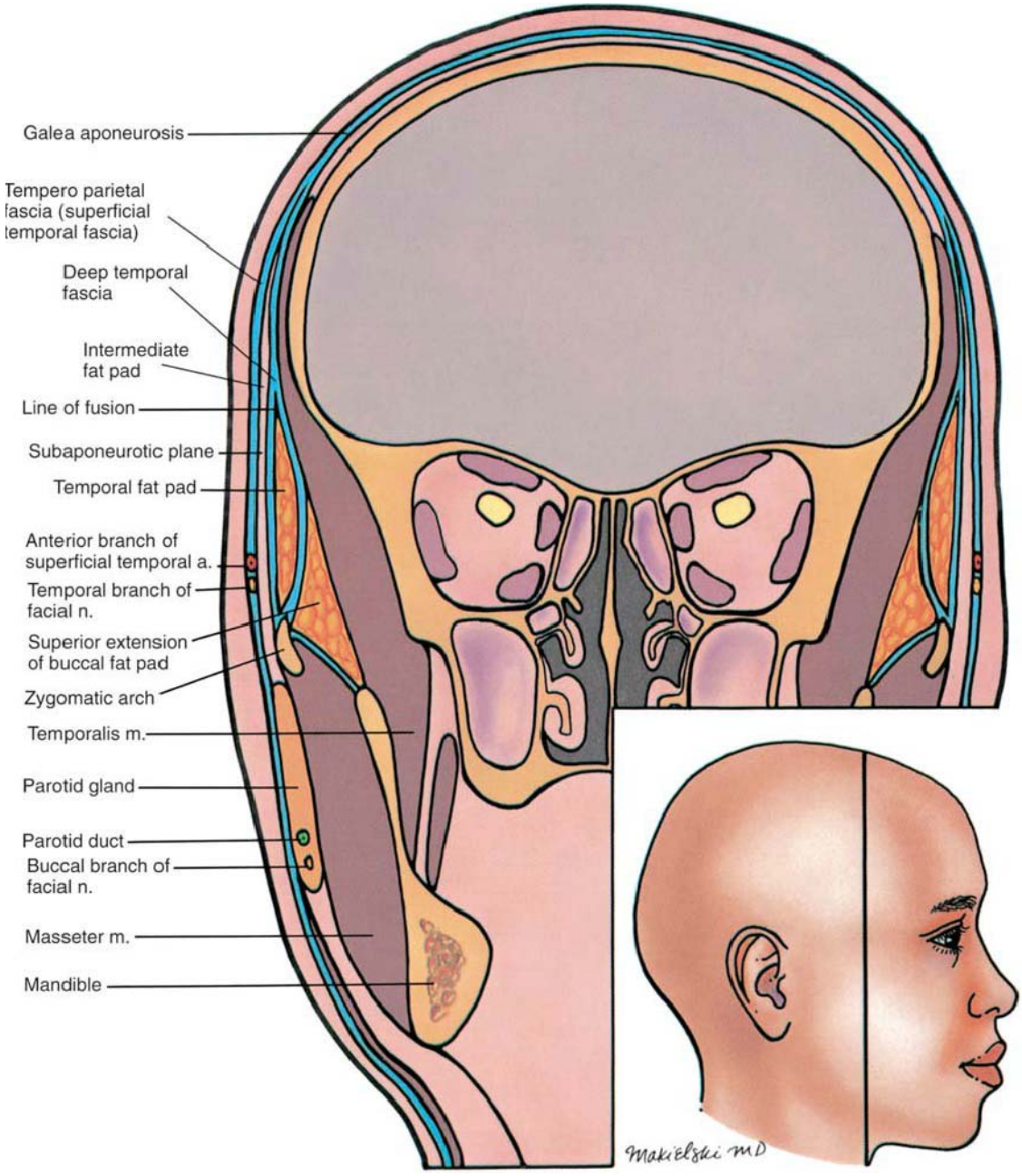


Figure 75.6 The unique anatomy of the temporal region with attention directed at the STF and the intimate relationship with the temporal branch of the facial nerve.

nerve, and caution should be exercised with deep closure in the pathway of this nerve, such as over the zygomatic arch.

The deep layers are closed in layers using a 5-0 polyglactic suture in an inverted buried manner. In the region of the eyebrow, only one or two dermal sutures should be used and superficial dermal sutures are avoided in order to avoid damage to the hair follicles. The cuticular closure consists of either a fine fast absorbing gut suture or a 6-0 polypropylene permanent suture, blue in color so that the sutures can be easily seen upon removal. This can be performed with simple interrupted or vertical mattress sutures. Sutures can be removed in 5 to 7 days. Scar revisions may be necessary, but the authors urge patients to wait 6 months after injury for appropriate healing and maturation.

Complications

Complications associated with hair follicle damage and avulsion injuries of the brow can lead to alopecia. With meticulous technique, hair loss can be minimized. Alopecia can occur despite appropriate technique, and hair transplantation can be considered.

Facial nerve injury, specifically the temporal branch, can result in frontalis muscle weakness or paralysis, causing

forehead paralysis and brow ptosis. Please see the following section on facial nerve injury.

Eyelids and Lacrimal System

The lower eyelid anatomy can be divided into anterior, middle, and posterior lamellae. The anterior lamella consists of skin and the orbicularis oculi muscle which is involved in squinting, blinking, and forced closure. The middle lamella consists of the orbital septum, whereas the posterior lamella includes the tarsus and conjunctiva. The distinct layers of the eyelid become extremely important as closure is attempted, with careful attention to reapproximation of the tarsus and muscular anatomy to restore the lid's protective functional role.

The upper eyelid lamellar anatomy is similar with the exception of the levator palpebrae superioris muscle, which forms an aponeurosis as it sweeps over the globe and fuses with the orbital septum. Dense attachments to the anterior lamella, as well as the anterior surface of the tarsus or posterior lamella are also formed (26). These attachments allow the levator muscle to elevate the upper lid. The sympathetically controlled Mueller's muscle adjoins the levator palpebrae superioris muscle and acts to provide tone and static position to the upper eyelid.

The lateral canthal tendon (LCT) connects the tarsal plates deep to Whitnall's tubercle along the lateral orbital rim. Superficial anterior and posterior fibrous attachments of the tarsal plate and fibers of the pretarsal orbicularis also attach to the lateral orbital rim (27).

The medial canthal tendon (MCT) is considered to be the tendon of the pretarsal orbicularis oculi muscle with an additional posterior limb of the MCT from the palpebral portion of the orbicularis oculi muscle. The lacrimal sac, encased in fascia, is then bounded anteriorly, laterally, and posteriorly by the constituents of the MCT and medially to the bony fossa of the lacrimal sac (28). Injuries at the level of the MCT are in close proximity to the lacrimal system making concomitant injuries common.

Evaluation

Significant morbidity can occur from injuries involving the periocular area, with a substantial percentage of eyelid injuries presenting with accompanying canalicular and/or underlying globe injury. Evaluation should include mechanism, ocular history, visual field changes, blurred vision, double vision, and visual acuity changes. Periocular swelling can be substantial, especially in delayed presentation, where a standard Snellen acuity cannot be established. In these cases near vision, finger counting, and light perception can be documented. Pupillary examination should be performed with any evidence of asymmetries, shape disturbances, or poor reactivity necessitating ophthalmology consultation. This can signify an underlying Horner's syndrome, afferent pupillary defect, third cranial nerve palsy, or damage to intraocular or intraorbital structures (26).

Extraocular muscle testing should then be performed with attention paid to limitations in movement, which can signify orbital soft tissue edema, extraocular muscle injury, or entrapment from underlying fractures. Examination of the globe and anterior segment must be performed to identify the presence of foreign body, corneal injury, hyphema, or ruptured globe (26).

Lacerations and avulsions should be examined with assessment of both surfaces of the upper and lower eyelid, along with adnexal structures. Injuries to the medial canthal region raise the possibility of canalicular injury and involvement. Facial sensation, eyelid position, and asymmetries as well as telecanthus from underlying fractures should also be noted (26).

Closure

After evaluation and removal of any debris or particulate matter with copious irrigation attention can be turned toward wound closure. Important considerations include the use of corneal protectors before any injections, or closures are attempted around the area of the globe. Debridement should be fastidious and limited only to tissue deemed necrotic. The authors recommend the surgeon to use loupes or magnification for closure of periorbital injuries, and in many cases repairs in an operating room are advocated. Appropriate and optimal use of anesthesia and operating room staff and equipment is often best for the patient even with a 24- to 48-hour delay in treatment, with the exception of ocular emergencies.

When performing closure of full-thickness eyelid margin lacerations, it is critical to address all layers using a three-suture technique to avoid and minimize long-term sequelae. Avulsed segments of up to one-fourth of the lid margin may be closed primarily. First, the cut edges of the tarsal plate should be identified with the edges freshened if needed. Murchison and Bilyk (26) recommends passing a single 6-0 prolene stitch at the meibomian gland line, found slightly posterior to the ciliary line (the lash line) and gray line, to temporally act as a traction suture and realign the eyelid margin, without tying it (Fig. 75.7).

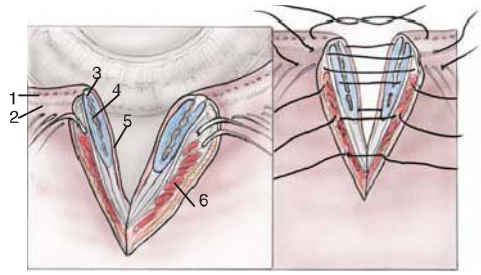


Figure 75.7 Closure of the eyelid defect highlighting the realignment of the tarsus and the three suture technique for lid margin repair. Sutures are placed at the level of the meibomian glands, gray line, and lash line. Lid margin sutures are left long to avoid contact with the cornea. *1*, meibomian orifice; *2*, gray line; *3*, mucocutaneous junction; *4*, inferior tarsus and meibomian glands; *5*, palpebral conjunctiva; *6*, orbicularis oculi m.

The tarsus is then reapproximated with partial-thickness sutures. Care must be paid to the lamellar boundaries being careful to not pass into the conjunctiva to avoid post repair corneal irritation from suture material. Begin near the eyelid margin and then proceed along the vertical length of the plate using a 5-0 or 6-0 polyglactin suture.

Once the tarsus is realigned the eyelid margin traction suture can be tied with long tails, followed by placement of an anterior single suture at the ciliary line and an additional suture at the gray line (Fig. 75.8). Care must be taken to avoid corneal irritation with the tails of the lid margin sutures left long and draped onto the skin of the eyelid



Figure 75.8 **A:** Full-thickness injury to the left eyelid with brow involvement. **B:** Exposed globe and periorbital fat concerning for levator injury. **C:** Reapproximation of the levator (grasped by forceps) with visualization of the insertion into the tarsus. **D:** Skin closure with long tails left long and incorporated into a separate skin suture in order to avoid corneal irritation. **E,F:** Postoperative outcome with appropriate brow realignment and mild lid contour deformity noted.

where they are sutured to the underlying skin. The skin and orbicularis are then closed with absorbable or nonabsorbable suture in an interrupted or running fashion. Suture material choices should be carefully considered in the trauma population. However, if the patient is unlikely to return a long-lasting absorbable suture may be used. The lid margin repair should be with a nonabsorbable suture to prevent premature dissolution or breakage.

Upper eyelid injuries with herniation of fat and ptosis are concerning for injury to the levator superioris muscle or aponeurosis. Care must be taken to thoroughly explore the wound and identify the levator muscle and/or aponeurosis with appropriate repair. The violated orbital septum should not be repaired for concerns of eyelid retraction.

Lateral canthal injuries, whether from blunt, sharp, or penetrating trauma put the globe at risk, given the poor bony protection laterally. Murchison and Bilyk advocate two tenets in repair of LCT injuries. First, repair begins by suturing and reapproximating the retinaculum of the LCT to the inner aspect of the lateral bony orbital rim at Whitnall's tubercle. This maneuver will allow for appropriate functional aesthetic curvature of the lid and avoidance of ectropion. The second principle addresses the lateral canthal angle with a separate suture from meibomian gland line on the lower lid to meibomian gland line of the upper lid. This allows for a sharp lateral canthal angle (26).

The intimate anatomic relationship of the lacrimal drainage system to the MCT make associated injuries more frequent. Injuries medial to the puncta or those associated with animal bites also confer an increased risk of canalicular injury (29). Examination should proceed with careful and methodical probing after anesthetizing the eye and lacrimal puncta with topical ocular anesthetic, as this can otherwise be quite uncomfortable for patients (Fig. 75.9). Especially in the case of canalicular injury, direct anesthetic injection can increase edema at the injury site making identification and cannulation of the canalicular orifice more difficult. Injured canaliculi are then intubated with silicone stents, either monocanalicular or bicanalicular. Once identified and intubated, further repair of the canalicular injury can be undertaken. Kersten and Kulwin (30) advocate repair of the pericanalicular orbicularis oculi muscle, with reapproximation from stenting and a single mattress suture. Repair of the MCT should be performed using a posterior medial vector with deep absorbable suture placement in the periosteum.

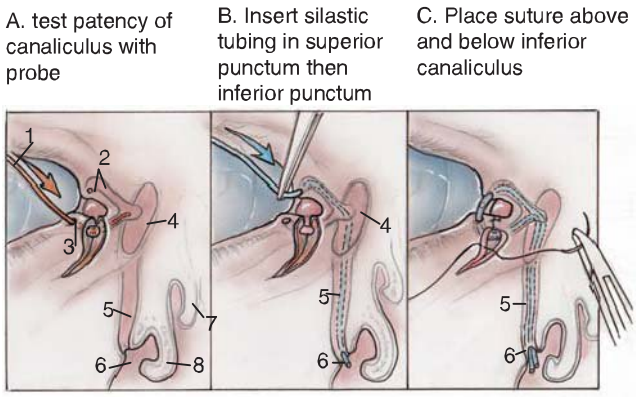


Figure 75.9 Approach to canalicular injuries. **A:** Probing the inferior canaliculus to test patency. **B:** Stent placement. *1*, probe; *2*, superior punctum and canaliculus; *3*, inferior punctum and canaliculus; *4*, lacrimal sac; *5*, nasolacrimal duct; *6*, NLD osteum; *7*, middle turbinate; *8*, inferior turbinate. **C:** Suture placement.

Avulsion injuries with subsequent tissue loss pose a complex reconstructive dilemma. In addition, adequate corneal protection is paramount. With eyelid avulsion injuries, the goals of repair are to create a functional eyelid with adequate tearing and preservation of vision. In selected cases, a lateral canthotomy with cantholysis can be performed for mobilization of additional tissue to aid in closure. In the rare cases of total avulsion, corneal lubrication and protection take precedence and delayed multistage reconstruction will be necessary. Bacitracin ophthalmic ointment should be applied twice daily in the care of wounds and lacerations of the periorbital region. Canalicular stents remain in place for 12 weeks and can be removed in the clinic setting.

Complications

Despite timely and appropriate care, these injuries can result in periorbital and eyelid complications. Many can be managed conservatively with observation, such as mild eyelid malposition treated with digital massage. However, those with moderate to severe dystopia, significant corneal exposure, lagophthalmos or ectropion, will require further intervention to avoid exposure keratopathy and improved cosmesis. Ptosis occurs with levator injuries and even with repair it may take several months for resolution. Other complications include notching of the lid margin and epiphora.

Nose

The nose is particularly susceptible to injury given its prominent position and is a commonly injured site following facial trauma. Injuries of the nose can result in disfigurement from scarring and distortion, as well as functional abnormalities such as nasal obstruction.

Nasal anatomical relationships become functionally important at the level of the nasal valves both internal and external. The external nasal valve is at the level of the nasal vestibule, alar lobule, and caudal septum. The internal valve is at the level of the caudal margin of the upper lateral cartilage, with the nasal septum medially, and the inferior turbinate at the inferolateral position.

Evaluation

Examination of nasal trauma should start with simple frontal inspection, and note any deviation or asymmetry to the nose. Associated facial, nasal, or septal fractures should be recognized. Anterior rhinoscopy should also be performed using either a nasal speculum or fiberoptic endoscope examining for acute septal deformity, dislocation, hematoma, mucosal tears, and CSF leak.

Next attention should be turned to cutaneous lacerations, noting any involvement of underlying cartilage, avulsed or

missing tissue or through and through involvement. Severe nasal injuries, such as nasoethmoid fractures warrant formal ophthalmologic examination, since up to 59% of midface fractures have associated ocular injuries (5).

Closure

Repair of soft tissue injuries to the nose follows the same guidelines as closure of all facial wounds, with excellent functional and cosmetic outcomes as the primary goal. Wounds are classified by depth and assessment of tissue loss in the case of avulsion injuries. Superficial lacerations extending into the subcutaneous tissues can be closed with the use of absorbable deep dermal sutures, and the surgeons preferred suture for skin closure.

Cartilaginous involvement is addressed with meticulous alignment and prevention of deviation or collapse. The use of nonabsorbable or long-lasting absorbable suture for reapproximation is preferred, and in the case of lower lateral cartilage involvement the use of interrupted nonabsorbable polypropylene suture is preferred for appropriate wound support and durability.

Full-thickness lacerations involving the skin and nasal mucosa are closed in layers beginning with the nasal mucosa using a 5-0 chromic suture in an interrupted fashion. Then this is followed by closure of the muscular, cartilaginous, dermal, and skin layers as outlined above. Many times the alar rim or alar lobule is involved and thus there is particular concern of post repair notching. Care must be taken to ensure appropriate alignment of these structures in particular.

Avulsive wounds of the nose are a common form of presentation, and repair may involve primary closure, skin grafts, composite grafts, or local flaps. Complex reconstruction is not appropriate in the acute setting.

An intranasal silastic stent can be placed to avoid or minimize vestibular stenosis or collapse.

Complications

Complications of nasal injury may result in vestibular stenosis and nasal obstruction. Deformities include scarring, alar sidewall collapse, and alar retraction. Hypertrophic scarring can also be seen in select individuals. Infection following an undiagnosed septal hematoma can be seen days later and must be kept in the differential if the patient reports acute onset of increased pain, nasal obstruction, and signs of fever. This would necessitate emergent incision and drainage.

Cheek and Parotid

The parotid gland is the largest of all salivary glands with its position in the retromandibular space between the ramus of the mandible and mastoid process. The gland is invested in a dense fibrous capsule derived from the investing layer of the deep cervical fascia, and over this fascia lays the SMAS. The SMAS also serves as the attachment for the muscles of facial expression. The deep aspects of the gland pass through the stylomandibular tunnel to rest within the parapharyngeal space (31).

The parotid duct (Stensen's duct) travels across the surface of the masseter in a horizontal plane. On reaching the anterior border of the muscle, the duct's course turns medially as it pierces the buccinator muscle toward the oral cavity. The mucosal papilla opening is found in the oral cavity opposite the second upper molar. Traveling along side the duct, in a predictable anatomic fashion, is the buccal branch of the facial nerve. This relationship on the superficial aspect of the masseter muscle makes the duct and nerve more vulnerable to injury, thus must be considered in soft tissue trauma of the cheek and parotid region.

Evaluation

Recognition of parotid injury is essential to avoid late complications. When examining the patient, the wound should be explored for evidence of clear drainage suspicious for saliva. This can be accomplished by massaging the gland and inspecting for presence of saliva within the wound. If an injury has been missed, the patient may report swelling in the area of the closed laceration, especially after meals over the course of the next few days.

If parotid injury is suspected, the wound should be thoroughly examined within 24 hours to avoid surrounding inflammation and edema from obscuring the ductal and nervous structures, and subsequent injury during exploration.

Facial nerve examination, with particular attention to the buccal nerve branch, should be conducted with any weakness documented. The course of the parotid duct and associated buccal nerve can be projected using a line drawn from the tragus to the midportion of the upper lip (Fig. 75.10). Injuries violating this line must then be inspected for ductal and neural injuries. Discussion of facial nerve injury is presented elsewhere in this chapter.

Patency of the ductal system can be assessed either with simple cannulation using a silicone catheter, retrograde injection with methylene blue or saline, or sialography. The author advocates simple cannulation using a lacrimal probe or silicone catheter.

Closure

In 1981, Van Sickels constructed a classification system for anatomical regions of injury in parotid trauma with a recent update of this schema (31,32).

Anatomic regions are divided into A, B, and C with divisions based on their relationship to the masseter muscle. Prognostic and treatment information can be derived from this classification system. Region A is the area posterior to the masseter with likely injury to the parenchyma of the gland. Wounds in this region can safely be closed in layers with particular attention paid at the level of the SMAS (31).

Region B is associated with the area overlying the masseter muscle, and carries the highest risk of ductal injury. Ductal injury increases healing time from continued salivary flow into the wound. If injury of the ductal system is visualized or suspected, cannulation of the duct through the papilla using a silicone catheter or stent should be passed retrograde. The lacerated end will be identified and

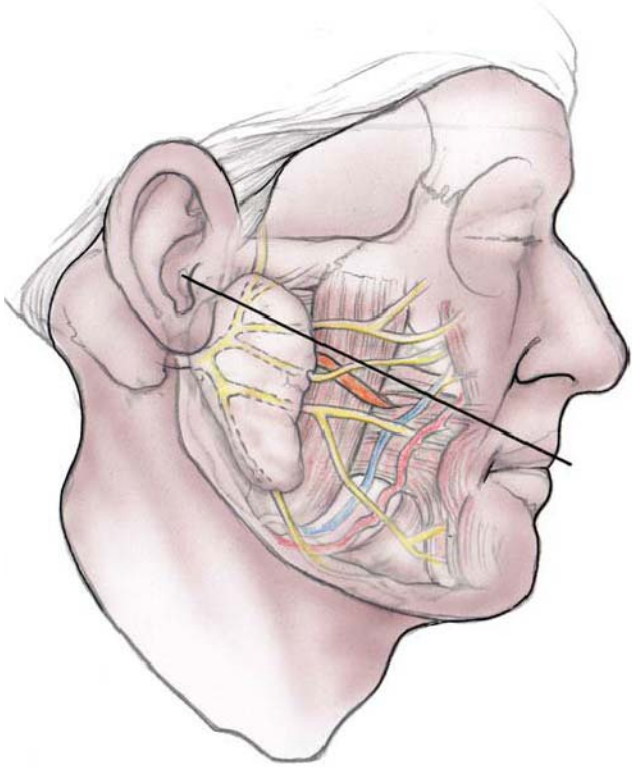


Figure 75.10 Parotid duct anatomy. Injuries violating a line drawn from the tragus to the upper lip should raise concern for injury to the parotid duct.

the opposing proximal transected duct identified. The ends are then dissected free to allow for tension-free closure of the severed ends over the silicone catheter. Microsurgical techniques, using a 7-0 to 9-0 monofilament suture, are employed for closure (Fig. 75.11). The catheter is then sutured to the buccal mucosa for 10 to 14 days to hold the duct and orifice open during healing. If the injury precludes this, the end of the proximal duct can be brought out to the buccal mucosa and sialodochoplasty is performed.

Region C is the area anterior to the masseter muscle. In this region, the distal duct or papilla is injured and reanastomosis may not be feasible. It may be necessary to divert the duct into the buccal mucosa, thereby creating a new duct orifice as noted above. A stent is left in place at the newly constructed papilla (31). Some authors mention parotid duct ligation of the proximal section resulting in acute parotid swelling, pain, and salivary back-flow with eventual glandular atrophy. We do not advocate this.

If appropriate, techniques to reduce salivary flow or reduce accumulation include placement of compressive dressings, and anticholinergic medications. In recent years, botulinum toxin A (Botox, Allergen Inc, Irvine, CA) has been successfully used in these circumstances as well. Some patients may require needle aspiration of accumulated saliva post closure.

Antibiotic coverage in the setting of injury or post injury sialocele should include coverage for *Staphylococcus aureus, Haemophilus influenzae,* and anaerobic Gram-negative bacteria (33). A second- or third-generation cephalosporin, clindamycin, or amoxicillin with clavulanic acid is usually sufficient, with considerations for methicillin-resistant *S. aureus* in persistent infections.

Complications

Injuries to the parotid and cheek region can result in prominent facial scarring and disfigurement. Specific to the this region one can also see gustatory sweating (Frey syndrome), sialocele formation, and salivary-cutaneous fistula.

Late complications are increased if the techniques noted are not employed or the injury goes unrecognized. Nonsurgical management is described above. Formerly, tympanic neurectomy was a consideration for those cases where a decrease in salivary flow was therapeutic. Now this has been largely abandoned due to the effectiveness of botulinum toxin injection. If all options have been exhausted in the setting of persistent fistula, parotidectomy may be entertained. This poses a challenge for safe facial nerve dissection in the setting of extensive scarring and fibrosis from the injury and fistula.

Facial Nerve Injury

The anatomical considerations of the facial nerve are summarized here as they relate to acute soft tissue injury of the face. Discussion is limited to the extratemporal course of the facial nerve as it exits the stylomastoid foramen and innervates the muscles of facial expression, posterior digastric belly, and posterior auricular and stylohyoid muscles. Innervation to the muscles of facial expression is all along the deep surface of the muscle with the exception of the levator anguli oris, buccinator, and mentalis muscles. This anatomical relationship is important in cases of penetrating injuries and exploration to avoid iatrogenic injury. Transection of the main trunk results in complete facial paralysis, while injuries distal to the pes anserinus or muscles themselves, will result in inability to move the involved area of the face (34).

Injury to the facial nerve can have devastating consequences resulting in diminished emotional expression for patients attempting to smile, frown, or grimace. The functional aspects affecting oral competence can be disabling and may limit social activities, eating habits, and speech. The protective mechanism of the facial nerve should also be considered, with innervation to the stapedius muscle as well as the orbicularis oculi muscle, providing eye closure and the blink reflex. Severe keratopathy from unrecognized chronic corneal exposure may lead to blindness.

Evaluation

Once the patient is stabilized and able to cooperate, facial nerve function should be tested. Other cues such as grimacing in the presence of a noxious stimulus can also aid in assessment for patients who are unable to perform

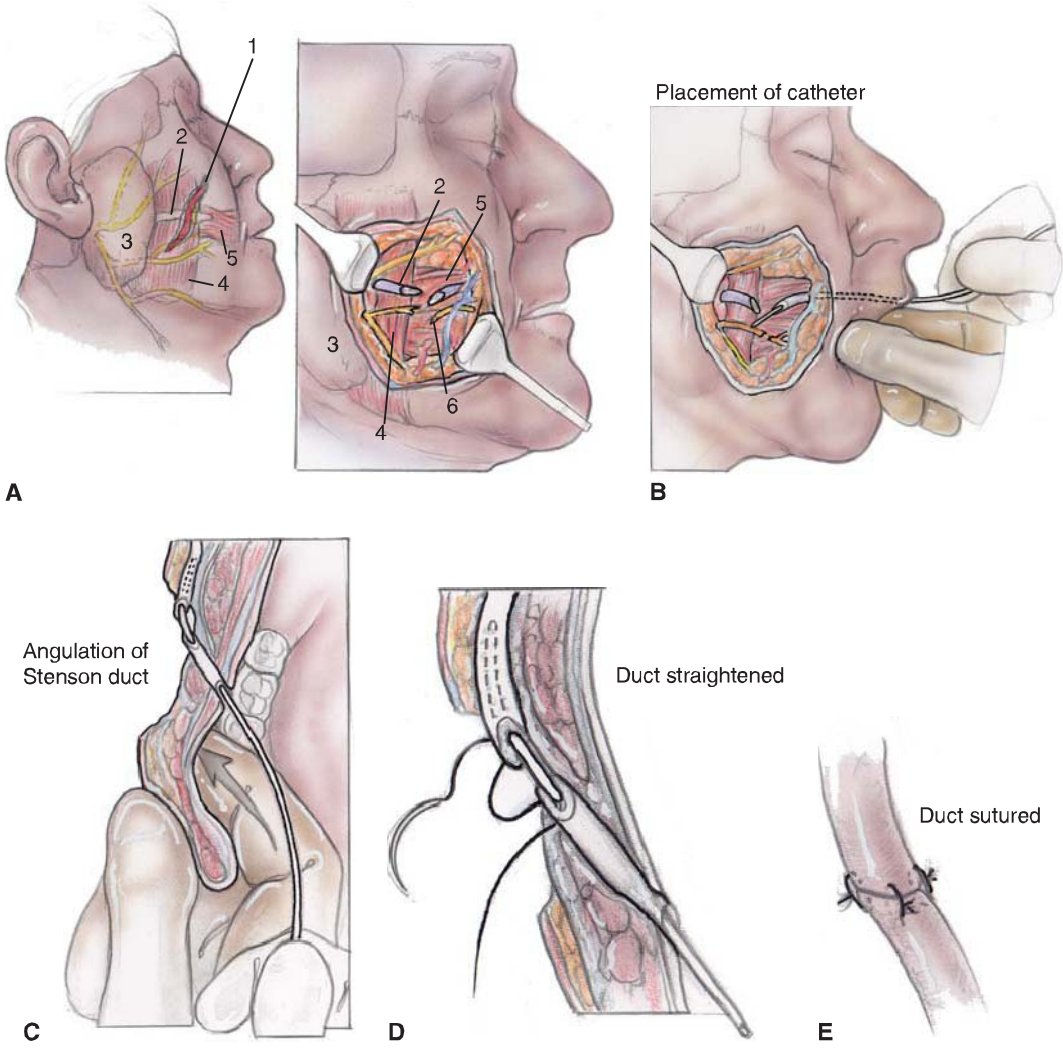


Figure 75.11 Cannulation and repair of parotid duct. *1*, laceration; *2*, Stenson's (parotid duct); *3*, parotid gland; *4*, masseter m.; *5*, buccinator m.; *6*, transected buccal branch. **A:** Right cheek laceration with severed duct and nerve branch. **B–E:** Duct cannulation and repair.

volitional movements. The examiner should ask the patient to raise their eyebrows, close their eyes, smile, purse and pucker the lips, and puff out their cheeks (34). Complete transection results in complete paralysis with no volitional movement. Crush injuries often present with normal function followed by partial or delayed paralysis, often with resolution with expectant management.

Several grading systems have been proposed with the most widely accepted and used being the House-Brackmann scale (see Chapter 155). Although other rating systems have been introduced, the authors prefer conscientious documentation using terminology that identifies the branches involved and the degree of paresis (34).

When evaluating the patient, an imaginary vertical tangent can be drawn from the lateral canthus inferiorly and injuries anterior to this line are not explored for facial nerve injury. The highly redundant collateral innervation from other branches makes recovery likely, as well as the fact that the small diameter of the nerves anterior to this line makes identification and reanastomosis difficult.

Exploration of the wound may reveal transected ends of the nerve. The use of a nerve stimulator for the distal branches can aid in identification for up to 72 hours, after which Wallerian degeneration occurs and compromises excitability of the nerve.

Closure

Facial nerve injuries should be explored and repaired as soon as possible. When nerve identification and repair is anticipated, the procedure should be done in the operating room under general anesthesia, as lidocaine would create inability to use a nerve stimulator. In the critically ill patient, the injured branches should be tagged with permanent suture or clips on adjacent tissue can be placed. Then reanastomosis can be performed once the patient is stable.

Primary neural repair provides the best chance for return of facial nerve function. This can performed with the operating microscope using 8-0 to 10-0 monofilament nylon suture. Tension-free closure of the epineural layer should be performed, although some authors recommend perineural repair as having the potential advantage of reducing synkinesis and mass facial movement (34–36).

When a tension-free direct repair is not possible, cable (interposition) grafting is advisable. The use of great auricular, sural, and medial antebrachial cutaneous nerves offers the best option for achieving volitional facial movement (37).

When facial nerve repair is not possible, facial reanimation procedures can be performed at a later date.

Complications

Complications in the setting of facial nerve injury include inability to repair the nerve injury, facial nerve paralysis, synkinesis, and mass facial movement. Often unpreventable, the risk of complications can be reduced with early recognition and management. Late complications include corneal injury from inability to attain complete eye closure with associated dry eye and keratopathy. In addition oral incompetence, brow ptosis, and dysarthria may result.

Auricle

The ear typically protrudes from the head at an angle of 25 to 30 degrees with 15 degrees of incline. This prominent position opens the ear to frequent lacerations and shearing forces leading to avulsions. The external ear consists of the auricle and EAC. The skin is tightly adherent over the compliant cartilaginous framework of the ear covered by perichondrium. The surface anatomy of the ear offers a complex topography making replication and reconstruction difficult (Fig. 75.12). Even if early repair is instituted, severe traumatic auricular injuries may require multiple procedures for reconstruction (38).

Evaluation

Examination should start with inspection of the EAC as lacerations at this site can potentially lead to EAC scarring and stenosis. The EAC should be cleaned of any debris or blood. Integrity of the tympanic membrane should be confirmed and hearing loss identified. Tuning fork examination is an appropriate initial measure and an audiometric testing can be performed if hearing loss is a concern.

Examination of the postauricular region for evidence of mastoid tenderness or ecchymosis (Battle's sign) concerning for basilar skull or temporal bone fractures should be performed. Radiographic imaging to evaluate for fractures or dislocations should be performed if concern exists. Cranial nerve examination should be performed with special attention paid to the ipsilateral facial nerve.

Inspection of the wound should be performed, noting the extent of cartilaginous involvement or loss. Height and width discrepancies can be compared with the contralateral ear. Debridement should be minimized given the relative lack of available skin for closure and cartilage coverage.

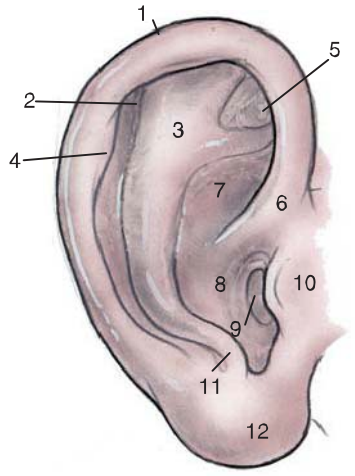


Figure 75.12 Anatomy of the external ear. *1*, helix; *2*, scaphoid fossa; *3*, antihelix; *4*, auricular tubercle; *5*, triangular fossa; *6*, crus helicis; *7*, cymba concha; *8*, cavum concha; *9*, external auditory meatus; *10*, tragus; *11*, antitragus; *12*, lobule.

Closure

Lacerations of the EAC rarely necessitate suture repair. Stenting with nonabsorbable sponges should be instituted if stenosis is a consideration, but only after tympanic membrane evaluation.

Isolated lobule injuries can be repaired with primary layered closure or z-plasty techniques to prevent any notching at the inferior margin of the lobule. Cutaneous injuries of the ear with cartilage exposure are managed by primary closure. Full-thickness skin grafts can also be used for cartilaginous coverage in cases of isolated skin loss or to avoid trimming cartilage in avulsion injuries as to not decrease the size of the ear (Fig. 75.13).



Figure 75.13 Auricular injury with exposed cartilage. Repaired with FTSG without further loss of auricle size (3 month result).

Patients with full-thickness loss of skin and cartilage present a challenge. For helical defects a wedge excision technique may be used. This can be safely performed up to 5 mm without threat of auricular deformity. Reconstructive options should aim at complete cartilaginous coverage with care to achieve a tension-free closure. If the full-thickness defect is small (less than 1.5 cm), the cartilaginous remnants can be trimmed and closed using a polydioxanone monofilament suture in an interrupted fashion using a taper needle to avoid cartilaginous tears. This allows for maintenance of auricular proportions, but may reduce the overall size of the ear dependent on the amount of missing tissue (39). Skin closure is accomplished using interrupted 5-0 polypropylene or absorbable monofilament suture (Fig. 75.14).

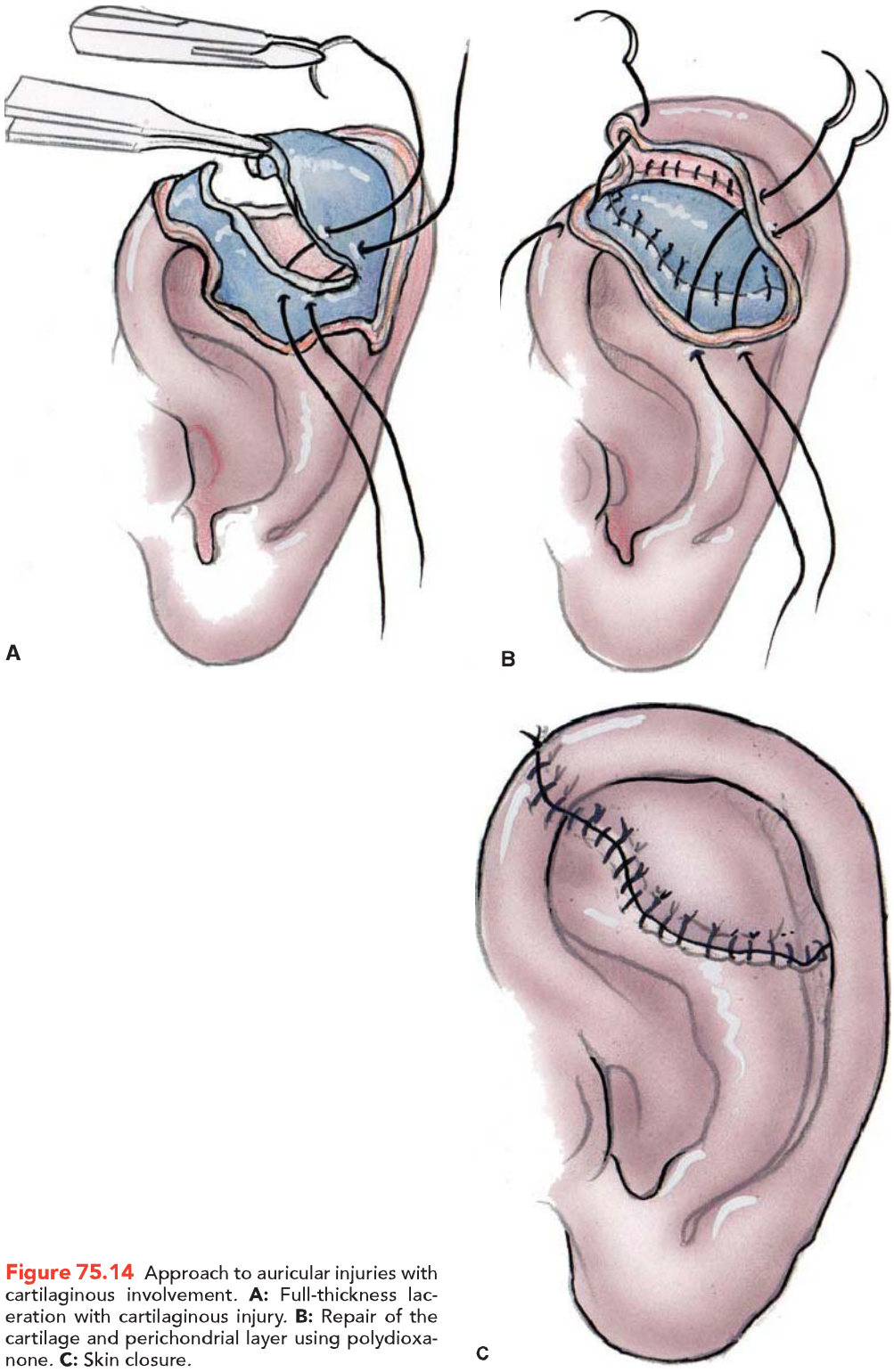


Figure 75.14 Approach to auricular injuries with cartilaginous involvement. **A:** Full-thickness laceration with cartilaginous injury. **B:** Repair of the cartilage and perichondrial layer using polydioxanone. **C:** Skin closure.

Avulsion injuries should be scrutinized for disruption of blood supply and degree of tissue loss. Injuries with a narrow vascular pedicle may be closed but the patient should be counseled about possible impending tissue loss. The authors feel that primary closure should be attempted, allowing further demarcation and necessary debridement. In the setting of complete auricular avulsion, reconstruction algorithms are dictated by whether the ear is found at the scene. In the case of a missing auricle, the wound should be closed over primarily and delayed reconstructive options discussed with the patient, including future auricular reconstruction using costal cartilage grafts versus prosthesis placement.

If the avulsed segment is found, care must be taken in the storage and transport of the ear. The tissue should be wrapped in gauze and placed in a plastic bag, which is placed in an ice bath at 4°C, avoiding direct contact with water. If microvascular expertise is available, the amputated segment should be evaluated using an operating microscope for identification of suitable vessels for microvascular reimplantation. This offers the highest survival rate for the reimplanted ear (38,39). Pocket techniques are described in which the segment is dermabraded, attached, and buried in the postauricular skin with later exposure of the attached segment (38). The authors generally advise against manipulating the postauricular skin in any way as this is the most useful skin in definitive reconstruction. The pocket principle has fallen out of favor and banking cartilage in remote soft tissue sites seems to add no advantage to reconstructive options.

Exposure or involvement of the cartilaginous framework increases the risk of perichondritis substantially. Cartilage-penetrating antibiotics effective against pseudomonas should be used with fluoroquinolones serving as a first-line therapy. In the event of EAC involvement, antibiotic otic drops are prescribed for 5 to 7 days.

Some ear injuries require a bolster to avoid auricular hematoma due to disruption of the cartilage with accumulation of blood within the cartilage fragments or the subperichondrial space. Bolsters can be fashioned using dental rolls or ointment-impregnated gauze with mattress sutures to eliminate dead space (Fig. 75.15). Undue pressure should be avoided as necrosis may result. Others have described use of thermoplastic splints as a shape-forming bolster (40,41). The bolster and EAC wick should be left in place until follow-up at the time of suture removal at 5 to 7 days.

Complications

Injuries involving the external ear can lead to a multitude of complications and concomitant injuries. Close follow-up should be maintained to evaluate for chondritis, temporal bone fracture, and associated hearing loss from ossicular disruption, tympanic membrane perforation, or EAC stenosis. Facial nerve integrity should be monitored as well.

Accumulation of intracartilaginous blood or blood in the subperichondrial plane can lead to auricular hematoma, which can be managed with simple needle aspiration (for small isolated hematomas) or incision and drainage with use of a bolster (for more extensive hematomas) (42). Unrecognized hematoma can result in cartilage loss, necrosis and formation of neocartilage and fibrosis giving the ear a cauliflower ear deformity. This deformity can be disfiguring and difficult to manage, with repair requiring surgical excision of the neocartilage and fibrosis

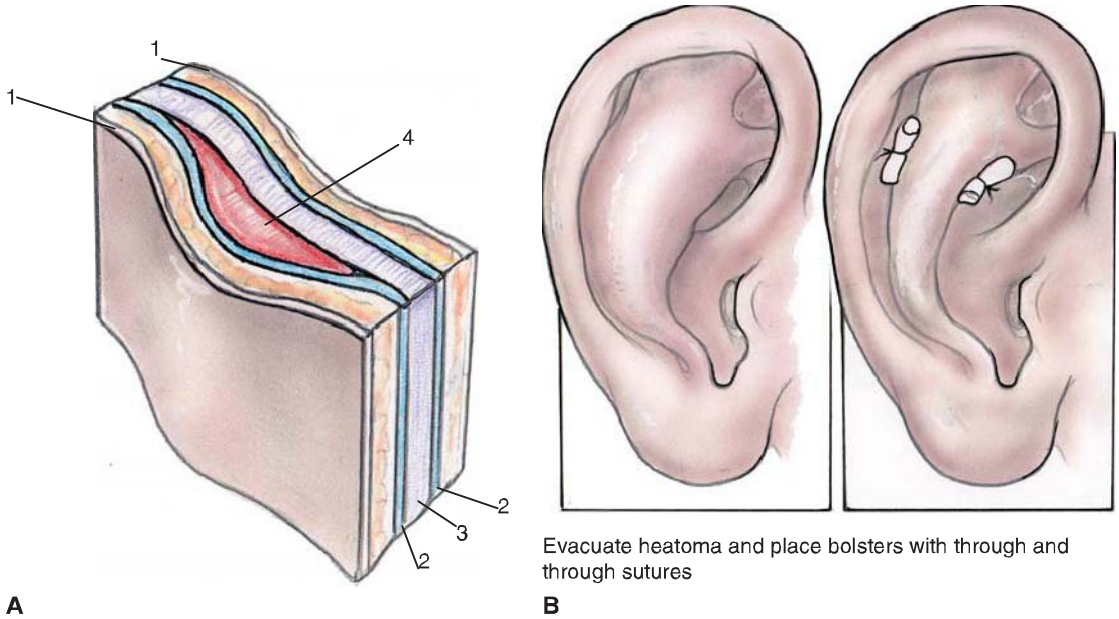


Figure 75.15 Auricular hematoma. **A:** Blood may accumulate within the cartilage fragments or in the perichondrial space. 1, skin; 2, perichondrium; 3, cartilage; 4, hematoma. **B:** Evacuation of the hematoma is followed by placement of a bolster dressing with through-and-through sutures.

using camouflaging incisions. Best practice is avoidance and the judicious use of bolsters.

Lips and Chin

The lip and perioral region embodies both aesthetic and functional components that must be considered in the setting of soft tissue repair. The anatomy of the lip demonstrates surface contours that the human eye is drawn to, such as cupid's bow, philtrum, and the vermilion border. The red lip is comprised of three layers, the outer vermilion layer, the middle muscular layer (of the orbicularis oris), and the inner mucosal layer. At the junction of the facial skin (white lip) and the vermilion (red lip) is the vermilion border with corresponding red and white rolls. The reflecting of light at these rolls makes any injury with even a one-mm misalignment at the vermilion eye-catching and aesthetically unpleasing (4). The mental crease is a horizontal groove between the area of the chin and lips influenced by the mentalis muscle. Realignment of lacerations in this area contributes to a natural division between the lip and chin regions.

The primary blood supply to the perioral region is the facial artery giving rise to the inferior and superior labial arteries which encircle the mouth. Injury here can lead to brisk bleeding making initial evaluation difficult.

Evaluation

As the lip and perioral region are examined, sensory and motor function should be documented, as well as depth and location of the injury. Any extension into the floor of mouth and buccal mucosa should alert the clinician to potential involvement of the salivary ducts. The lips and mucosal surfaces should be examined for associated injuries including changes in dental occlusion and broken or missing teeth. If injuries are present, consultation with the dental team may be necessary prior to repair in order to avoid undue tension and retraction on the suture line during dental repair (4,7).

Closure

The first step of repair is marking of the vermilion border before its boundaries are lost from edema or injections around the site of injury. When appropriate, the use of regional blocks allows the surgeon to evaluate and repair the vermilion border without distortion.

The main tenant of primary closure of lip lacerations is the layered closure, with reapproximation of the orbicularis oris muscle and alignment of the vermilion border. Whether first or last, the mucosa should be closed, usually performed with interrupted absorbable 4-0 polyglactin sutures, using large bites to avoid sutures tearing or eroding mucosa. Critically important is reapproximation of the orbicularis oris muscle to restore sphincter function, and to avoid muscular dehiscence of contraction with healing. A soft tissue deficiency, usually seen months later, is apparent in those cases where the muscle layer is not well approximated.

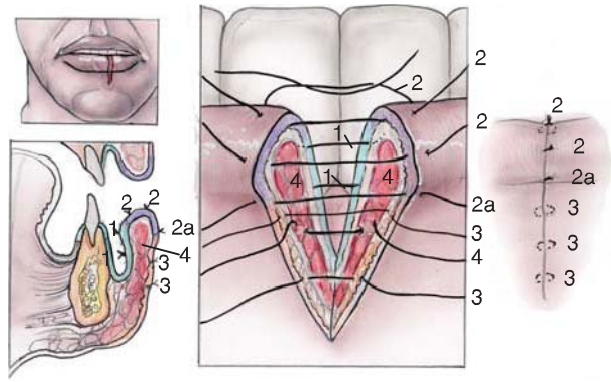


Figure 75.16 Layered lip closure. Layered closure of the lower lip highlighting the realignment of the vermilion and orbicularis oris muscle. Mucosal and skin closure also depicted. *1*, mucosal sutures; *2*, vermilion sutures; *2a*, suture at the vermilion cutaneous border; *3*, skin (dermal) sutures; *4*, orbicularis oris muscle sutures.

The most important stitch in lip reconstruction is next. Marking its importance, placing this suture first could also be considered. Using a permanent monofilament suture, such as a 6-0 polypropylene (Prolene), a single stitch is placed to align the vermilion border. This will allow accurate reapproximation, while the remainder of the vermilion (red lip) is then closed using simple interrupted 6-0 prolene sutures (Fig. 75.16). Facial skin closure is performed in standard layer fashion.

Chin lacerations should focus on recreation of the natural borders and surface landmarks without creating any traction on the lower lip, which is subject to inferior displacement.

If there is more than 30% loss of the lip, primary closure may lead to relative microstomia and undue wound tension. If the defect is too large for primary closure the edges of the defect can be closed and the full-thickness defect can be reconstructed at a later date. Closures outside of primary repair should be deferred for secondary reconstruction using various lip flaps such as Abbe, Estlander, and Karapandzic flaps and are beyond the scope of this chapter.

Complications

Post-traumatic lip deformity is the most common complication following injury. This is not unexpected given the delicate and intricate anatomical features of the lip. The degree of the deformity is directly related to the severity of the injury and the complexity of the repair. Resulting deformities include misalignment of the vermilion, cutaneous scars, and contour deformities of the red or cutaneous lip. Skill, experience, and expertise help minimize this risk and meticulous closure must be performed with special attention paid to alignment of surface landmarks and layered closure. Muscular contracture and notching of the lip are common sequelae following inaccurate closure. Functional complications, such as microstomia or oral incompetence, may occur and appropriate delayed reconstruction must be considered.

SPECIAL CONSIDERATIONS

Bites

Injuries from bites are becoming more common with 15% of all bite wounds occurring in the head and neck. According to Gilchrist et al. (43) 4.37 million people were bitten annually in 2001 to 2003, and, of these, 836 000 (19%) required medical attention, with more than 31,000 patients undergoing acute repair procedures in 2007 as the result of dog bites. Dog bites makeup the majority of animal bites (80% to 90%), with cats as the second most common (5% to 15%). Human bites account for 3% to 23% (19). Most injuries are from the patients' own pet, or pets that are known to them, as opposed to stray or mongrel animals. The size and age of the child is inversely proportional to the level of risk for bite injuries to the head and neck (44). Other bites from more exotic and less common pets are beyond the scope of this chapter. Yet, it should be mentioned that the type of animal bite becomes important in antibacterial management, and a thorough history should be elicited.

Microbiology

Infection after bites can originate from the bacterial flora of the animal or human's oral cavity, as well as the skin of the victim. The overwhelming majority of bite infections are polymicrobial, with 2.8 to 3.6 bacterial species isolated in wound cultures of both aerobic and anaerobic bacteria (44). Life-threatening viruses may also be transmitted from animal bites and must be considered during the evaluation.

Dog bites offer the lowest infection rate of common animal bites, with risk factors of significant crush injury, devitalized tissue, deep puncture wounds, exposure of cartilage, or delay in seeking care beyond 6 to 12 hours all resulting in increased infection rates (19,45,46). *Pasteurella* species are often discussed as the most common pathogen involved in dog bite infections, but the overwhelming majority are polymicrobial with numerous studies isolating various species including *Staphylococcus sp., Streptococcus sp., Corynebacterium sp., Moraxella sp., and Neisseria sp., Bacteroides fragilis, Fusobacterium, and Peptostreptococcus* (19,44,45). Additionally, the possibility of transmission of the rabies virus exists with dogs accounting for the majority of human rabies cases worldwide. In the United States, however, human transmissions are more commonly from wild animals such as skunks, raccoons, bats, and foxes (19,44).

Cat bites have higher rates of infection with more rapid progression when compared to dogs. Cats' teeth often produce deeper puncture wounds, given their shape, inoculating bacteria deeper into the wound. *Pasteurella multocida* is the pathogen most commonly involved, resulting in 50% to 75% of cases of infections from cat bites, although infections are frequently polymicrobial (19,45).

Human bites are less common than dog and cat bites, but carry the highest infection rate at 25% in the head and neck region, likely secondary to the composition of the bacterial oral flora in humans (19,47). Although polymicrobial, the most common pathogens isolated in human bite wounds include *S. aureus, Staphylococcus epidermis*, viridans streptococci, *Eikenella corrodens*, and anaerobic bacteria such as *B. fragilis* (19,44,45). Additionally, viral transmission of hepatitis B and C, herpes simplex virus, and human immunodeficiency virus (HIV) through human bites have been reported (48). Although not common, in cases of known or suspected infection by the assailant, appropriate screening and prophylaxis should be implemented. Hepatitis B immunoglobulin should be administered to victims if they are not already vaccinated, in cases of known Hepatitis B-infected attackers. If the biter is HIV positive, the victim's baseline serologic testing should be obtained, with retesting at 3 and 6 month intervals. If possible, titers for HIV viral load should be obtained from the attacker, and if elevated, prophylaxis should be offered to the victim (19).

Evaluation

Animals are often drawn to the nose and cheeks of children when attacking, making ocular examination an integral part of the examination. The patient's immunization status should be elicited and appropriate tetanus treatment given.

Classification systems have been proposed, with the majority of superficial wounds repaired in the emergency department, while those with extensive or deep injuries managed in the operating room (19). The wounds should be copiously irrigated with normal saline to reduce the inoculum. The wound should be debrided of devitalized or necrotic tissue to promote healing and reduce the risk of infection.

Closure

Most head and neck bite wounds managed acutely can be closed primarily. This decision has been controversial, with the risk factors of delayed presentation, type of wound, and species inflicting the bite all modifying the debate. Current recommendations are to repair all bite wounds of the head and neck on presentation within 24 hours of the injury, assuming there are no signs of infection (19,45,47). For those wounds presenting outside of the 24-hour period, many authors feel that wound care and treatment with antibiotics before definitive closure will decrease infection rates. Wounds not amenable to primary repair may require more complex repairs using skin grafts and local flaps (19). For massive midface tissue loss, facial composite tissue allotransplantation has been reported. In these cases, frequently, dog bite injury is cited as the inciting event.

Antibiotics

Prophylactic treatment of bite injuries is controversial as little data exists to support their benefit in cat and dog bite wounds presenting within 6 hours (49). The authors support recommendations for antibiotic treatment in all deep injuries with muscle and cartilage involvement, children,

wounds older than 6 hours, cat bites, human bites, and individuals with immunosuppressive comorbidities (19,50). Stierman et al. (47) recommends 48 hours of intravenous prophylactic antibiotic therapy prior to closure for human bites to the ear, given the significantly increased risk of infection noted at this particular site.

Empiric oral prophylaxis for cat, dog, and human bites can be covered with amoxicillin and clavulanate 875 mg/125 mg twice daily or the combination of doxycycline with metronidazole in penicillin-allergic patients. Alternative regimens include clindamycin plus ciprofloxacin, whereas trimethoprim-sulfamethoxazole is appropriate for children. Azithromycin is also acceptable for use in penicillin-allergic children and pregnant women (19).

Bite wounds found to be infected at delayed presentation merit intravenous antibiotic treatment. Recommended first-line agents are ampicillin and sulbactam, piperacillin with tazobactam, or clindamycin in penicillin-allergic patients. The parenteral course is given for a minimum of 48 hours followed by oral equivalents totaling 10 to 14 days of treatment (19).

Burns

The head and neck region accounts for only 9% of the total body surface area when calculating involvement in burns. However, significant facial burns require specialized trauma protocols for airway establishment and fluid resuscitation, preferably in the setting of a certified burn center. Considerations for tracheotomy are delayed due to increased risk of infection.

The depth of burns is a critical factor in making treatment decisions. Superficial burns are isolated to the epidermal layer and may be managed with saline irrigation and strict wound care using topical antibiotic ointments and specialized dressings, while avoiding systemic antibiotics because of the tendency to develop bacterial resistance. Superficial partial thickness burns may be treated similarly with resulting scars and contractures addressed secondarily. Deep partial-thickness and full-thickness burns vary in their treatment regimens amongst burn specialists. Many advocate for early excision and grafting using split-thickness skin grafts to the face, while conservative wound management is practiced by others (51). When planning skin grafts, the concepts of facial aesthetic units are used as a guide to optimize future contracture by grafting thick grafts over entire aesthetic units. Physical and occupational therapists play an essential role, helping avoid contracture through the use of range-of-motion exercises, pressure dressings, and splints.

Certain areas of the head and neck have unique considerations in treatment. The ear is quite often involved in head and neck burns given its prominence. The resulting burn is susceptible to suppurative chondritis, which should be managed with incision, drainage, and debridement along with local wound care. If there is evidence of cartilaginous exposure or damage then considerations for graft or flap coverage should be instituted. The authors favor local wound care with wet to dry dressing changes, allowing granulation formation, followed by STSG or FTSG.

Eyelids are involved in up to 27% of burn patients, and initial management should be directed at examination and protection of the globe (52). The globe is often spared due to protective mechanisms such as the blink reflex and instinctive protective movements of the arm to cover the face (53). Management begins with lubrication of the globe and protective dressings. In the setting of lagophthalmos placement of a temporary tarsorrhaphy suture is recommended (26,54). If both eyes are involved requiring suturing the lids closed, the patient should be sedated for comfort. Definitive treatment for major full-thickness burns will require early intervention with the use of split-thickness and full-thickness skin grafting (26).

Lip and perioral injuries from burns sometimes are secondary to electrical injuries from children biting electrical cords. Early eschar removal is not advocated, with many delaying surgical treatment to allow demarcation of the involved area. Nonsurgical conservative management after epithelialization has gained favor, using oral appliances and splints to reduce microstomia even in the setting of circumferential burns (4). Scar revision or contracture release can be performed secondarily with a variety of reconstructive techniques available.

Frostbite

Cold injury to the head and neck region most often involves the ears, nose, and cheek due to reflexive vasoconstriction in the setting of cold exposure. This directs blood away from these tissues allowing local temperature drops in the skin and eventual tissue freezing. Ice crystals may form on the skin surface drawing intracellular fluid from out of the cells and leading to irreversible injury. Hypoxia ensues followed by ischemia with thrombosis, dermal necrosis, and acidosis with cell death (5,55). Initial treatment is conservative and is directed to rapid rewarming through use of heated compresses or immersing the body part in a warm bath maintained at 100°F to 108°F. Although once considered optimal treatment, slow rewarming has been shown to lead to further tissue damage (55). It is critical to provide appropriate analgesia as the rewarming process is extremely painful. Antibiotics may be indicated as well as tetanus prophylaxis. Sufficient time should be allowed for demarcation before surgical intervention is recommended.

PEDIATRIC SOFT TISSUE INJURY

The same tenants of soft tissue injury evaluation and management should be followed in the pediatric age group as is recommended in the adult population. With anxious and uncooperative children, judicious use of sedation or general anesthesia may be needed for wound evaluation and repair. In hopes of avoiding postoperative struggle and fear during suture removal, the preferred choice of sutures used in most

repairs is absorbable skin sutures or closure with subcuticular sutures. In the appropriate setting, wound closure may be performed with cyanoacrylate glue (Dermabond, Ethicon Inc., Somerville, NJ). If the mechanism of injury does not fit the wound pattern or if suspicious behavior is recognized, the surgeon should consider abuse as a potential cause.

HIGHLIGHTS

- The evaluation begins with stabilization following the ABCDE's of trauma management.
- Liberal use of irrigation and gentle tissue handling optimize tissue healing minimizing the risk of tissue loss and infection.
- Local wound care and secondary healing should be considered in patients with grossly contaminated wounds, those with delayed presentation, and patients with extensive skin and soft tissue loss.
- Delayed closure is appropriate for grossly contaminated wounds, selected animal bites, infected wounds, and when presentation is greater than 24 hours from injury.
- Tetanus vaccination history is of critical importance in any trauma patient.
- Once the sutures are removed extreme care must be taken to avoid sun exposure, and the use of broad spectrum UV-A and UV-B sun block with a SPF greater than 45 should be recommended for a minimum of 6 months to 1 year to prevent scar hyperpigmentation.
- When performing repair of full-thickness lacerations of the eyelid margin, it is critical to address all layers and the use of the three suture technique for the lid margin alignment.
- Upper eyelid injuries with herniation of fat and ptosis are concerning for injury to the levator muscle or aponeurosis.
- Any eyelid injury, which involves the punctum or the tissue medial to the punctum likely involves the canalicular system. Repair involves cannulation and stenting of the lacrimal drainage system.
- The parotid duct and buccal branch of the facial nerve lie in a vulnerable location as they cross the masseter muscle, and both must be considered in soft tissue trauma of the cheek and parotid.
- Accumulation of blood in the subperichondrial space or within the cartilaginous fragments can lead to auricular hematoma, which can be managed with simple needle aspiration for focal collections versus incision, drainage, and a bolster for larger ones.
- The main tenant of lip laceration repair is layered closure of the vermilion, skin, muscle, and mucosa.
- Dog bites makeup the majority of animal bites (80% to 90%), with cats as the second most common (5% to 15%). Human bites account for 3% to 23% of cases.
- Human bite injuries can be associated with viral transmission of hepatitis B and C, herpes simplex virus, and HIV.
- For severe facial burns, many advocate early excision and grafting using split-thickness skin grafts.
- With frostbite injuries, the initial treatment is conservative and revolves around rapid rewarming through use of heated compresses or immersing the body part in a warm bath maintained at 100°F to 108°F.

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Penetrating Face and Neck Trauma

76

Michael G. Stewart

Head and neck surgeons are often called upon to manage penetrating trauma to the face and neck. Knowledge of ballistics, injury patterns, and pertinent anatomy are all essential to the assessment and management of these potentially serious injuries.

The energy imparted into tissue by a penetrating projectile is determined by its kinetic energy (KE): KE = ½ MV^2, where M = mass and V = velocity. Since the velocity term is squared in the equation, high-velocity projectiles can potentially impart significantly larger amounts of energy into the tissue impacted. In other words, a projectile with twice the velocity will have four times the KE of a lower-velocity projectile. However, the actual degree of wounding will also depend on the energy transfer from the projectile into the tissue (1). Typically, firearms are divided into two groups by their muzzle velocity: low velocity (less than 1,000 ft/s) and high velocity (more than 1,000 ft/s) (2). Most handguns are low-velocity weapons, with muzzle velocities between 300 and 800 ft/s. A typical shotgun has a muzzle velocity of 1,200 ft/s, and a 30-30 rifle has a muzzle velocity of 2,200 ft/s.

Gunshot wounds cause tissue injury by two main mechanisms: direct tissue injury and temporary cavitation. In the past, there was some consideration about distant injury from the transmission of shock waves; however, this theory is controversial and has been discounted by many (3). Cavitation refers to the creation of a pulsating temporary cavity surrounding the actual bullet path, as illustrated in Figure 76.1. This temporary cavity results in tissue damage and tissue loss adjacent to the missile path. This is an important concept for the treating physician to understand: anatomic structures may be significantly damaged by a gunshot wound without being actually penetrated by the projectile. Because of their high KE, high-velocity weapon injuries tend to have greater cavitation and transmission effects than low-velocity injuries. Clinically, low-velocity injuries are usually characterized by tissue *damage*, whereas high-velocity injuries are typically characterized by tissue *loss*. This can be an oversimplification; for example, a high-velocity, high-energy projectile may pass through tissue and exit with a significant amount of energy remaining. So, high velocity does not always equal high-energy transfer and tissue damage.

In addition, bullets or pellets in flight have several components to their rotation, as illustrated in Figure 76.2. These rotational characteristics increase the potential that a bullet may take an erratic course after impact, and also may increase the amount of direct tissue injury (1,3). Further, projectiles may shatter on tissue impact, resulting in secondary projectiles with the potential for additional injury. Similarly, impacted bone may also shatter, and secondary bone fragments may cause further tissue damage.

GENERAL TRAUMA PRINCIPLES

The basic principles of trauma management apply to all patients with penetrating face and neck trauma. These trauma principles may be remembered using the mnemonic "ABCDE." "A" denotes assessment of *airway* and *cervical spine*, "B" stands for assessment of *breathing*, "C" refers to assessment of *circulation*, "D" denotes assessment of *disability and neurologic status*, and "E" stands for *exposure* and overall *evaluation* of the patient for other injuries. The overall prevalence of cervical spine fracture in patients with isolated facial trauma is 5% to 8% (increasing to as much as 11% when two or more fractures were present) (4), but all patients should be considered to have a cervical spine injury until proven otherwise.

In the emergency center, in addition to cervical spine x-rays, all patients with penetrating face trauma should have an AP and lateral skull and face x-ray. These films can identify remaining bullets, pellets, bullet fragments, and bony fragments, and may help define the path of the projectile. In stab wounds where the weapon is still present,

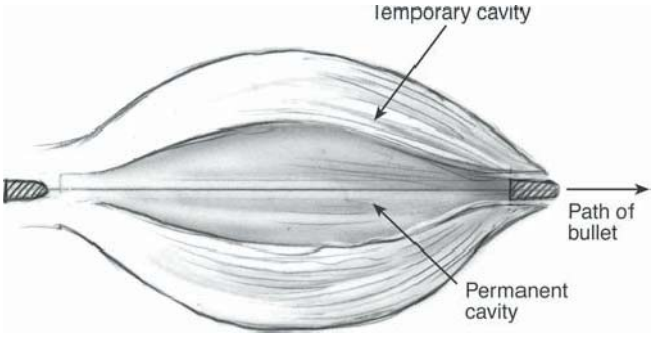


Figure 76.1 Cavitation effects of a bullet wound to soft tissue.

the depth of penetration may be identified. Further, these roentgenograms may reveal the presence of subcutaneous air or tracheal deviation.

Evaluation of the airway should be the first priority in the emergency center for all patients with penetrating face or neck trauma. The techniques of airway establishment are discussed in detail Chapters 63 and 64 of this textbook, but most patients can be carefully intubated transorally; if a cervical spine injury is suspected, the patient may be intubated while continuous in-line neck stabilization is applied. If the airway is unstable, and there is significant bleeding or edema in the oral cavity or pharynx, the patient should undergo cricothyroidotomy or urgent tracheotomy in the emergency center. Blind nasotracheal intubation should be avoided, although in the stable patient a fiberoptic-guided transnasal approach may be appropriate. In penetrating injuries to the neck with obvious tracheal injury (e.g., sucking wound, significant subcutaneous emphysema), the trachea may be carefully intubated through the entry wound itself using an armored/reinforced endotracheal tube.

Once the airway has been stabilized, the remainder of the examination may be completed, including a careful assessment of entry and exit wounds. When possible, information on the number of stab or gunshot wounds, the type of weapon, distance from assailant, etc., may be helpful in wound assessment. In patients with a stable airway, flexible fiberoptic laryngoscopy is a very helpful part of the evaluation, and helps assess the presence and extent of laryngopharyngeal injury. The physician should be aware that projectiles and bones may fragment or shatter, and projectiles may ricochet and change directions through the tissue—both of which may lead to secondary injuries. Probing entry and exit wounds or removing blood clots in the emergency center should be avoided, because this may precipitate significant bleeding. In addition, all patients with penetrating face or neck trauma should be considered for tetanus prophylaxis.

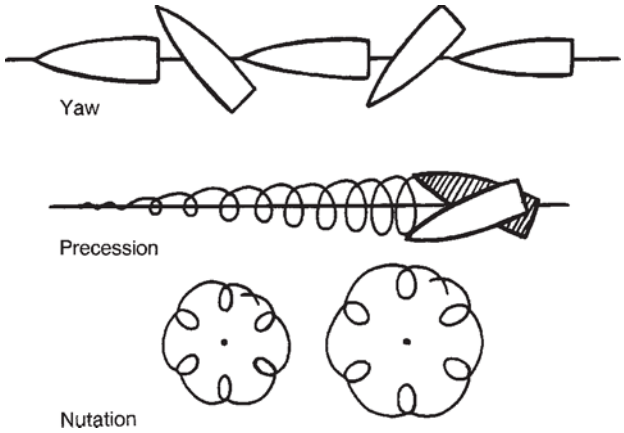


Figure 76.2 The rotational ballistics of a missile, demonstrating yaw, precession, and nutation.

PENETRATING FACIAL INJURIES

Although much attention has been focused on treatment algorithms for patients with penetrating trauma to the neck, chest, and abdomen, there is less written about penetrating injuries to the face. The first attempt to create a staging system for penetrating facial trauma was made by Gant and Epstein in 1979 (5) and later demonstrated pictorially by Gussack and Jurkovich (6). The Gant and Epstein system divided the face into entry zones I, II, and III, which was potentially confusing since neck entry zones used the same nomenclature. Further, zone I was superior to the supraorbital rims—which actually could be considered a penetrating intracranial (rather than facial) injury. The Gant and Epstein system was modified by Dolin et al. (7) into entry zones A, B, and C, but the demarcation points between zones were unclear, and two zones (A and B) actually had similar patterns of injury. Subsequently, Chen et al. (8) attempted to simplify facial zoning by designating two entry zones, "midface" and "mandible" (Fig. 76.3).

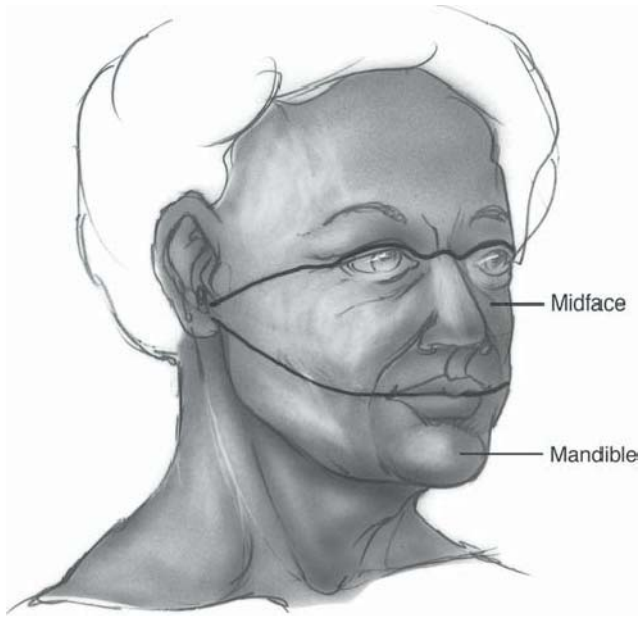


Figure 76.3 Midface and mandible zones for penetrating injuries to the face. Reprinted from Chen AY, et al. Penetrating injuries of the face. *Otolaryngol Head Neck Surg* 1996;115:464–470, with permission. Copyright 1996 by C.V. Mosby Year Book, Inc.

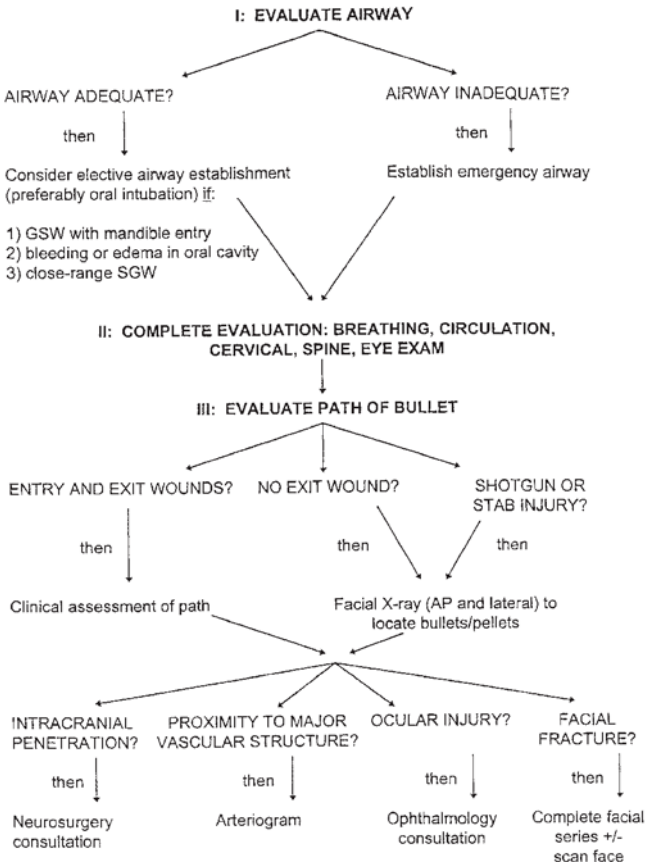


Figure 76.4 Algorithm for the initial management of patients with penetrating injuries to the face. Reprinted from Chen AY, et al. Penetrating injuries of the face. *Otolaryngol Head Neck Surg* 1996;115:464–470, with permission. Copyright 1996 by C.V. Mosby Year Book, Inc.

Injury patterns to these zones are distinct, and the system is easy to remember. An algorithm for the care of patients with penetrating facial trauma is depicted in Figure 76.4.

Shotgun Injuries

It is important to remember that shotguns have fairly high muzzle velocity, and close-range shotgun injuries may impart significant KE to facial tissue. Recognizing that the distance from weapon to victim was a key point in shotgun injuries, an early classification system classified shotgun injuries into three groups: long-range injuries (type I—more than 7 yards distance between weapon and victim) were characterized by subcutaneous or deep fascia injuries only, medium-range injuries (type II—3 to 7 yards distance) were characterized by injuries to structures deep to the deep fascia, and close-range injuries (type III—under 3 yards distance) typically created massive tissue destruction. Currently, trauma surgeons usually divide shotgun wounds into only two groups: close range and long range (9). The concept is the same: close-range injuries have very high kinetic injury and behave similarly to high-velocity rifle injuries. In addition, in close-range shotgun injuries, the "wadding" material from the shotgun shell may become imbedded into the soft tissue, and must be thoroughly removed to avoid subsequent problems with infection.

In one series (8), all patients with shotgun wounds to the face invariably had pellet penetration of both midface and mandible entry zones, so the zoning system was not helpful in predicting injury pattern. Therefore, shotgun wounds should probably be considered as a separate group. This high prevalence of ocular injury has been noted in other series as well (9,10). Shotgun wounds to the face also have a relatively high prevalence of globe injury, so careful ophthalmologic assessment is important. Shotgun wounds to the face may also cause facial fracture or vascular injury, or rarely may achieve intracranial penetration.

Stab Wounds

Stab wounds to the face may result in globe injury, vascular injury, and even intracranial penetration. If the weapon is still in place, AP and lateral skull x-rays can help predict the depth of penetration and direct further evaluation. Many authors have noted that in cases where the knife or weapon is still in place, it is important to *not* remove or dislodge it, since it may be providing tamponade of injured vascular structures. Rather, the patient should be taken for angiography with the protruding weapon in place. If major vascular injury is identified, intravascular balloons may be placed by the interventional radiologist (or proximal vessels may be isolated by the surgeon), and the weapon may then be removed under controlled circumstances in the operating room (11).

Gunshot Wounds

The midface/mandible zoning system is particularly applicable for gunshot injuries to the face, since the two entry zones have distinct patterns of injury. Gunshot wounds to the midface have a high prevalence of vascular injury, globe injury, intracranial penetration, and facial fracture requiring open reduction and internal fixation (8,10,12).

The indications for vascular evaluation in penetrating wounds to the face can be remembered as the two "P"s:

1. *Proximity* to a major vascular structure
2. *Penetration* posterior to the mandibular angle plane (MAP).

If the path of a penetrating projectile traverses near a major vascular structure, vascular evaluation is indicated. This may be difficult to assess because the path of a projectile after tissue penetration is not always predictable, and due to cavitation, the bullet may be somewhat distant from the vessel and still cause a significant injury. A useful anatomic landmark is the MAP as described by Gussack and Jurkovich (6). The MAP is an imaginary

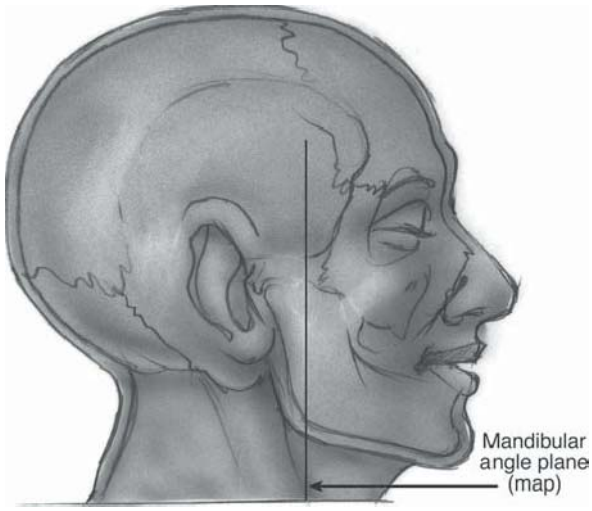


Figure 76.5 Lateral view of the face demonstrating the Mandibular Angle Plane (MAP).

vertical coronal plane at the level of the angle of the mandible (Fig. 76.5) and penetration of a projectile or weapon posterior to this plane is an indication for vascular evaluation. The appropriate radiologic test depends on the situation, and this point is discussed later in the chapter.

Gunshot injuries to the mandible entry zone often require emergency establishment of an airway because of bleeding, edema, or hematoma formation in the oral cavity or pharynx (8,12). Although these patients may appear initially to have a stable airway, they can quickly decompensate and require an emergency airway. Although more common with mandible entry, patients with midface gunshot wounds may also require an emergency airway (8,10,12). Therefore, a high index of suspicion and early elective airway establishment are important in patients with gunshot wounds to the face.

The computed tomography (CT) scan has significantly changed the management of penetrating facial injuries. Although airway establishment, hemodynamic stabilization, treatment of other serious injuries, and vascular evaluation should take precedence, axial and coronal CT scans of the face often significantly aid the head and neck surgeon in the assessment of damage, and improve treatment planning. In addition, CT scans clearly demonstrate the extent and severity of bony fractures.

Management of Specific Injuries

Facial Nerve Injury

Patients with penetrating facial trauma and immediate paralysis of one or more branches of the facial nerve are likely to have transection of the nerve. If their medical condition permits, these patients should undergo local exploration with primary nerve repair or nerve grafting, if the wound is lateral to the lateral canthus. Nerve injuries medial to the lateral canthus are typically not explored because nerve regeneration is usually adequate. Branches to the forehead and ramus mandibularis should be repaired because cross-innervation to these areas is poor; branches to the midface *may* recover function through cross-innervation even if completely transected (12,13). Severed distal branches retain electrical excitability for about 48 hours, and a nerve stimulator may be used intraoperatively. However, it is common that patients have other medical issues which delay facial nerve exploration and repair, and that is acceptable since the results after cable graft are not dependent on time of repair (12). The preferred neurorrhaphy technique is to trim back the perineurium away from the anastomosis and perform epineurial repair with 9-0 or 10-0 monofilament suture (13). Facial nerve injuries which progress from partial to total paralysis following injury, or paralysis which develops several hours after injury, are usually secondary to edema and may be treated expectantly.

Parotid Duct Injury

Wounds to the cheek below the zygomatic arch, which injure the buccal branch of the facial nerve are also likely to injure the parotid duct. If parotid duct injury is suspected (e.g., clear saliva draining from a penetrating cheek wound, or sialocele formation), the wound should be explored and the duct primarily repaired over a stent.

Facial Bone Fracture

These injuries are discussed in more detail in other chapters. Not all facial fractures will require open reduction internal fixation, but many will (10). Some fractures will require debridement only, or can be managed with closed reduction.

Complications

Even without intracranial penetration or major vascular injury, penetrating wounds to the face have the potential for early and late complications in 15% to 35% of patients. Potential complications are listed in Table 76.1. While some are directly attributable to the injury—such as blindness or facial nerve injury—some complications are potentially preventable with early recognition and aggressive management. In particular, nasal obstruction and synechia, sinusitis, and choanal stenosis may be prevented with intranasal debridement, placement of nasal stents, and the techniques of functional endoscopic sinonasal surgery to restore adequate sinus drainage. In addition, diplopia and orbital or periorbital infections may be prevented with careful reconstruction of the orbital floor to restore orbital anatomy and isolate the maxillary sinus from the orbital contents. Further, trismus and malocclusion may be prevented with adequate maxillomandibular fixation, and early mobilization and stretching of the temporomandibular joint.

TABLE 76.1 COMPLICATIONS PENETRATING FACE AND NECK INJURIES

Facial injuries
- Blindness
- Visual loss
- Diplopia
- Facial nerve paralysis
- Cerebrospinal fluid leak
- Soft tissue loss
- Bony malunion
- Malocclusion
- Trismus
- Orbital/periorbital cellulitis
- Sinusitis
- Oral–antral fistula
- Nasal obstruction/stenosis
- Choanal stenosis

Neck injuries
- Airway obstruction
- Pharyngocutaneous fistula
- Neck abscess
- Mediastinitis
- Vocal cord paresis
- Cervical spine osteomyelitis

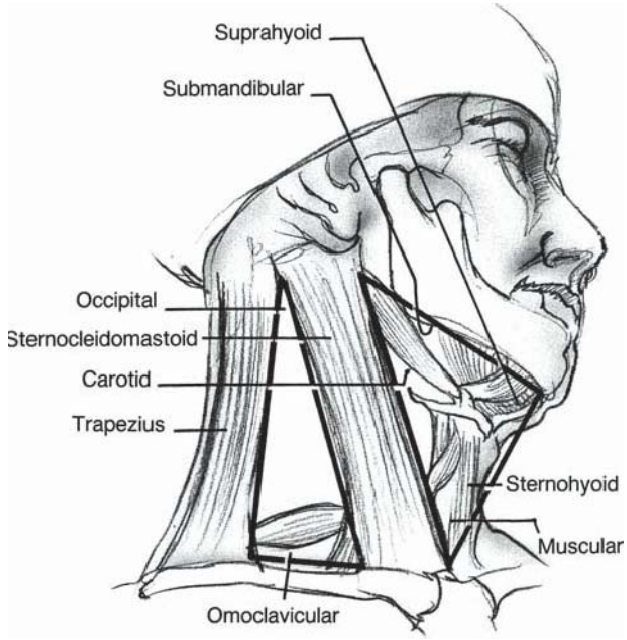


Figure 76.6 Anatomic triangles of the neck: the neck is divided into anterior and posterior triangles by the sternocleidomastoid muscle.

PENETRATING NECK INJURIES

The complex anatomy of the neck requires careful assessment of missile trajectory and site of entry. The neck can be divided into two triangles using the sternocleidomastoid muscle (Fig. 76.6). The anterior triangle contains most of the major anatomic structures of the neck: the larynx, trachea, pharynx, esophagus, and major vascular structures. The major structures of the posterior triangle are muscles, the spinal accessory nerve, and the spinal column. The platysma muscle lies just deep to the skin of the neck only in the anterior triangle. Wounds which penetrate the platysma have the potential for serious injury; wounds, which do not penetrate the platysma are superficial by definition, and do not require further evaluation.

The neck has been divided into three entry zones (Fig. 76.7). Zone I comprises the lower neck below the inferior border of the cricoid cartilage. Zone II consists of the neck between the angle of the mandible and the inferior border of the cricoid cartilage, and zone III comprises the neck superior to the angle of the mandible up to the skull base. Zone II is the largest zone and the most common site of entry in penetrating neck trauma (14,15). McConnell and Trunkey combined the results of 16 large series and found that the most commonly injured structures in the neck were the larynx and trachea (considered as

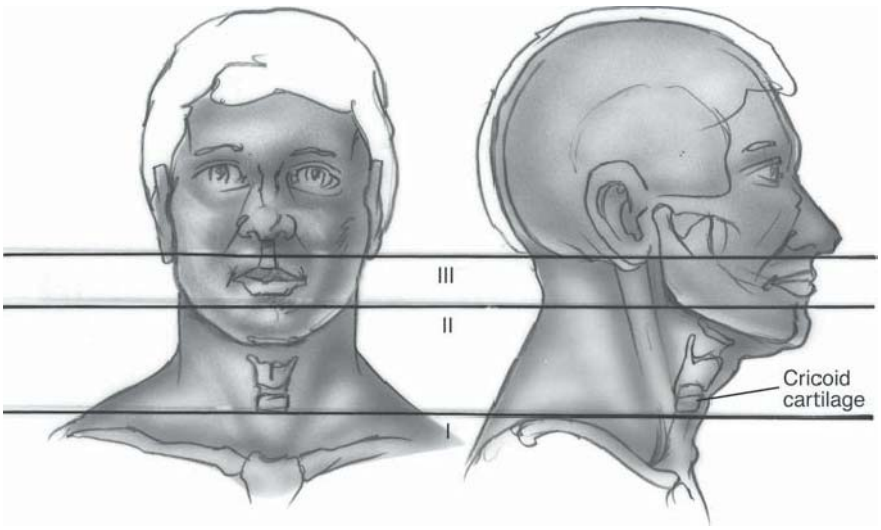


Figure 76.7 Horizontal entry zones of the neck for penetrating injuries to the neck. Modified from Jurkovich GJ. In: Moore EE, ed. *The neck.* Toronto: Becker, 1990:126.

TABLE 76.2 DIAGNOSIS PENETRATING NECK TRAUMA

Diagnosis	Signs and Symptoms	Tests
Vascular injury	Shock Hematoma Hemorrhage Pulse deficit Neurologic deficit Bruit or thrill in neck	Angiogram CT angiogram Doppler ultrasound Neck exploration
Laryngotracheal injury	Subcutaneous emphysema Airway obstruction Sucking wound Hemoptysis Dyspnea Stridor Hoarseness or dysphonia	Laryngotracheoscopy Neck exploration CT scan
Pharynx/esophagus injury	Subcutaneous emphysema Hematemesis Dysphagia or odynophagia	Contrast esophagogram Esophagoscopy Neck exploration

a group: 10% of patients), and the pharynx and esophagus (considered as a group: 10% of patients). The most common vascular structures injured were the internal jugular vein (9%), the internal and common carotid arteries (7%), the subclavian artery (2%) and the external carotid artery (2%). The vertebral artery was injured in only 1% of patients in the combined review.

The overall mortality rate for penetrating neck trauma at most major centers is 3% to 6% (14,16). The major cause of death in patients with penetrating neck trauma is exsanguinating hemorrhage from a vascular injury. Other causes include spinal cord injury, cerebral ischemia, airway obstruction, air embolism, and pulmonary embolism. Most series report at least some mortality from missed esophageal injuries, which usually manifest as sepsis.

A careful clinical exam is often an accurate predictor of the extent of injury. The clinical signs and symptoms of significant neck injury are listed in Table 76.2. Of course, patients with refractory shock, uncontrollable hemorrhage, or evolving neurologic deficit should undergo immediate neck exploration (Table 76.3). The surgeon should be prepared to control and repair major injuries to the carotid artery or jugular vein. Patients who are clinically stable but have signs or symptoms of injury to a major neck structure should undergo directed evaluation with subsequent repair of injured structures. The management of the *asymptomatic* patient with penetrating neck trauma is controversial, however.

Traditionally, all patients with penetrating neck wounds, which penetrated the platysma—whether symptomatic or not—underwent neck exploration. The rationale was that the sensitivity of neck exploration was high, and the morbidity of the surgery itself was low, whereas the morbidity of a missed injury was potentially fairly high. When mandatory neck exploration was performed, negative exploration rates of 30% to 50% could be expected. In the 1980s and 1990s as imaging and flexible endoscopic technology advanced, trauma surgeons began using serial examinations and evaluations in selected neck injuries—based on zone and clinical presentation (16). In addition, many vascular injuries are now amenable to definitive endovascular treatment by the interventional radiologist. There is good evidence that directed examination with observation and serial examinations may be as effective as mandatory exploration in selected patients (16,17); these issues will be discussed further below. An example of a simplified protocol for penetrating neck trauma is depicted in Figure 76.8.

As in penetrating injuries to the face, the mechanism of injury is important for the treating physician to consider. Although the depth of penetration of stab wounds may be difficult to assess, stab wounds tend to injure only the tissue directly penetrated. Gunshot wounds, however, may cause significant tissue loss as well as damage to adjacent structures because of cavitation and the high energy of the projectile.

TABLE 76.3 EMERGENCIES PENETRATING FACE AND NECK INJURIES

Diagnosis	Emergency
Vascular injury	Hemorrhage Neurologic deterioration Airway compression
Larynx or tracheal injury	Airway obstruction Pneumomediastinum Pneumothorax

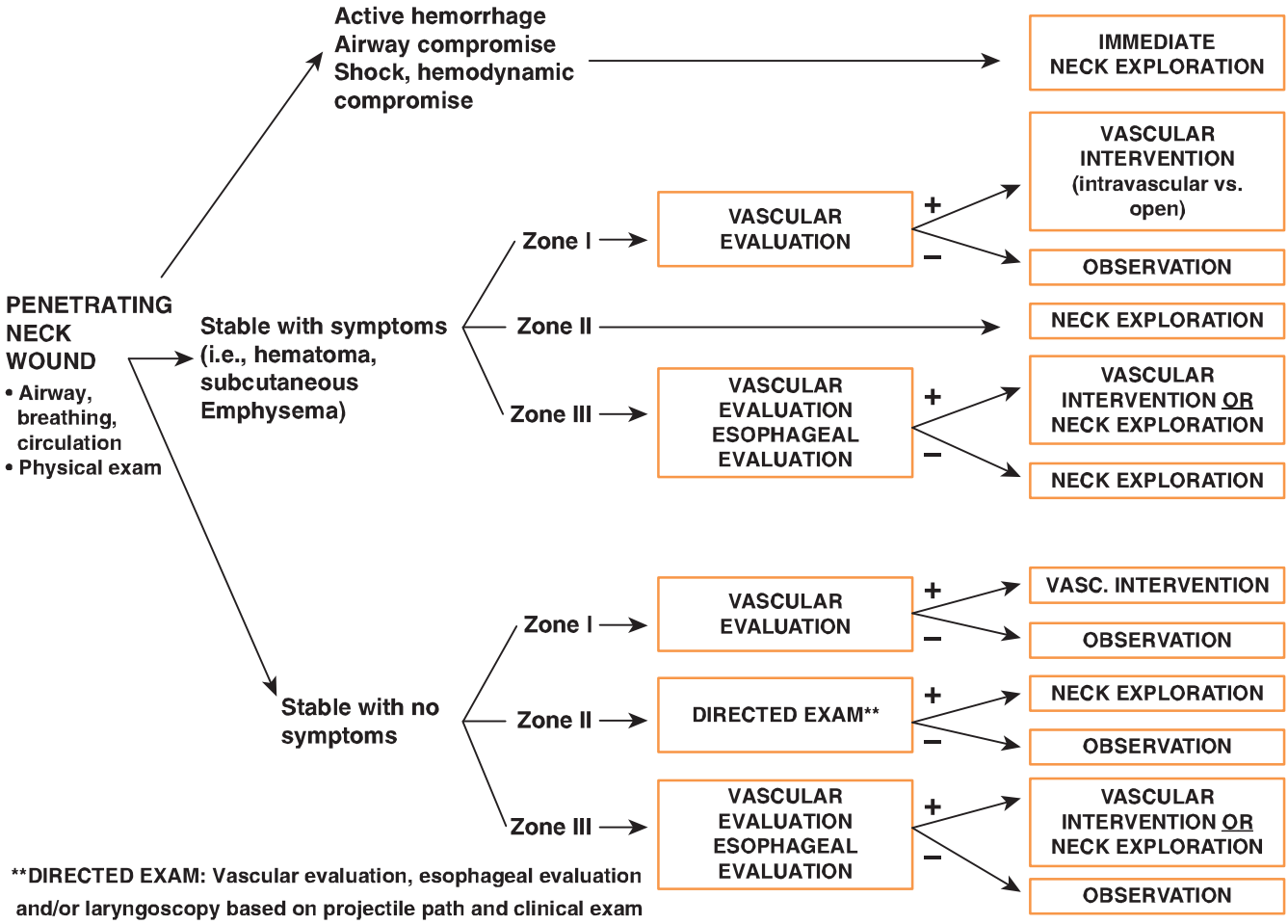


Figure 76.8 An example algorithm for the initial management of patients with penetrating injuries to the neck. Modified from Mansour MA, et al. Validating the selective management of penetrating neck wounds. *Am J Surg* 1991;162:517–521, Copyright 1991 by Excerpta Medica, Inc.

Zone I Injuries

Penetrating injuries which enter zone I of the neck are potentially lethal because of the potential for injury to the great vessels of the neck and mediastinum, as well as the cervical and thoracic esophagus. Most trauma centers advocate routine vascular evaluation of the aortic arch and great vessels, along with an esophageal evaluation—whether or not the patient is symptomatic, since up to one-third of patients with a clinically significant zone I injury may have no symptoms at presentation. Mandatory esophageal evaluation is also recommended because a missed zone I esophageal injury is potentially different from a missed zone II injury. An esophageal or pharyngeal injury in zone II will usually develop clinical signs or symptoms (such as subcutaneous emphysema) within a few hours, and overall morbidity and mortality may not be affected. A missed esophageal injury in zone I, however, may be clinically silent until mediastinitis and sepsis develop.

Opinions on the ideal diagnostic test for the esophagus and pharynx differ, and the options include endoscopy, contrast esophagram using barium or gastrografin, or CT scan. If a contrast esophagram is used, there is also a question about which contrast medium to use. Barium-based contrast is thicker, and if a penetrating injury is present, the barium is more likely to demonstrate it. However if barium leaks into the tissues of the neck, there is significant risk of infection. Gastrografin (meglumine detrizoate) is a thinner contrast material, and is less likely to promote infection if leaked into the neck, but many feel it is a poorer agent because smaller injuries can be missed. One potential solution is to first study with gastrografin. If there is a large leak, then the diagnosis is made. If there is no leak, then do a second study with barium—to ensure there is not even a small leak. A different option is to use "thin barium," or dilute barium as the initial evaluation.

Studies on the sensitivity and specificity of radiologic tests to detect pharyngeal or esophageal injury have reported as high as 90% to 100% (18,19). Similarly, flexible or rigid esophagoscopy both have high specificity and sensitivity (19), so the method can be chosen based on operator preference. Some have noted that in all cases of penetrating injury, at least *one* of the diagnostic tests—rigid or flexible

esophagoscopy, or barium swallow—demonstrated the injury (18). Therefore a combination of those tests should not miss an injury.

Another option for assessment is the CT scan (20,21). CT scans have been found to be very helpful in determining the path of the projectile (using the tract of air bubbles, damaged tissue, or projectile particles), which then helped guide decision making for further evaluation and treatment. In fact, in one study additional radiologic imaging and surgery were avoided in some patients (21).

Zone II Injuries

As previously discussed, patients with penetrating zone II injuries who are symptomatic should undergo neck exploration. Asymptomatic patients with penetrating zone II injuries may be treated with either mandatory exploration or directed evaluation and serial examinations (16,17,19). In earlier decades, mandatory neck exploration was the standard of care, and many negative explorations were acceptable. However, several prospective studies have shown that careful observation (with radiologic and endoscopic evaluation) of the asymptomatic zone II injury is an effective protocol. Patients usually underwent some additional evaluation, such as CT scan, vascular evaluation, or flexible endoscopy, and also serial examinations. If patients developed findings of injury, such as subcutaneous emphysema, they were then taken for surgical exploration and repair. Studies have shown that the observed patients did very well as a group, with virtually no missed injuries, morbidity, or mortality, and perhaps a shorter average length of stay than patients who underwent exploration. In another study, physical examination alone—using defined criteria for a positive examination—was shown to have high sensitivity (93%) and negative predictive value (97%) when used for the assessment of potential vascular injury (22).

However, these protocols require frequent availability of additional testing, and serial examinations. So in some centers, surgical exploration might be a more appropriate plan for asymptomatic penetrating zone II injuries. In addition, some surgeons still prefer mandatory exploration over observation and selective exploration, citing the prevalence of previously undetected injuries when mandatory exploration is performed. Others note, however, that many of those injuries (e.g., small vascular injuries) might never have caused a problem if simply observed.

In summary, asymptomatic patients with penetrating zone II injuries may be treated with either mandatory neck exploration, or directed evaluation and serial examinations. However, a treatment protocol utilizing observation with serial examinations requires adequate physician manpower as well as a 24-hour facility prepared for emergency testing and surgery at any time. Early neck exploration with prompt discharge home for negative explorations is an efficient and time-tested method of managing penetrating zone II injuries, and in some settings, may be preferred over multiple tests and observation.

Zone III Injuries

Penetrating injuries to zone III have the potential for injury to major blood vessels and the cranial nerves near the skull base. Some patients with arterial injuries may be asymptomatic at presentation, and surgical exposure and control of bleeding in this location may be quite difficult. In addition, many vascular injuries are amenable to definitive treatment by an interventional radiologist. Therefore, the injury can be potentially treated in the same setting as the diagnostic angiogram. Although vertebral artery injury appears to be relatively rare, this may be the result of infrequent use of four-vessel angiography in many series. Therefore, the benefit of routine four-vessel angiography is not clear. Certainly, however, if the bullet path is near the vertebral column, the vertebral arteries should be imaged.

Vascular Evaluation in the Head and Neck

As the speed of scanners and resolution of images have improved, the recommended protocols for vascular evaluation have also evolved. The American College of Radiology recommendations note that formal catheter angiography, CT angiography, MR angiography, and color Doppler ultrasound could all have a role in vascular evaluation of the head and neck (23). However, CT angiography and catheter angiography are the most practical, with the highest level of recommendation (23). The resolution of multidetector CT angiography is excellent, and the evaluation is quite sensitive, even to small intimal injuries—sensitivity is 90% to 100%, specificity is 94% to 100%, and positive and negative predictive values are 93% to 100% and 98% to 100%, respectively (24). Furthermore, the speed of modern scanners means that the scan can be quickly completed and processed. In addition, the soft tissue CT data is also very useful in evaluation of the penetrating neck injury. So CT angiography can yield very valuable information. However, obviously, CT angiography does not allow intervention if an injury is discovered. Catheter angiography does allow for both diagnostic assessment and endovascular intervention if needed. However, catheter angiography is more invasive, has the potential for increased complications at the catheterization site and intracranially, and it requires the presence of an interventional radiologist. And, in many cases of penetrating trauma, no intervention will be required. So, the selection between high-resolution CT angiography and catheter angiography could be based on clinical suspicion of vascular injury, with high-probability injuries going directly to catheter angiography—as one potential strategy. However, as discussed earlier, many patients with vascular injury are asymptomatic, so making this clinical distinction could be difficult. Finally, color Doppler ultrasound has excellent

resolution and sensitivity, but it is highly operator dependent, cannot be automated, and cannot be reliably used in certain situations when there is bone or air in the intervening space. And of course, no intervention can be performed. So, under certain situations it can be quite useful, but it is not a widely used modality.

Management of Specific Injuries

Vascular Injuries

As noted earlier, blood vessels are commonly injured in penetrating neck trauma. Whenever possible, primary repair of the injured vessel is ideal. The value of arterial repair in the face of focal neurologic deficit or coma is controversial, but most vascular surgeons tend to favor revascularization in cases of *traumatic* vascular injury (15). In any event, the assistance of an experienced vascular surgeon is strongly recommended in these cases.

Laryngotracheal Injuries

The management of penetrating injuries to the larynx has been well described by Schaefer (25) and is covered in this textbook, in Chapter 77. If the thyroid or cricoid cartilage has been damaged and is unstable, open repair with internal fixation is recommended. If the cartilage is calcified, 1.0 or 1.3 mm bone plates and screws may be used; if the cartilage is not fully calcified, wires and bolsters can be used as described by Austin (26). If the endolaryngeal mucosa has been significantly disrupted, tracheotomy with midline thyrotomy and direct repair of mucosal injuries with small absorbable sutures is used. Endolaryngeal stents are seldom used in penetrating trauma because the structural framework of the larynx is usually intact (unlike in blunt trauma), although stents may be used if the anterior commissure has been injured.

Tracheal injuries are managed with either tracheotomy through the injury or direct closure. Stab wounds can typically be closed primarily in two layers: an inner layer of absorbable suture incorporating the mucosa (with the knots on the outside of the lumen) and an outer layer of permanent suture securing cartilage ring to cartilage ring in a submucosal plane. Patients are usually kept intubated for 2 to 3 days, then extubated under controlled circumstances. Gunshot wounds to the trachea may result in tissue loss, which may compromise the safety of primary closure since minimal tension at the suture line is a key component of successful tracheal repair. Once the wound edges have been debrided, superior or inferior tracheal release techniques may be necessary to achieve a tension-free closure.

Pharynx and Esophageal Injuries

Missed injuries to the pharynx and esophagus are a significant source of morbidity and mortality in penetrating neck trauma. All patients with clinical signs or symptoms of pharynx or esophagus injury (e.g., subcutaneous emphysema, hematemesis, hypopharyngeal blood, etc.) should undergo neck exploration. Intraoperative esophagoscopy may be helpful in identifying the location of pharyngeal or esophageal penetration, especially in stab injuries. In addition, instillation of saline, methylene blue, or air into the pharynx and esophagus can assist in injury location.

However, up to 50% of patients with pharyngeal and esophageal injury may be asymptomatic at presentation. In an asymptomatic patient, if injury is suspected based on missile trajectory, the combination of esophagoscopy and contrast esophagography is probably most sensitive at detecting injury.

Esophageal injuries should be closed directly; if not, the saliva leak is a significant cause of morbidity and mortality. In fact, delay in exploration and repair beyond 24 hours after injury has been associated with poorer outcome in many studies. In earlier literature, the cervical esophagus and hypopharynx have been grouped together and considered as a unit. However, there is evidence that hypopharyngeal injuries may not always require direct closure (27,28); this is similar to oropharynx injuries.

Penetrating injuries to the hypopharynx, which are superior to the level of the arytenoid cartilage may be treated somewhat differently than hypopharyngeal injuries inferior to the level of the arytenoids (27). Primary closure is not always necessary in penetrating injuries to the upper hypopharynx; patients may be treated with parenteral antibiotics, and kept without oral intake for 5 to 7 days. Injuries to the hypopharynx *inferior* to the level of the arytenoid cartilage (e.g., in the dependent portion of the hypopharynx, where saliva and secretions tend to pool) should be treated with exploration and primary watertight closure using absorbable suture with drainage of the adjacent neck space. The patient should be kept NPO while the repair heals—typically 5 to 7 days. Injuries to the cervical esophagus should be treated similar to those of the inferior hypopharynx, with watertight closure and drainage. External drainage and bypass procedures (e.g., cervical pharyngostomy) should generally be avoided, although with severe injuries and tissue loss, diversion procedures may play a role.

Complications

The complications of penetrating neck injuries are listed in Table 76.1. Most complications are directly attributable to the injury itself, but some are potentially preventable. The potentially preventable injuries (such as neck abscess, pharyngocutaneous fistula, etc.) are usually due to missed or delayed diagnoses, so the best way to avoid these complications is to be thorough and vigilant in the initial evaluation for injuries and the immediate follow-up period after treatment. Although less common than 50 years ago, the mortality of penetrating neck trauma remains 3% to 6%.

HIGHLIGHTS

- Patients with penetrating trauma to the face and neck should undergo systematic evaluation using the ATLS protocol ("ABCDE"). Airway establishment is the first priority, particularly in gunshot wounds to the mandible and midface zones.
- High-velocity gunshot wounds have high KE, and tend to cause tissue loss and secondary injuries.
- Close-range shotgun wounds have high KE, and may cause massive tissue destruction. Always remove the "wadding" material from soft tissues in close-range shotgun wounds.
- Shotgun wounds to the face have a high prevalence of globe injury. Gunshot wounds to the midface may cause injury to the globe, may injure major vascular structures, or may achieve intracranial penetration.
- The indications for arteriogram in penetrating facial wounds are (a) proximity to a major vascular structure or (b) penetration posterior to the MAP.
- Classification of penetrating neck wounds into entry zones I, II, and III helps to direct management. Injuries that penetrate the platysma have the potential to damage important neck structures. Most of the vital structures of the neck are in the anterior neck.
- Bleeding, expanding hematoma, shock, and evolving neurologic deficit suggest vascular injury.
- Subcutaneous emphysema, dyspnea, airway obstruction, hoarseness, or stridor suggest laryngotracheal injury.
- Subcutaneous emphysema and dysphagia suggest pharyngoesophageal injury, but up to 50% of patients will have no clinical signs of injury.
- Patients with symptoms of injury to important neck structures should undergo neck exploration, except stable patients with zone I or zone III injuries; preoperative vascular evaluation and esophageal evaluation may help direct the surgical approach, or may identify vascular lesions amenable to treatment by the interventional radiologist.

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Laryngeal Trauma

77

J. Randall Jordan *Byron K. Norris* *Scott P. Stringer*

Laryngeal trauma is a relatively uncommon event requiring timely, proper management of injury to preserve the patient's life, airway, and voice (1). Each case of external laryngeal trauma presents a unique set of problems, but despite the diversity of injuries, specific management guidelines can be applied. Adhering to such an approach assists in attaining the best possible outcome after blunt or penetrating external laryngeal trauma. Severity of injury and delay in treatment correlate with poor outcome.

PATHOPHYSIOLOGY OF LARYNGEAL INJURIES

Blunt Trauma

Blunt trauma to the larynx is caused mainly by motor vehicle accidents including all-terrain vehicles, personal assaults, or sports injuries. Although the mandible and sternum normally protect the larynx, the neck can be hyperextended during the trauma, which allows the laryngeal skeleton to be crushed between the impinging object and the cervical vertebral column. With a moderate blow to the larynx, the momentum of the vocal folds causes a shearing effect between the vocalis muscle and the internal perichondrium. This results in injuries such as endolaryngeal mucosal tears, edema, or hematoma. More severe trauma produces fractures of the laryngeal cartilages and disruption of the laryngeal ligaments.

Subluxation or dislocation of the arytenoid cartilage can produce an immobile vocal fold. Unilateral injury to the recurrent laryngeal nerve often is associated with cricoarytenoid joint injuries owing to the proximity of the recurrent laryngeal nerve to the cricoid cartilage. Fractures of the cricoid cartilage can occur alone or with other injuries, especially after lower cervical trauma. As the only complete ring of the airway, structural integrity of the cricoid cartilage is essential in airway maintenance.

The so-called clothesline injury that occurs in association with blunt laryngeal trauma deserves special attention because of its severity. This injury typically occurs when the neck of an individual (typically an adolescent or young adult) riding a motorcycle, all-terrain vehicle, or snowmobile strikes a stationary object such as a wire fence or tree limb. The transfer of such a large amount of force confined to a relatively small area of the neck crushes the laryngeal cartilages and commonly causes cricotracheal separation. The airway is held together precariously by the intervening mucous membrane and pretracheal fascial sleeves. Bilateral injury to the recurrent laryngeal nerve often is associated with cricotracheal separation.

Associated structures also can be injured during blunt cervical trauma. Fractures of the hyoid bone and associated epiglottic injuries can cause airway obstruction. The greater or lesser cornu of the thyroid cartilage can lacerate the pharyngeal mucosa as it is pressed against the cervical vertebrae. Sex and age differences among adults have been hypothesized as leading to different types of injuries after blunt trauma. Women are considered more likely to incur supraglottic injuries than are men because they have long, thin necks. Elderly persons have been described as being at higher risk of sustaining comminuted laryngeal fractures than are younger adults because older persons have increased ossification of the laryngeal cartilage. Neither of these hypotheses has been verified with clinical observation (2).

Blunt trauma tends to affect the larynx of a child differently from that of an adult. The larynx in children is situated higher in the neck and is better protected by the mandible than it is in adults (3). While laryngeal fractures are less common in children, the incidence is increasing paralleling the incidence of motor vehicle collisions (4). Pediatric injuries tend to be less severe than adults due to the elasticity of the pediatric cartilaginous skeleton; however, the lack of extensive fibrous tissue support and the

relatively loose attachments of the mucous membranes increase the likelihood of soft tissue damage in children, and may account for the poorer prognosis of those with more severe injuries (5,6). Additionally, relatively innocuous trauma may precipitate airway distress secondary to the small laryngotracheal diameter in children (6). Several cases of membranous rupture of the pediatric trachea due to seemingly minor blunt cervical injury have also been reported (7).

Manual strangulation or hanging-type injuries produce different patterns of laryngeal injury because the applied force is fairly static and of low velocity. This can cause multiple cartilaginous fractures without immediate mucosal laceration, submucosal hematoma, or marked displacement of the fractures (8).

Penetrating Trauma

Knife and gunshot wounds are primarily responsible for penetrating trauma. Injuries vary from minor lacerations to severe disruption of the cartilage, mucosa, soft tissue, nerves, and adjacent structures. Gunshot wounds are more likely than knife wounds to be associated with severe tissue damage, and high-velocity projectiles cause greater tissue destruction and wound contamination than low-velocity projectiles (9). Knife wounds cause less peripheral soft tissue damage than gunshot wounds and are cleaner, but it is difficult to determine depth of penetration. Injuries to deep structures, such as the thoracic duct, cervical nerves, great vessels, and viscera, can occur well away from the entrance wound. Death from penetrating trauma may be caused by complete disruption of the larynx, massive soft tissue edema, or associated neurovascular injuries. Most injuries to civilians from penetrating trauma tend to be limited to the path of the missile because they are caused by lower-velocity bullets or stabbing (9).

DIAGNOSIS AND EVALUATION

History

Any patient with anterior neck trauma is considered to have an upper airway injury. The classic symptoms of laryngeal trauma include hoarseness, laryngeal pain, dyspnea, and dysphagia (Table 77.1). It is surprising that no single symptom seems to correlate well with the severity of injury (2). When the laryngeal lumen is severely compromised, aphonia and apnea occur, signifying the need for immediate establishment of an alternative airway.

Physical Examination

After trauma, a thorough physical examination of the neck is needed to identify associated neurovascular injuries. Cervical spinal injuries must be ruled out for all patients with neck trauma. Active bleeding, expanding hematoma, bruits, and the loss of pulses are signs of vascular injury. The usual signs of laryngeal trauma include stridor, hemoptysis, subcutaneous emphysema, and tenderness or deformity of the laryngeal skeleton. The presence of tenderness to palpation helps to differentiate an acute laryngeal fracture from an old deformity. The type of stridor can suggest the location of the lesion. Inspiratory stridor typically indicates partial supraglottic airway obstruction, as might occur from edema, hematoma, foreign body, soft tissue injury, or cartilaginous fractures. Expiratory stridor may portend a lower airway abnormality caused by a tracheal injury. Combined inspiratory and expiratory stridor suggests partial obstruction at the level of the glottis.

TABLE 77.1 DIAGNOSIS LARYNGEAL TRAUMA

Symptoms
Hoarseness
Pain
Dyspnea
Dysphagia
Signs
Stridor
Hemoptysis
Subcutaneous emphysema
Laryngeal tenderness
Loss of thyroid cartilage prominence
Vocal fold immobility
Laryngeal hematoma
Laryngeal edema
Laryngeal lacerations
Radiology
Computed tomography
Arteriography
Cervical spine radiography
Contrast esophagography

Cervical subcutaneous emphysema is associated with loss of the integrity of the upper aerodigestive tract and is thought to occur through shear forces of the laryngeal cartilage against the vertebral bodies (10). The amount of air can range from slight soft tissue emphysema to massive pneumomediastinum. Associated soft tissue derangements of the larynx can produce a ball-valve effect that forces massive amounts of air into the neck and chest as well. Further compromise of the airway can be caused by tracheal displacement or tension pneumothorax. Care should be taken to avoid excessive mask ventilation in patients with laryngeal trauma as this can worsen subcutaneous emphysema and potentially cause a pneumothorax (11).

Direct fiberoptic laryngoscopy is an integral component for evaluation of the patient with blunt laryngeal trauma. The larynx is examined for mobility of the vocal folds, position of the arytenoid cartilages, hematoma, lacerations, and airway patency. Rigid esophagoscopy is the best way to examine the hypopharynx and esophagus

when indicated, but should only be carried out after cervical spine injury has been excluded (12). In patients with minor laryngeal injuries, strobovideolaryngoscopy should be performed to better assess subtle intricacies of vocal fold function (13).

Radiologic Evaluation

Computed tomography (CT) (Fig. 77.1A and B) has clearly become the most useful radiologic examination for evaluating laryngeal trauma (12,14–16). CT is most useful when the results influence treatment, as opposed to documentation of an obvious injury when management will not be changed. Two groups of patients may not benefit from CT examination: (a) Patients with minimal anterior neck trauma and normal physical findings and (b) Patients with obvious fractures, large endolaryngeal lacerations, or severe penetrating injuries. While the latter patients will most often need tracheotomy, direct laryngoscopy, and open exploration, many authors now agree that CT can be of benefit even in this group in planning structural repair (15). The practical side of this is that most patients in this category will have been intubated and had a CT of the neck already performed by the time one is consulted. All patients in the intermediate group should undergo CT to assess the extent of laryngeal injury. When used, CT helps to confirm indirect or flexible laryngoscopic findings, to detect cartilage fractures that are not clinically apparent, to

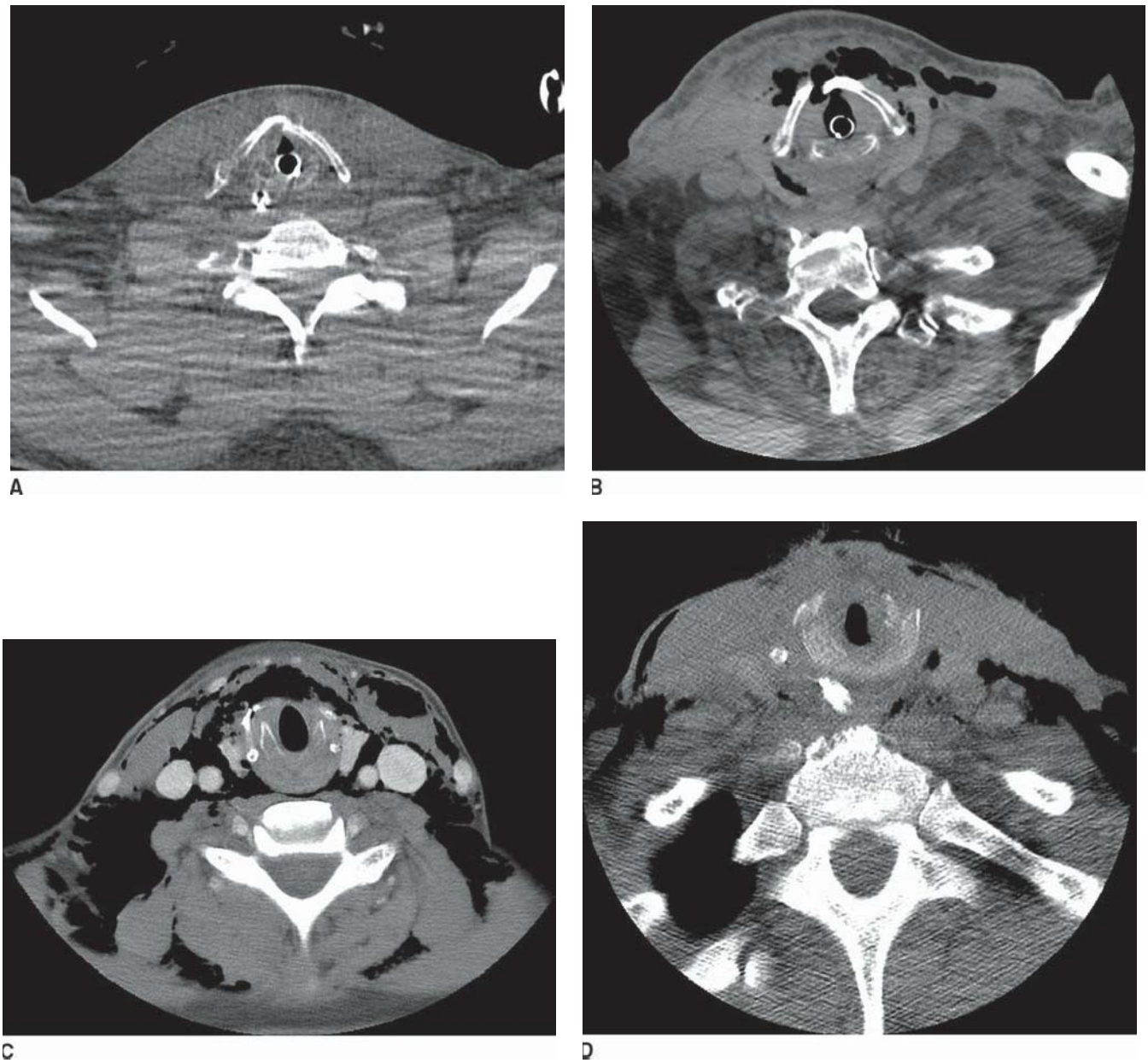


Figure 77.1 **A:** Minimally displaced laryngeal fracture. **B:** Moderately displaced laryngeal fracture. **C:** Severely displaced laryngeal fracture. **D:** Displaced cricoid fracture.

assess poorly visualized areas, such as the subglottic and anterior commissure regions, and to identify associated cervical injuries (14).

Special radiographic studies can be useful in identifying injuries associated with laryngeal trauma, especially with penetrating trauma. Cervical or "arch" arteriography continues to be most commonly used to identify vascular injury, although helical CT, MR angiography, and color duplex ultrasonography are replacing this in some institutions (12,17). Pharyngeal and esophageal mucosal penetration can be identified with the use of a Gastrografin followed by barium swallow examination, although this should be pursued with caution due to the risk of aspiration associated with laryngeal injury. Radiographs of the cervical spine are needed to rule out vertebral injury. Particular care is taken to visualize the entire cervical spine to avoid missing injuries of the lower cervical vertebrae. Ultrasonography has been considered as an adjunctive diagnostic aid in acute laryngeal trauma due to its mobility and easy handling; however, it is not widely utilized (18).

MANAGEMENT

Figure 77.2 shows a management protocol for acute injuries to the larynx. There are two primary goals in the management of acute laryngeal trauma—preserving life by maintaining the airway and restoring function as judged by lack of dependence on a tracheostomy and by voice quality. These goals are universally accepted, but the most appropriate methods to achieve them are controversial (19).

Emergency Care

The initial evaluation and treatment of a trauma patient consists of airway preservation, cardiac resuscitation, control of hemorrhage, stabilization of neural and spinal injuries, and a systematic investigation for injuries to other organ systems (Table 77.2). Controversy exists regarding the best way to establish an alternative airway in the presence of laryngeal trauma (19). If orotracheal intubation is performed in the setting of laryngeal trauma, it is best done under direct visualization by experienced personnel using a small endotracheal tube with a high-volume, low-pressure cuff with an otolaryngologist present (12). These requirements cannot always be met when laryngeal trauma is present. However, the attempted endotracheal intubation of a traumatized larynx can cause iatrogenic injury or the loss of an already precarious airway. For these reasons, some authors strongly recommend tracheotomy with local anesthesia rather than endotracheal intubation for persons who have sustained laryngeal trauma and need an alternative airway (2,15,20). Patients with minimal laryngeal

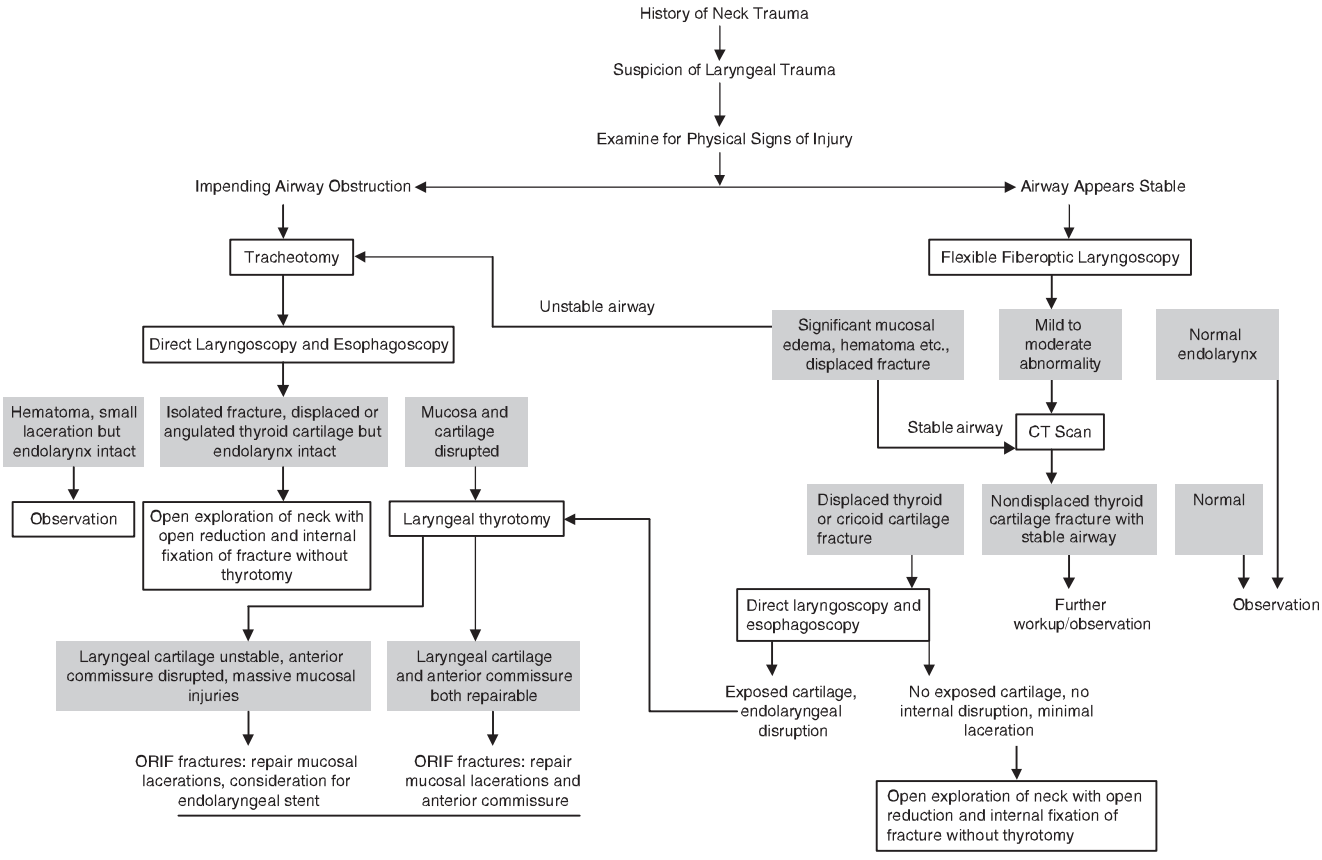


Figure 77.2 Management algorithm for suspected laryngeal injury.

TABLE 77.2 EMERGENCY CARE LARYNGEAL TRAUMA

Multisystem trauma
- Establish airway
- Cardiac resuscitation
- Control of hemorrhage
- Stabilization of spinal injuries

Adult airway
- Tracheotomy under local anesthesia or rigid bronchoscopic intubation
- Alternatively, endotracheal intubation only with:
  - Experienced personnel
  - Small-diameter endotracheal tube

Pediatric airway
- Rigid bronchoscopic intubation followed by tracheotomy

TABLE 77.3 TREATMENT LARYNGEAL TRAUMA

Medical
- Voice rest
- Systemic steroids
- Elevate head
- Humidified air
- Antibiotics
- Antireflux measures

Surgical
- Tracheotomy
- Endoscopy
- Exploration
- Thyrotomy
- Closure of lacerations
- Insertion of stents for disrupted anterior commissure
- Grafting for severe mucosal loss only
- Fixation of fractures

injury, documented with flexible laryngoscopy and CT, can safely undergo careful endotracheal intubation if it is needed to manage other injuries. Such intubation should be performed by a highly experienced physician to avoid further injury to the larynx.

A child with a traumatized larynx presents a special case because it usually is difficult to perform tracheotomy under local anesthesia in this situation. Inhaled anesthesia with spontaneous respirations is used to achieve bronchoscopic intubation, which allows direct visualization of laryngeal injuries and prevents additional iatrogenic injury (11,21). Some authors recommend needle cricothyroidotomy and jet insufflation for patients younger than 12 years (22). However, obtaining a needle cricothyroidotomy may be difficult with loss of laryngeal landmarks, and jet insufflation may worsen subcutaneous emphysema or pneumomediastinum (22).

Treatment Decision Making

Management is divided into medical and surgical treatment according to the extent of injury as determined at physical examination and CT (Table 77.3). The decision to treat a patient medically or surgically is determined by the likelihood that the injury will resolve without surgical intervention. The following conditions are likely to resolve spontaneously without serious sequelae: edema, small hematoma with intact mucosal coverage, small glottic or supraglottic lacerations without exposed cartilage, and single nondisplaced thyroid cartilage fractures in a stable larynx (15,16,20). Some evidence, however, suggests that the repair of even single nondisplaced angulated fractures can prevent subtle vocal changes, as shown by acoustic impedance (23). Strobovideolaryngoscopy may be useful in determining which minor injuries may cause phonatory disorders (13) Injuries likely to necessitate open laryngeal exploration and repair include lacerations involving the free margin of the vocal fold, large mucosal lacerations, exposed cartilage, multiple and displaced cartilage fractures, avulsed or dislocated arytenoid cartilages, and vocal fold immobility (15,16,20).

Injuries likely to necessitate the additional use of endolaryngeal stenting include disruption of the anterior commissure, multiple and displaced cartilage fractures, and multiple and severe endolaryngeal lacerations. In general, stenting is avoided if possible, but may be indicated in the management of these injuries to prevent loss of the normal scaphoid shape of the anterior commissure, to stabilize severely comminuted fractures or lacerations, and to prevent endolaryngeal stenosis. Penetrating trauma is more likely to necessitate open exploration than is blunt trauma.

Medical Treatment

The goals of adjuvant therapy are to eliminate further injury and to promote rapid healing. The clinical course after blunt trauma to the neck is uncertain; therefore, hospitalization in a monitored environment for at least 24 hours is recommended to observe for signs of progressive airway compromise and worsening of laryngeal edema (24,25). Preparations are made for possible emergency tracheotomy.

Bed rest with elevation of the head of the bed for several days helps resolve laryngeal edema. A period of voice rest can minimize further edema or reduce the progression of a hematoma or subcutaneous emphysema. The use of cool, humidified room air helps prevent crust formation in the presence of mucosal damage and transient ciliary paralysis. Additional oxygen is usually not needed unless there is evidence for oxygen desaturation, the advent of which should prompt further investigation.

Nebulized racemic epinephrine and systemic corticosteroids have been used sporadically in the management of laryngeal trauma in an effort to reduce edema and subsequent fibrosis, but no convincing clinical or experimental evidence supports use of this therapy. If used, they are most likely to be of benefit in the first few hours after injury. If there is evidence of a mucosal tear or laceration, antibiotics with coverage toward mixed upper aerodigestive track flora can be useful as prophylaxis against infection, although this has not been proven clinically (25).

A patient with a laryngeal injury is restricted at first to a clear liquid diet with intravenous supplementation as necessitated by other injuries. Nasogastric feedings usually are unnecessary, and passage of a nasogastric tube can worsen the injury. Prolonged use of a nasogastric tube can traumatize the posterior larynx and promote gastric acid reflux. The use of H_2-blocking agents and proton pump inhibitors can help prevent the development of reflux laryngitis, which may be important in preventing scar formation and stenosis in the presence of laryngeal mucosal injury (12,25). Patients with hypopharyngeal tears are given nothing by mouth initially, and if associated with severe laryngeal injury, may benefit from gastrostomy tube placement early on as opposed to placement of a nasogastric feeding tube.

Surgical Treatment

The optimal timing of endoscopic evaluation and surgical management of laryngeal trauma is controversial (2,15,16,20). Some reports indicate that waiting several days after trauma allows the edema to resolve so that endolaryngeal lacerations can be better identified and approximated (11). Currently, most authors agree that early exploration offers the opportunity for complete assessment of the injury and may result in a lower postoperative infection rate, quicker healing, less granulation tissue, and less scarring. Results of several large laryngeal trauma case series suggest that early surgical intervention is associated with better outcomes and is more effective in allowing accurate identification of mucous membrane, muscle, and cartilage injuries, which can then be repaired primarily (15,20,26). In practicality, some delays in treatment may be unavoidable due to associated injuries such as an unstable cervical spine or traumatic brain injury.

Endoscopy is used to ascertain the extent of injury to the larynx and adjacent aerodigestive tract when further surgical management is being considered. A thorough direct laryngoscopic examination is performed in which the entire larynx and hypopharynx are visualized. If dislocated arytenoid cartilage is found, endoscopic reduction should be performed with efforts focused on restoring proper height of the vocal process (27). Bronchoscopy also is used to evaluate the subglottis and trachea. Esophagoscopy is performed to rule out unsuspected esophageal perforation. When injuries that clearly necessitate surgical management are identified at endoscopy, open exploration is performed immediately.

The extent of injury found at endoscopy or open exploration determines the extent of surgical therapy. It may be as limited as tracheotomy to establish an airway or as extensive as open reduction and internal fixation with stenting. Endoscopic or CT evidence of laceration of the mucous membrane, exposed cartilage, immobility of the vocal folds, or displaced or comminuted fractures of cartilage are indications for open exploration. Open reduction and fixation of cartilage fractures is definitely preferable to closed reduction over a bronchoscope and subsequent placement of a stent because of the difficulty of obtaining an adequate reduction in a closed manner and because the dynamic nature of the stresses on the larynx necessitate continued fixation to provide stability. In the management of severe injuries, such as large mucosal lacerations involving the anterior commissure, comminuted cartilage fractures, and avulsion of the arytenoid cartilage, open exploration through a laryngofissure or thyrotomy with stenting is indicated (15,20).

Exploration is performed through a horizontal skin incision in a skin crease at the level of the cricothyroid membrane. Subplatysmal flaps are elevated superiorly to the level of the hyoid bone and inferiorly to just below the cricoid cartilage. The incision can be extended to explore and repair associated neural, vascular, or visceral injuries. The infrahyoid strap muscles are separated in the midline and retracted laterally to expose the laryngeal skeleton and fractures. The thyroid cartilage is incised at the midline, or a preexisting vertical fracture in close proximity to the midline can alternatively be used, and the endolarynx is entered through the cricothyroid membrane. Under direct vision, the incision is extended superiorly through the anterior commissure to the thyroid membrane. The entire endolarynx is examined to identify the extent of the injury (Figs. 77.3 and 77.4). The arytenoid cartilages are palpated to assess their position and mobility.

All mucous membrane, muscle, and cartilage with a viable blood supply are preserved and restored to their original position. Because it is the primary factor responsible for formation of granulation tissue and fibrosis, exposed cartilage must be covered primarily. Failure to do so necessitates grafting and healing by secondary intention. Lacerations are meticulously approximated with 5-0 or 6-0 absorbable suture material (Fig. 77.5). Mucosal advancement flaps may be needed to relieve tension on suture lines and to achieve complete cartilage coverage.

Cartilaginous fractures may be repaired with wire, nonabsorbable suture, resorbable miniplates, or permanent miniplates. Miniplates offer increased opportunity for reconstitution of the skeletal anatomy of the thyroid or cricoid cartilage as compared to less rigid means of fixation (28,29), and have become the mainstay of many authors' armamentarium (30–33). Resorbable plates generally resorb within 1 to 2 years and are particularly attractive due to their relative ease of adaptability (34). However, screws of both resorbable and nonresorbable type tend to pull out easily in cartilage, and an untapped, undersized drill bit

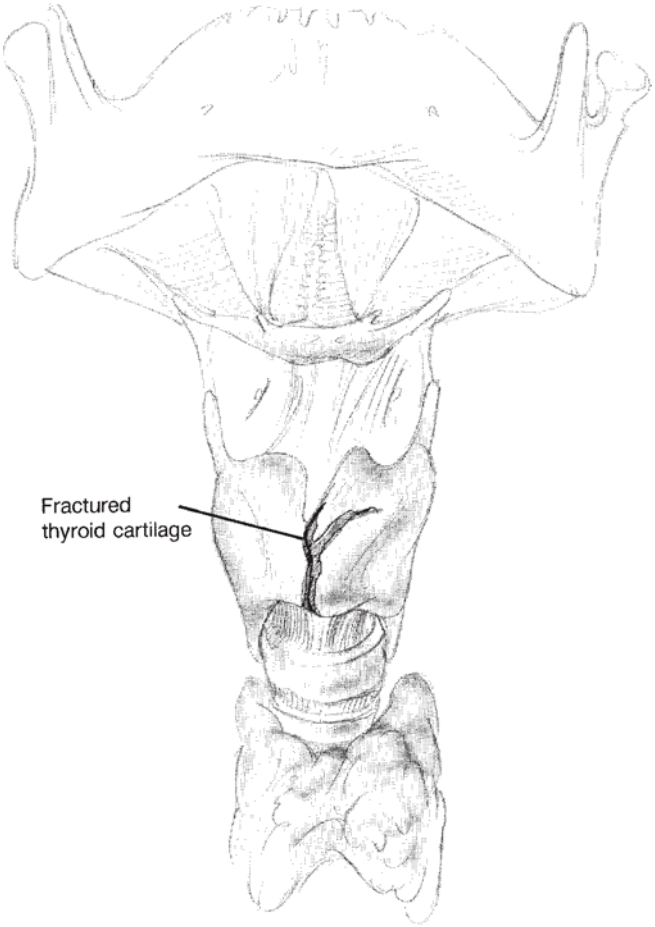


Figure 77.3 Fracture of thyroid cartilage.

should be used along with careful insertion technique in order to avoid shear failure (31,33,34). If a screw does strip, nonresorbable or long-lasting resorbable suture can still be used to secure the cartilage to the plate, while still gaining increased rigidity from the plate itself. Small fragments of cartilage with no intact perichondrium are removed to prevent chondritis. The anterior margin of each true vocal fold is sutured to the thyroid cartilage or its external perichondrium at the thyrotomy site to reconstitute the anterior commissure (Fig. 77.5). If the anterior commissure is devoid of epithelium, a preformed keel or reinforced polymeric silicone sheeting can be placed to prevent web formation. The thyrotomy is closed with wire, nonabsorbable suture, or miniplates (Fig. 77.6). If part of the anterior cricoid ring is lost, suturing the infrahyoid strap muscles into the defect can help maintain the airway and voice.

Grafting

Adhering to the principles of conservation of normal anatomic relations and immediate surgical management makes the need for a graft rare. Mucous membrane or skin grafts have been used to cover areas of exposed cartilage that cannot be closed primarily; however, these wounds must heal by second intention, which causes greater scar

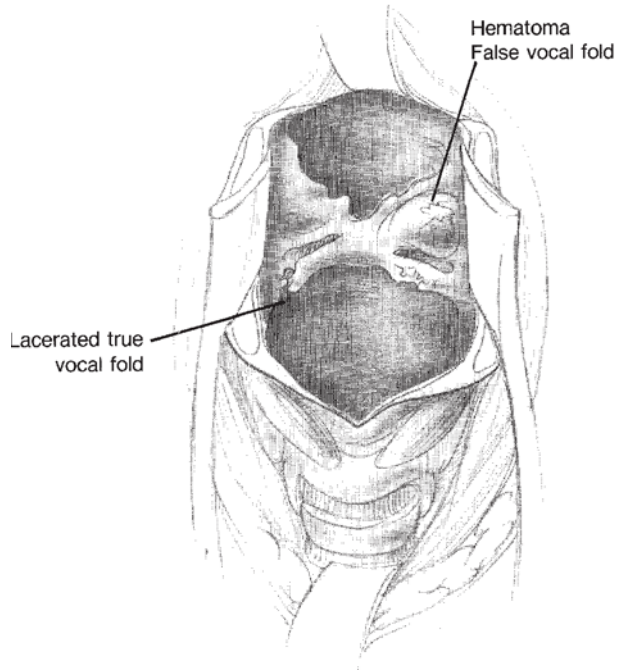


Figure 77.4 Laceration of true vocal fold and hematoma of false vocal fold.

formation than with primary closure. In the rare situation in which a graft is needed, mucous membrane, dermis, and split-thickness skin are suitable. Mucous membrane most closely resembles the normal endolaryngeal epithelium, but use of this tissue carries high donor-site morbidity and necessitates entering the oral cavity. Grafting never is a substitute for careful closure of laryngeal lacerations.

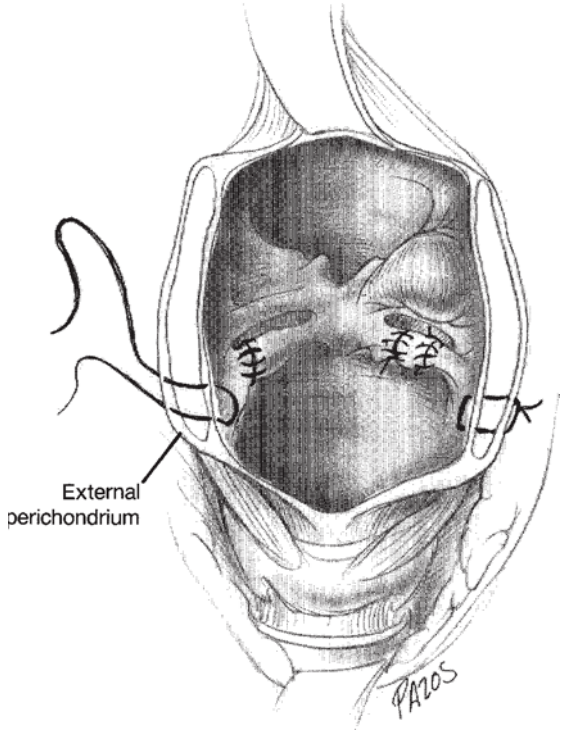


Figure 77.5 Repair of lacerations.

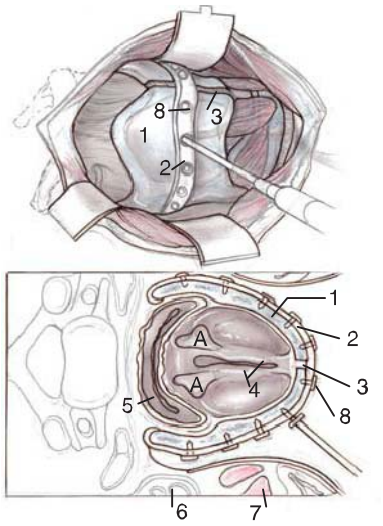


Figure 77.6 Resorbable plate fixation of laryngeal fracture. *1*, thyroid cartilage; *2*, biomaterial; *3*, gap; *4*, swollen vocal cords; *5*, esophagus; *6*, carotid sheath; *7*, anterior strap muscles; *8*, screws placed in biomaterial and thyroid cartilage.

Stents

Laryngeal stents can be used initially for internal fixation devices and thereafter prevent endolaryngeal scarring and maintain the internal configuration of the larynx. Although the presence of a stent can increase the risk of infection and formation of granulation tissue, the clinical findings sometimes dictate stenting (35). Multiple cartilaginous fractures that cannot be stabilized adequately with open reduction and internal fixation and extensive lacerations involving the anterior commissure are specific indications for the use of stents. In the presence of a stable laryngeal skeleton with an intact anterior commissure before thyrotomy, stenting is not needed. Massive mucosal injuries may necessitate stenting to prevent mucosal adhesions (Fig. 77.7). Stents alone, however, are not a substitute for primary closure of mucosal lacerations and careful reduction and internal fixation of fractures (15,20).

The stent must be fixed in the larynx in such a way that it moves with the larynx during swallowing and can be consistently and easily recovered by means of endoscopy alone. A useful method is to pass a heavy, nonabsorbable suture through the stent and the larynx at the level of the laryngeal ventricle and another at the cricothyroid membrane. These are tied over buttons outside the skin. There is some controversy about how long to leave a stent in place. The desired laryngeal stabilization must be achieved and scar formation prevented, but the risk of infection and wound necrosis associated with prolonged stenting must be considered (36). If an analogy can be drawn with pediatric single-stage laryngotracheal reconstruction with endotracheal tube stenting, stenting for longer than 1 week does not confer any advantage (37). The stent is removed by means of direct laryngoscopy, and the operative result is assessed. Granulation tissue can be removed with conservative use of a carbon dioxide laser or laryngeal microdebrider. An association has been suggested between

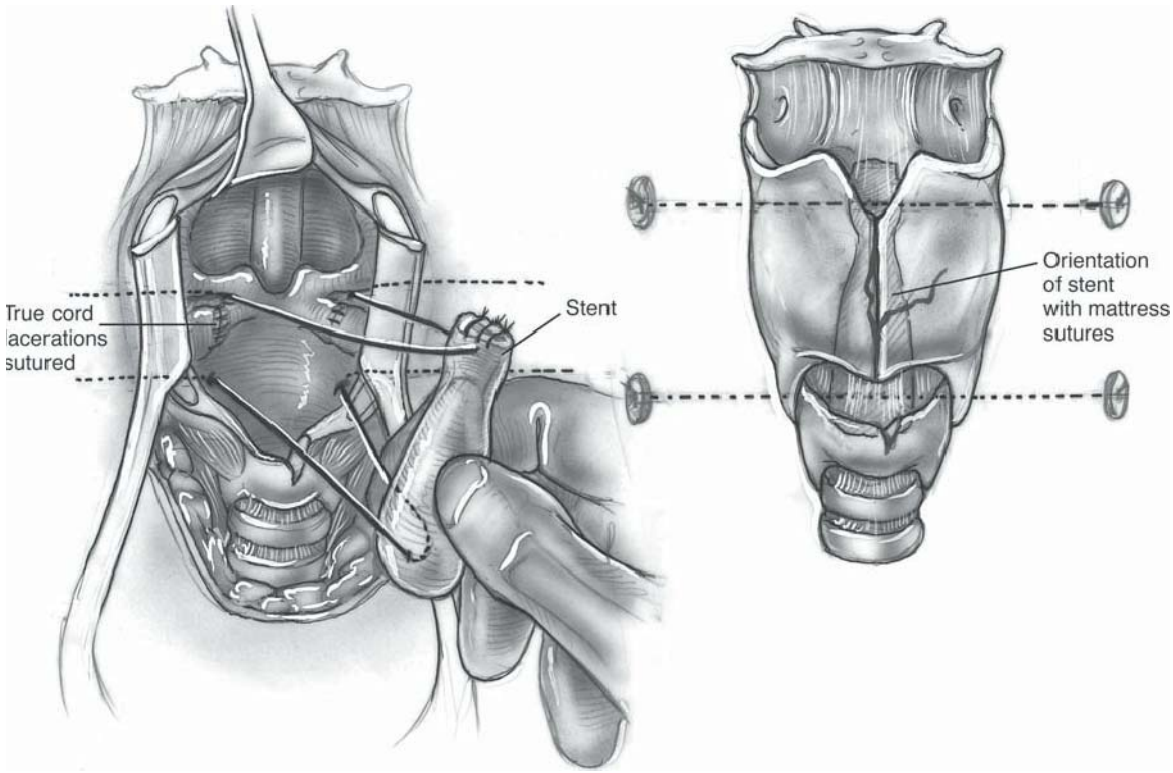


Figure 77.7 Fixation of endolaryngeal stent using nonabsorbable sutures.

the development of granulation tissue and stent colonization with *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and it is recommended that prophylactic antibiotics be used (38). The need for additional endoscopic manipulation is determined with serial flexible laryngeal examinations. Decannulation is best deferred until the patient can tolerate a reasonable period of plugging of the tracheotomy tube.

Cricotracheal Separation

Cricotracheal separation is one of the more severe injuries associated with anterior cervical trauma and commonly occurs from clothesline injuries (39). Several factors unique to this injury must be considered including a precarious airway, loss of cricoid support, injury to the recurrent laryngeal nerves, and late development of subglottic stenosis. While cricotracheal transection often is associated with asphyxiation at the time of trauma, respiratory distress may not be present if prefascial tissues remain intact. Therefore, a high index of suspicion is required for diagnosis of this type of injury. The airway is best controlled by means of tracheotomy with the patient under local anesthesia. When this is impossible, tracheotomy is performed after careful passage of a ventilating bronchoscope. Intubation of the patient with laryngotracheal separation can result in loss of airway due to placement of the endotracheal tube through the mucosal laceration into the soft tissue of the neck, with disastrous consequence. If the patient has successfully been intubated before evaluation, the diagnosis may not be established until extubation. CT may aid in diagnosis of the intubated patient showing balloon overinflation or herniation (40).

If the cricoid cartilage is intact, the mucous membrane is repaired directly with absorbable suture. To distribute the tension on the wound away from the cricotracheal anastomosis, nonabsorbable sutures are placed from the superior aspect of the cricoid cartilage to the inferior aspect of the second tracheal ring. If the cricoid is fractured, the effectiveness of repair is limited by the stability of the cricoid cartilage after internal fixation. Reconstitution of the severely injured cricoid cartilage, with the assistance of internal fixation and stenting, is preferable to extensive resection of the cricoid and thyrotracheal anastomosis.

Severed Recurrent Laryngeal Nerve

Management of a severed recurrent laryngeal nerve continues to be controversial. Even with careful microscopic repair of the transected nerve, vocal fold mobility is not regained owing to the mixture of abductor and adductor fibers in the nerve (41). Additionally, vocal fold synkinesis may develop after neurorrhaphy. Nerve regeneration can prevent muscle atrophy, help maintain some strength of voice, and decrease rate of aspiration (41). Therefore, it appears that the best acute-phase management is immediate reapproximation of the nerve under an operating microscope.

COMPLICATIONS

Early recognition of laryngeal injuries and the application of consistent management principles have decreased the morbidity and mortality from laryngeal trauma (Table 77.4). Success is measured in terms of restoration of the voice, airway, and deglutition. Bent has proposed a modification of Shaefer's original grading system that may be useful in predicting successful outcomes (Table 77.5) (5,20). Among patients with edema, hematoma, or minor lacerations, excellent recovery of both voice and airway usually can be achieved without surgery or with minimal surgical intervention, such as tracheotomy or endoscopy. With severe lacerations and cartilaginous fractures, good results can be achieved with early primary repair of lacerations and internal fixation of fractures. In the two largest published series of laryngeal trauma, greater than 97% of patients were able to be decannulated using these treatment protocols (16,20). In these same series, voice quality was graded as poor in only 1 patient out of the combined total of 251 patients (16,20). If present, suboptimal voice outcome may be related to impaired lengthening of the vocal folds secondary to scarring or superior laryngeal nerve injury (42).

The most common problem in the immediately postoperative period is development of granulation tissue, which most often happens in the presence of bare cartilage. This problem often is the precursor to fibrosis and stenosis. Many techniques have been used in attempts to arrest formation of granulation tissue, including the use of systemic and intralesional corticosteroids, long-term splinting, and

TABLE 77.4 COMPLICATIONS LARYNGEAL TRAUMA[a]

Granulation tissue
Prevent by covering all exposed cartilage
Avoid stents when possible
Careful excision
Laryngeal stenosis
Excision with mucosal coverage
Stenting selected cases
Laryngotracheoplasty
Tracheal resection with reanastomosis
Vocal fold immobility
Observe
Vocal fold injection
Thyroplasty-type vocal fold medialization
Arytenoidectomy and vocal fold lateralization for bilateral paralysis

[a]Manifested as failure to decannulate and inadequate voice.

TABLE 77.5 INJURY GROUPS

Group 1: Minor endolaryngeal hematoma/lacerations without detectable fracture
Group 2: Edema, hematoma, minor mucosal disruption without exposed cartilage; nondisplaced fractures on CT scan
Group 3: Massive edema, mucosal tears, exposed cartilage, vocal cord immobility, displaced fractures
Group 4: Group 3 plus three or more fractures and massive mucosal damage requiring stenting
Group 5: Laryngotracheal separation

low-dose irradiation, but these methods have had little success. Probably, the most effective technique is to minimize the initial formation of granulation tissue by attempting to cover all exposed cartilage meticulously in primary closure of laryngeal lacerations. Control of reflux through the postoperative use of H_2 blockers and proton-pump inhibitors may be beneficial in decreasing the formation of granulation tissue (12). Using intraluminal stents only in highly selected cases, as described earlier, and keeping the stents in place for the minimum amount of time needed decreases the amount of granulation tissue that forms.

Despite strict adherence to proper principles of management of laryngeal trauma, fibrosis and stenosis can occur. Therapeutic measures depend to some extent on the level of stenosis. Supraglottic stenosis often can be corrected with simple excision of the scar tissue and local advancement flaps for wound coverage. Stenosis repair may be performed through an open or endoscopic approach (3). Extensive areas of stenosis may necessitate the removal of a large portion of the epiglottis or aryepiglottic fold. In rare instances, supraglottic laryngectomy may be necessary if depending on the degree of stenosis or cartilaginous injury (43). A keel or stent can be used as needed to maintain the repair.

Rehabilitation from glottic stenosis depends on the extent of the lesion. Thin anterior glottic webs can often be lysed and repaired using a microflap technique (see Chapter 68) (44). Posterior glottic webs or interarytenoid scarring may require arytenoidectomy or related procedures (see Chapter 69). Extensive glottic stenosis often necessitates a laryngofissure with direct excision of the stenotic area followed by placement of a rib cartilage graft with or without a stent.

Subglottic stenosis continues to be difficult to manage, no matter what the cause. Less extensive lesions can be managed with repeated dilation or conservative noncircumferential laser excision of the scar tissue. Balloon dilation has been shown to be safe and effective while maximizing the "radial direction of dilation" compared to standard bogie dilation (45). More serious stenosis may necessitate anterior or posterior cricoid splits with cartilage grafting to increase the size of the subglottic lumen. Stenting usually is needed as are numerous endoscopic procedures to excise granulation tissue after removal of the stent. Mitomycin C has shown promise as a topical agent to help prevent recurrent scar formation (3,46). While the exact mechanism of action of Mitomycin C is unknown, it is believed to decrease scar formation through inhibition of fibroblast migration (3). Marked tracheal stenosis in a short segment is managed by means of resecting the stenotic area and performing end-to-end tracheal anastomosis (47). Lesions up to 4 cm in length can be resected with laryngeal release techniques; however, the results with many of these techniques are disappointing, and prevention of these complications continues to be the optimal treatment (see Chapter 62).

After blunt trauma, persistent immobility of the vocal fold may be caused by recurrent laryngeal nerve injury or by cricoarytenoid joint fixation or dislocation. Differentiating these causes is essential in selecting the proper form of therapy, and is best accomplished by observing vocal fold motion with fiberoptic laryngoscopy and videostrobolaryngoscopy followed by direct palpation of the arytenoid to assess its mobility (27). Laryngeal electromyography (EMG) may be necessary to distinguish vocal fold paralysis from arytenoid dislocation (27,48). If the arytenoid cartilage is mobile, the vocal fold is observed for as long as 1 year to await the possible spontaneous return of recurrent laryngeal nerve function; however, laryngeal EMG can shorten the waiting period by providing key prognostic information regarding spontaneous recovery possibilities (see Chapter 69). If aspiration or dysphonia is severe, injecting the vocal fold with an augmenting material such as gelfoam, fat, hydroxyapatite paste, hyaluronic acid, or one of many available materials can be a temporizing measure (49–52). Persistent paralysis resulting in an inadequate voice can often be rehabilitated with appropriate laryngeal framework surgery (53,54). In the case of unilateral fixation of the arytenoid cartilage with adequate voice and airway, no treatment is needed. Bilateral arytenoid fixation or recurrent laryngeal paralysis with a compromised airway often is managed with arytenoidectomy and vocal fold lateralization (see Chapter 69).

CONCLUSION

Although each instance of laryngeal trauma presents a unique therapeutic challenge, using basic primary treatment principles greatly simplifies the management plan. When clinically possible, flexible laryngoscopy provides essential information on the nature and severity of injury, which subsequently directly factors into treatment decisions. The use of CT scans in some cases of laryngeal trauma may obviate the need for open exploration and often is helpful in diagnosis and treatment planning. Tracheotomy rather than endotracheal intubation often is the most controlled method for establishing an airway when necessary.

Immediate open exploration for serious injuries allows primary closure of all mucosal lacerations and prevents some long-term complications of laryngeal trauma. Stenting is not needed when the cartilaginous skeleton is stable after internal fixation and when mucosal coverage of the anterior commissure can be reconstituted. Use of an early primary management protocol to manage laryngeal trauma should predictably maintain laryngeal function.

HIGHLIGHTS

- A high index of suspicion is the most valuable aid to early diagnosis.
- CT is the most useful radiologic examination in the evaluation of laryngeal injury.
- Management is determined by the findings at flexible laryngoscopy and CT.
- Hematoma, small lacerations, and edema are likely to resolve with medical therapy alone.
- Cartilage fractures, large lacerations with exposed cartilage, disruption of the anterior commissure, and arytenoid injuries necessitate surgical repair.
- Tracheotomy is the most controlled method for establishing an airway with an injured larynx.
- Mucosal repair is best accomplished immediately.
- Primary mucosal coverage of exposed cartilage most effectively prevents development of granulation tissue.
- Grafts are used for coverage of exposed cartilage only when primary mucosal coverage is impossible.
- Stents are used only in the presence of anterior commissure injuries or cartilage fractures that are unable to be adequately stabilized.

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78 Principles in Rigid Fixation of the Facial Skeleton

Robert M. Kellman *Sherard A. Tatum*

In this age of rapid transportation and increasing urban violence, severe facial trauma is an entity that the otolaryngologist–head and neck surgeon is likely to encounter. Complex facial trauma may refer to blunt and/or penetrating trauma resulting in multiple facial fractures and varying degrees of soft tissue injury or loss.

Skeletal facial trauma is frequently subdivided into fractures of the frontal sinus, nasoethmoid complex, zygomaticomaxillary complex, midface, dentoalveolar structures, mandible, and other unusual fracture patterns. Complex facial trauma can then refer to either the multiplicity of areas involved (i.e., panfacial fractures) or the degree of severity of involvement of a given area. For purposes of this chapter, massive facial trauma refers to high-energy blunt or penetrating trauma leading to severe bony displacement, comminution or frank bone loss, and/or involvement of multiple anatomic areas and reducing the availability of anatomic reference points for fracture reduction. These injuries may be associated with severe soft tissue lacerations, avulsions, or globe or central nervous system injuries. Regardless of the precise definition of massive facial trauma, it is our contention that these injuries can be managed successfully by adherence to the same basic principles that lead to successful outcomes from less complex trauma.

BONE HEALING

Bone is a complex tissue made up of a collagen matrix mineralized with calcium phosphate (hydroxyapatite) crystals. Interspersed within bone are cellular components that mediate bone resorption, deposition, and metabolism. Thicker areas of bone typically involve two structural components: an outer cortical or dense bone layer and an inner cancellous or spongy bone layer. Thinner sections of bone are lamellar and lack significant cancellous bone or marrow space. Nutrition is supplied to bone through the outer layer of periosteum and inner open circulation of the marrow space (1).

Fracture results in disruption of the bone matrix, surrounding soft tissue and, if applicable, marrow space. This disruption allows blood and inflammatory cells to flood the area. A hematoma forms, which matures through granulation tissue, fibrous tissue, cartilage, and then bone or directly from fibrous tissue to bone depending on the embryologic origin. This callous formation allows indirect healing to occur when the edges of the bone are not approximated. Mineralization eventually occurs if motion is not excessive. If not anatomically reduced, segments heal in a new position, which may lead to deformity and dysfunction (2).

If the distance between bone fragments is decreased by anatomic reduction of the fracture, then healing will occur with less callous formation and diminished alteration of anatomy. Areas of the fracture that are abutted and compressed will heal by contact healing or direct osseous formation without significant callous formation. Direct osseous healing is not likely to occur along the full length of a fracture even if it is well reduced. Microgaps heal by callous formation or gap healing in which bone is laid down directly perpendicular to its normal orientation followed by remodeling to change this orientation. Regardless, the fragments heal in anatomic position (3).

Problems with the bone-healing mechanism can lead to clinical complications of fractures. Delayed union refers to reduced or absent mineralization of a fracture line 8 to 12 weeks after immobilization. Malunion occurs when a fracture heals by osseous union with segments in nonanatomic position. Fibrous union occurs when progression of indirect healing to ossification does not occur. A nonunion can refer to fibrous union, although it typically connotes a wider gap with very poor function, whereas fibrous unions may not result in a functional deficit. Pseudoarthrosis refers to a fibrous union that is mobile enough to function

like a joint. This phenomenon might be a desirable result for a subcondylar fracture that has resulted in temporomandibular joint ankylosis. Otherwise the mobility leads to dysfunction and pain. Inadequate stabilization and infection are major causes of these healing problems (4).

FRACTURE PATHOPHYSIOLOGY AND CLASSIFICATION

Fractures occur when forces are applied that exceed the stress capabilities of bone, leading to a disruption of the mineralized matrix with additional disruption of the associated soft tissue. Fractures may be simple, involving a single disruption between two bone segments, or comminuted, meaning multiple bony fragments exist in the separation between bone segments. Displacement refers to the alteration in anatomic relationships of bony segments. This alteration can occur as a result of the energy of the blow itself or because of unopposed muscle pull. Angulation is the change in angle of the long axis of the bone across the fracture. Distraction refers to the distance between bone segments across a fracture, and rotation is the orientation alteration of bone segments along their long axis. A fracture is considered favorable if it is oriented such that muscle pull vectors act to compress the fracture. An unfavorable fracture is one oriented such that muscle pull vectors act to displace the fragments (Fig. 78.1).

The concept of open or compound fractures relates to the exposure of fractured bone outside the soft tissue, leading to bacterial contamination. This idea is a little confusing in the face because of the oral, nasal, and sinus cavities. Certainly, fractures involving gross lacerations of facial skin or oral mucosa exposing bone are open fractures. Typically, fractures involving tooth-bearing bone even without mucosal laceration are considered open because of exposure to the oral flora through the periodontal tissue. Fractures through the nasal cavity involving mucosal lacerations are likewise exposed to nasal flora. Fractures through an uninfected sinus cavity may not initially involve bacterial contamination; however, a blood-filled sinus is likely to become colonized fairly quickly. Therefore, few facial fractures would not be considered open. Isolated mandibular ramus or subcondylar fractures and zygomatic arch fractures are among these.

The amount of energy associated with the injury tends to affect the characteristics of the injury. Low-energy impacts such as fist blows tend to lead to less comminuted and less displaced fractures. High-energy impacts are more typically associated with comminution, greater displacement, and a greater degree of soft tissue injury. The rate of energy dissipation into the tissue is the true determinant. A hard object striking the face is more likely to lead to comminution than a fist striking with the same energy because the energy of the blow is transferred to the tissue more quickly. The kinetic energy of the object may be greater as well. Penetrating trauma is similar, with low-energy missiles creating less injury than high-energy missiles. However, missile design comes into consideration. A high-energy missile with a hard surface may exit the body fairly quickly, not dissipating all its energy into the body. A lower-energy missile designed to expand, spiral, or tumble and dissipate most of its energy before exit can be more damaging. However, the amount of shock wave energy from the missile impact determines the degree of collateral tissue damage. Point-blank gunshot wounds have the added soft tissue injury of the expanding propellant gases. This blast injury can lead to poor healing, infection, and fibrosis. Ballistics information is helpful, but wound evaluation is still the best guide (5).

RATIONALE FOR RIGID FIXATION

Regardless of the etiology or classification of the fracture, the healing mechanism can be assisted with reapproximation of the fragments followed by fixation to create stability and reduce movement of the bone fragments. Decreasing

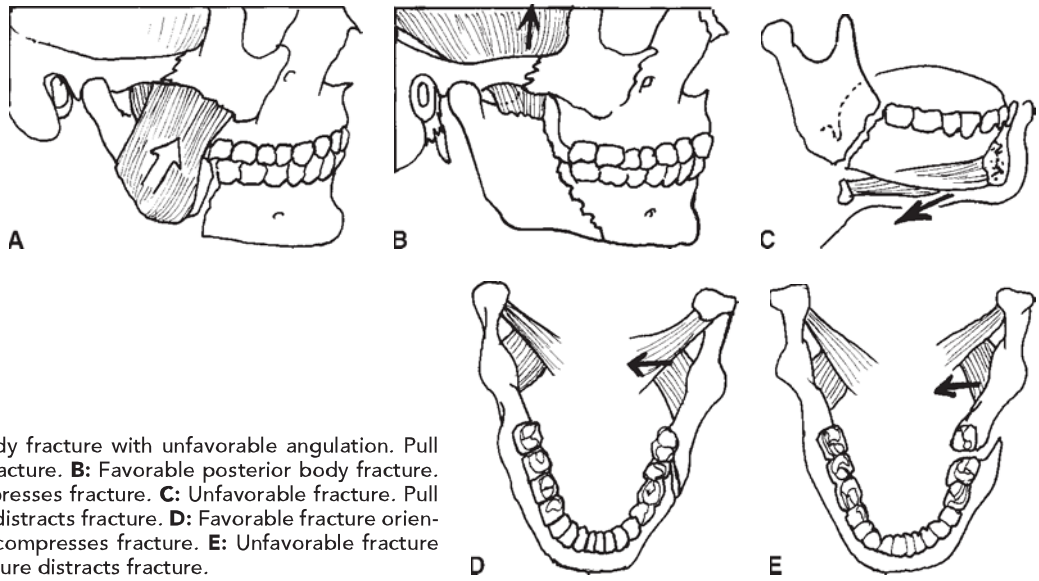


Figure 78.1 **A:** Posterior body fracture with unfavorable angulation. Pull of masseter muscle distracts fracture. **B:** Favorable posterior body fracture. Pull of temporalis muscle compresses fracture. **C:** Unfavorable fracture. Pull of hyomandibular musculature distracts fracture. **D:** Favorable fracture orientation. Pterygoid musculature compresses fracture. **E:** Unfavorable fracture orientation. Pterygoid musculature distracts fracture.

movement of the bone fragments enhances ossification and the progression to a bony union. Reestablishment of blood supply to devascularized bone fragments or bone grafts is also enhanced by immobility. This lack of movement or stability requires overcoming the biomechanical forces acting on the bone fragments. Varying degrees of stability are imparted by different fixation techniques. Rigid fixation of fractures with plates and screws is thought to provide superior stability by overcoming functional forces applied by the musculoskeletal system across a fracture (6). This concept is not universally accepted, however. Enhancements in imaging capabilities and surgical exposure techniques and a greater interest in maxillofacial trauma have paralleled the development of plating technology. These developments may account for improved trauma outcomes. Additionally, plates have been criticized for being palpable, occasionally being visible, causing temperature sensitivity, inhibiting growth, and weakening bone by stress shielding. Some of these criticisms are more theoretic than others, but absorbable plating systems promise to alleviate most of these problems. To obtain comparable strength, characteristics of absorbable plating systems currently require larger plates and screws than their metal counterparts, so they are not suitable for every indication. However, newer reinforced materials may alleviate this problem (7,8).

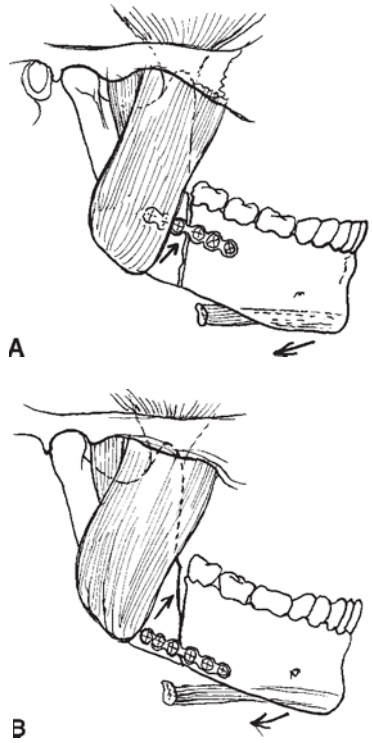


Figure 78.2 Muscle pull distracts superior border of fracture and compresses inferior border of fracture. Plate placement in (**A**) prevents superior distraction. Plate placement in (**B**) does not.

BASIC PRINCIPLES OF RIGID FIXATION

The central concept of rigid fixation is to return skeletal fragments to their anatomic position and rigidly fixate them in that position with an implantable device that provides sufficient strength across the fracture to maintain the reduction against musculoskeletal forces. Fixation plates are designed to span a fracture and provide stress shielding and fracture stability. The plates are fixed to the bone with screws. Each screw placed in the bone is a fixation point. Larger plates made of stiffer material provide greater stress shielding and stability. Large screws provide stronger fixation than small screws. Bicortical screws provide greater stability than monocortical screws, and increasing the number of screws or fixation points anchoring a plate to a bone segment increases stability. Compression or loading of the bone across the fracture enhances stability by increasing the friction between the fracture edges (9). Additionally, plate location relative to bone thickness and the many complex forces acting on the bone are important. Generally speaking, greater bone thickness is found when the forces acting on the bone are greater; however, more bone thickness allows for longer screws, providing increased stability. Forces acting to angulate a fracture distract one end of a fracture and compress the other. A plate placed closer to the end being distracted is more likely to overcome those forces than a plate located at the end being compressed because of mechanical advantage related to the lever principle (Fig. 78.2).

The previous statements are true within certain limitations. The more rigid a plate is, the more precise the bending of the plate has to be to conform to the surface contours of the bone where it is to be applied. Otherwise, as the screws are tightened, the bone may be pulled toward the plate, creating distraction (Fig. 78.3). To overcome this problem, locking-screw plates have been developed. These allow the threaded screw head to lock into a corresponding threaded plate hole, so the screw head locks to plate. This obviates the need for the preciseness of the bend, because the bone will not be pulled to the plate. In mandibular repair, monocortical miniplates have been found to be adequate to replace a heavy bicortical plate so long as they are properly positioned to overcome the distracting forces that occur during function (10). Additional fixation points (i.e., screws) provide additional stability; however, the incremental increase in stability decreases as the number of fixation points increases (11). The increase in stability must be weighed against the additional exposure required and higher bulk of the larger implant. Increasing screw diameter must be weighed against the weakening of the residual bony buttress created by increasing the screw hole size. Increasing screw length into cancellous bone adds little additional strength unless a second cortex is engaged. Screw length beyond the applicable bone thickness certainly adds no strength, and damage to underlying structures such as tooth roots could occur.

FIXATION DEVICE CLASSIFICATION AND TERMINOLOGY

The terminology applied to plating systems is confusing and nonuniform, because it is applied differently by different manufacturers. Plating systems are usually identified

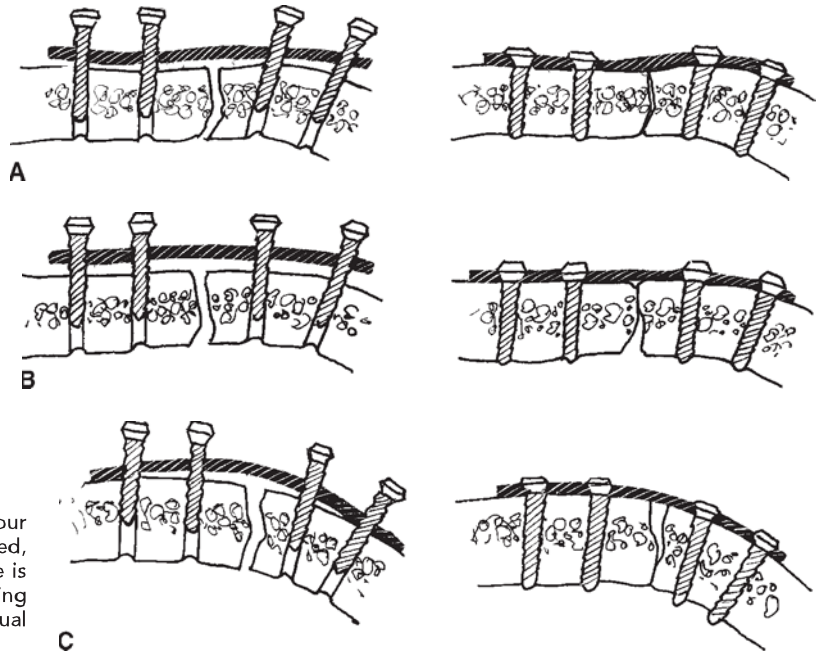


Figure 78.3 **A:** Plate is bent to appropriate contour with bony cortex so that when screws are tightened, lingual and buccal cortices are approximated. **B:** Plate is underbent, approximating buccal cortex but distracting lingual cortex. **C:** Plate is overbent, approximating lingual cortex but distracting buccal cortex.

either by their dimensions or by their application. The term *miniplate* typically refers to plates designed for screws in the 1.2- to 2.5-mm range. The term *microplate* refers to plates designed for screw diameters around 1 mm. There are several intermediate sizes and now modular systems with multiple plate and screw dimensions. Larger systems are designed specifically for the mandible with screw diameters up to 2.4 mm or more and greater lengths for bicortical applications, including lengths up to 40 mm for lag screw applications. Usually, as screw size increases, so does plate thickness. So-called three-dimensional (3-D) plates are available in mini and micro sizes. These plates have added strength due to a lattice design (12).

Plating systems are sometimes designated according to their proposed function, such as maxillary or zygomatic miniplates or mandibular miniplates. Although screw dimensions may be the same, mandibular miniplates are thicker than maxillary and zygomatic miniplates. Mandibular miniplates are typically 1 mm thick. Mandibular systems are further delineated as trauma sets or reconstruction sets, with the reconstruction sets offering the thickest (3 mm or more) stiffest plates in the greatest lengths and with the largest screws. Condylar prostheses may be included. Specialty plates also exist that are prebent for orthognathic surgery or with special configurations useful for microvascular reconstruction of the mandible. Various mesh designs are used to replace defect areas in non–load-bearing areas such as the orbital floor. Newer orbital floor plares have been designed from human models to mimic the anatomical contours (convexities and concavities) of the orbital floor and medial wall providing for more precise repairs.

Dynamic compression plates are designed to push fracture fragments together as the screws are driven. The plate holes are ovoid, and the edges of the hole are slanted. The holes for the screws are drilled eccentrically within the plate holes so that when the screw is tightened, the head slides down the slant, bringing the bone with it. The plate hole orientation determines the direction of movement and compression. Standard dynamic compression plates compress parallel to the plate across the fracture. Eccentric dynamic compression plates have holes on the end that are oriented to provide angular compression for the superior border of the mandible. Today, compression plates are used less frequently than in the past, and eccentric dynamic compression plates are rarely used.

Absorbable plates and screws can be used as well, though to obtain strengths similar to titanium, larger implants are required (13).

PRINCIPLES OF SCREW APPLICATION

For a screw placed in bone to serve as a stable fixation point, the threads of the screw must engage or grip the bone around the drill hole. Factors leading to inherent bone weakness such as osteoporosis or osteitis are beyond the surgeon's control. Adherence to good surgical technique, however, will enhance the stability of the screw in the bone. The drill hole must match the inner screw shaft diameter. If the hole is too small, excessive friction and stress will result. This excess can lead to shearing of the screw head or local bone ischemia and resorption. The screw is held by a functional sleeve of bone around the drill hole that is the thickness of the screw threads (Fig. 78.4). This thickness varies from screw to screw but is typically on the order of 0.1 to 1.0 mm. Any imprecision in drilling can lead to reduction of this sleeve of bone and a larger than desired drill hole. High-speed drill chatter, bent drill bits, drill angulation

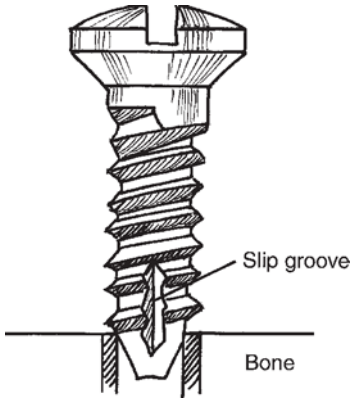


Figure 78.4 Detail of fixation screw in bone. The diameter of the hole in the bone matches the inner core diameter of the screw, not the outer thread diameter of the screw.

change (i.e., hand movement), or continued drilling once the hole is complete can lead to attrition of the bone around the drill hole. Excessive heat leads to delayed attrition from osteocyte death. Therefore, ideal drilling is achieved with a sharp straight drill bit, a low-speed drill, a drill guide, a steady hand, and copious irrigation. The diameter of the drill bit should match the diameter of the screw shaft without threads, not the diameter with threads. If a drill bit's diameter matches the screw's outer diameter with threads, then the screw can be pushed or pulled through the drill hole without turning the screw. This situation is termed *gliding* and is desirable only in lag screwing.

Tapping refers to the cutting of screw threads in the drill hole. Most systems now have self-tapping screws that have flutes beginning at the tip of the screw and extending several threads up the screw to allow for the cutting of the bone into a thread pattern. Residual bone dust from the drilling should be irrigated away from the hole before screw application. The act of tapping itself creates additional bone dust as the threads are cut. This material can lead to binding and excessive wear of the threads. The bone dust should be released by intermittent back turns while tapping and irrigated away. Some systems require or offer as an option tapping as a separate step. The tap thread must match the screw threads exactly, and the subsequent screw must be placed carefully to avoid cross-threading. If inadequate bone exists around the drill hole to hold the screw, then it will fail to tighten as it is screwed into the bone and will begin to slip. Overtightening of the screw can lead to microfracture or stripping of the bone threads as well. Because this is a fairly frequent occurrence, most plating systems contain emergency (rescue) screws, which are screws with the same shaft diameter but a greater thread diameter to allow for bone engagement beyond the stripped portion of the hole. If the emergency screw fails to engage, then another fixation site must be sought. If the plate has extra holes beyond what is needed for adequate fixation, the stripped screw or "spinner" may still be useful. That screw can be left in to anchor the reduction and plate position until the other screws are placed. Then it should be removed and when possible replaced with a larger screw. An advance in screw design eliminates the need for drilling. The tip of the screw is like a drill bit, and the screw is driven directly into the bone. Self-drilling screws allow placement of the screws directly into the bone, avoiding drilling altogether. These are especially helpful in thin bone.

LAG SCREW APPLICATION

A lag screw presses two pieces of bone together by compressing the first piece of bone between the second piece in which the tip of the screw is engaged and the head of the screw (Fig. 78.5). In this situation, a hole is drilled relatively perpendicular to a fracture line traversing the fracture. The hole is double drilled such that the part of the hole on the screw head side of the fracture matches the diameter of the screw with threads, allowing the screw to glide or to be pushed through the hole to the fracture. On the other side of the fracture, the hole diameter is drilled to match the screw shaft diameter without threads. This allows the screw threads to engage the bone on the other side of the fracture. As the screw is tightened, the top fragment is compressed between the head of the screw and the second fragment in which the threads are engaging on the other side of the fracture. An enhancement of this technique has occurred through the development of a tapered drill bit. This bit allows a single drilling motion to provide a larger gliding hole on the screw head side of this fracture and a smaller engaging hole on the other side of the fracture. Because of the often near-tangential angulation of the screw relative to the cortical surface, a countersink hole is drilled to allow the screw head to seat better. Sometimes, drilling the countersink hole first facilitates drilling for the lag screw. The countersink hole should not be too deep or the screw head as it is tightened will pull through the residual cortex into the marrow space and will not be stable.

It is very important to distinguish a lag screw from a positioning screw. A positioning screw is used in very specific circumstances such as fixation of a mandibular sagittal split osteotomy. There, lag screw compression may overcompress the mandibular neurovascular bundle or overtorque the condyle. When a position screw is desired, the drill holes on either side of the fracture or osteotomy are of the screw shaft diameter without thread. The screw threads then engage the bone on either side, making compression across the fracture impossible. The bone segments are fixated into position relative to each other, but a gap exists between them, and there is no compression.

PLATE APPLICATION

A myriad of plate dimensions and shapes exists that conform to multiple anatomic applications (14) (Table 78.1). The variety allows the surgeon to maximize the number

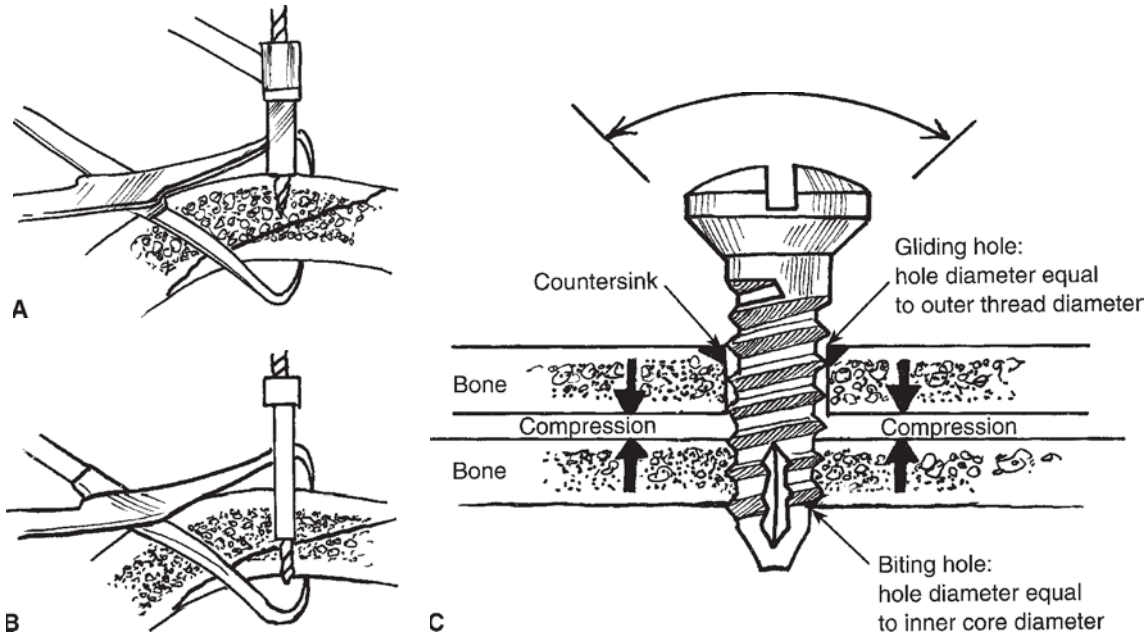


Figure 78.5 **A:** Drilling gliding hole for lag screw placement. The diameter matches the outer screw thread diameter. **B:** Drilling biting hole for lag screw placement. The drill bit diameter matches the inner core diameter of screw. **C:** Detail of lag screw. Diameter of bone hole closest to the head of the screw matches the outer diameter of the threads of the screw, allowing the screw to be pushed through or glide through the first hole without being turned. Diameter of the hole closest to the tip of the screw matches the inner core diameter of the screw. When the screw is tightened, the two pieces of bone are compressed together.

of fixation points in solid bone while minimizing potential injury to underlying structures and working through sometimes difficult exposures. At least two fixation points, one on either side of a fracture, are required for a plate to function as a tension band (resisting distraction forces only). However, there is no rotational stability with two points of fixation. Three points of fixation, two screws on one side of the fracture and one on the other, will prevent plate rotation. However, the fragment with only one point of fixation would still have rotational instability. Four points of fixation, two on either side of the fracture, should be the minimum goal for providing stability of the plate and both fragments. Additional fixation points up to five or six on either side of the fracture may be desirable when bony defects are bridged or healing complications are present. Compression or loading of the bony segments across a fracture, as mentioned before, increases stability. This compression can be provided before plate application by compressing the segments together with a forceps such as a modified towel clip or by the plate itself.

TABLE 78.1 RECOMMENDED PLATE APPLICATIONS

Location[a]	Plate Size
Skull/frontal sinus/supraorbital rims/nasoethmoid complex	Microplates/3-D microplates
Lateral orbital rim	Microplates or low-profile miniplates
Inferior orbital rim	Microplates
Piriform aperture	Low-profile, standard, or 3-D maxillary miniplates or 3-D microplates
Posterior maxillary buttress	Standard or 3-D maxillary miniplates or 3-D microplates
Mandible	Mandibular (thicker than maxillary) miniplates, standard mandibular plates (DCP or EDCP), 3-D mandibular miniplates
Mandible with comminution, infection, or defect	Reconstruction plates

[a]In any location, depending on the situation, wires, heavy sutures, or no fixation at all may be appropriate.
DCP, dynamic compression plate; EDCP, eccentric dynamic compression plate.

INSTRUMENTATION

Application of plates and screws to bone requires specialized instrumentation. Typically, plating systems are self-contained in that they provide all the specialized instrumentation needed for application of the plates. Standard instrumentation for obtaining exposure of the fracture site, however, is not included. Scalpels, scissors, clamps, retractors, and periosteal elevators typically must be supplied in addition to the plating set.

The plating set itself has drill bits that are precisely matched to the screw size. As previously mentioned, a

hole that is too large will prevent the screw from engaging the bone. A hole that is too small may prevent adequate driving of the screw or, in the case of microsystems, cause shearing of the head off of the screw shaft as it is being driven. Typically, there is only one appropriate drill bit diameter for a given screw diameter, and it is usually the size of the screw shaft (i.e., the screw without its threads). An exception to this is found in some microplating systems where drill bits of two different diameters are appropriate for one particular screw diameter. The larger drill bit is used in areas where the bone is harder and thicker to reduce screw head shearing. A smaller bit is used where the bone is thinner or softer, particularly in pediatric cases, to increase screw thread hold. Drill bits with stop collars allow for drilling of a hole to a predetermined depth. The collar prevents overpenetration of the bit, protecting underlying structures.

Drill guides serve several purposes. They protect the surrounding soft tissue from injury by the rotating drill bit and allow for percutaneous drilling. The guide also serves to stabilize the rotating bit, allowing a more precise drill hole. Additionally, guides provide for more precise placement of a drill hole relative to a plate hole. Concentric drill guides place the drill hole in the center of the plate hole. Eccentric guides place the drill hole off center, allowing for compression as the screw head seats in the center of the plate hole. An addition is a guide with a curved extension that points to the drill bit exit site for through-and-through drilling. This extension allows more predictable drilling.

Depth gauges allow precise selection of an appropriate screw length for a given application. When bicortical fixation screws or lag screws are placed, the screw should be long enough to engage the inner cortex without protruding more than a millimeter or two beyond the cortex. When monocortical screws are being placed, the surgeon should have a general idea of the appropriate depth before drilling to avoid damage to underlying structures before a screw is ever placed. For example, monocortical screws being placed over tooth roots should not be longer than 3 to 5 mm depending on location, and the drill hole should not be drilled any deeper than this. Drill bits with collared stops predetermine the drill hole depth and allow appropriate screw length selection without a depth gauge. When tapping is a separate step, the depth gauge should be used before tapping to avoid damage to the threads in the bone.

Some systems contain bone reduction forceps that allow fracture reduction and/or temporary fixation while plates are being bent and applied. Some of these devices are designed to apply compression across the fracture. These devices are useful because they make it possible to avoid having to continually rereduce the fracture for testing of plate contour, which may result in a less precise final reduction and fixation. The bulkier devices require an extraoral approach. Towel, Kelley, or Kocher clamps often will suffice. Drilling of small holes flanking a fracture will sometimes improve the purchase of reduction clamps. Wires can be passed through drill holes on either side of the fracture away from the area needed for plating and used for temporary reduction. Incompletely driven screws can be placed on either side of the fracture and wired or clamped together for temporary reduction.

Various screwdriver tip and screw head configurations exist, and the interface between the two is the important factor. Ideally, the interface provides sufficient strength (i.e., resistance to stripping) so that appropriate torque can be applied to drive the screw into the bone. The interface should also allow retention of the screw on the tip of the driver while it is being brought into position. This retention is achieved in several ways. One is through friction at the interface. The other is for a clamping mechanism that slides down the screwdriver shaft and grips the edges of the screw head. This clamp device can be too bulky for working through percutaneous instrumentation and in other tight locations. Bone wax on the tip of the screwdriver is a third option when the clamp is too bulky and interface friction is inadequate for screw retention. Additionally, the interface affects how quickly the screw can be mounted on the driver, an important factor in dealing with multiple fractures and long repair procedures. It is also important to know what screw type is present when removing hardware so the appropriate screwdriver can be available. Some manufacturers now have screwdriver sets containing all of the common types.

FRACTURE REDUCTION

The structure of the facial skeleton can be viewed as a lattice framework of thick bony buttresses that impart the 3-D strength necessary to withstand the functional forces of mastication (Fig. 78.6). The intervening thin bone adds little additional strength but serves as a partition separating various facial components such as the sinuses, orbits, pharynx, and nasal and cranial cavities. Reestablishment of the anatomic position and continuity of these buttresses is the key to fracture reduction (15). Although of secondary importance, anatomic reduction of the intervening thin bone should be obtained as well, particularly when that bone forms one of the walls of the orbit. Otherwise, orbital contents will sag through the defect into an adjacent cavity, resulting in globe malposition.

Anatomic reduction predisposes a frame of reference that guides the replacement of a malaligned bony fragment into an aligned position. With massive facial trauma, anatomic reference points may be further away and more difficult to expose and/or they may be so comminuted that they cannot provide a reliable indication of the proper reduction. For example, in a simple zygomaticomaxillary complex fracture, the medial aspect of the infraorbital rim, the superior aspect of the lateral orbital rim, the zygomatico-sphenoid relationship in the lateral orbit, and the posterior maxillomalar buttress provide adequate reference points for anatomic reduction. Panfacial fractures resulting in comminution or mobility of these reference points may

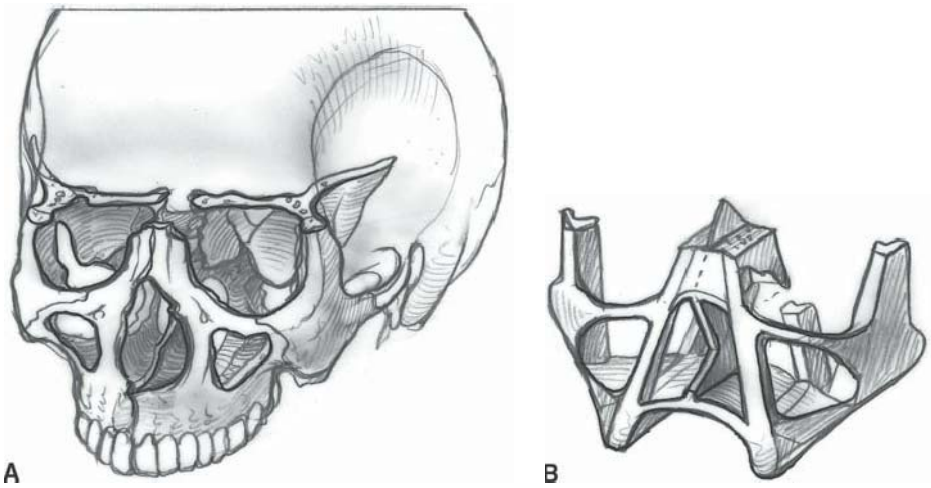


Figure 78.6 **A:** Facial skeleton showing bony buttresses with removal of intervening bone. **B:** Representation of structural buttressing of the midface.

necessitate exposure of the root of the zygomatic arch as another reference point for appropriate placement of the zygomaticomaxillary complex (16). Preoperative virtual surgical planning systems and intraoperative 3-D positioning systems offer some promise in aiding with this problem (17–22).

High-energy injuries may lead to severe comminution or even pulverization of intervening segments of bone. In this case, bony structure is reduced to its anatomic position based on existing reference points, and intervening gaps in the buttresses are bone grafted. Reestablishing bony continuity of the buttresses is imperative because they must ultimately transmit the forces of mastication to the skull base. Sometimes, a bony fragment from a less crucial area can be borrowed and reoriented to establish buttress continuity. Frequently, additional bone is required, however, and outer table calvarial bone is our preferred source for bone grafting because of its reliability and proximity to the injury site (Fig. 78.7). Minimal donor site morbidity and frequent preexisting exposure due to use of the coronal approach to the face are benefits. Other relatively popular donor sites include the ilium and ribs. Hydroxyapatite cement offers promise for dealing with bony defects without attendant donor site morbidity particularly when fiber reinforced (23).

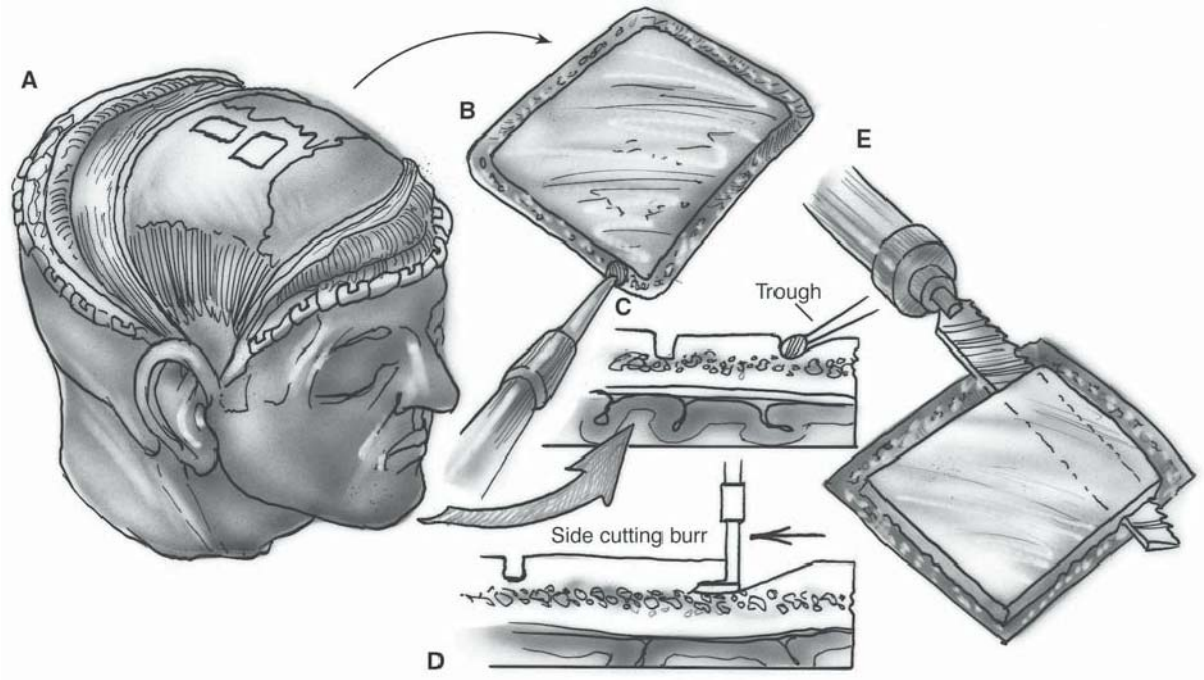


Figure 78.7 *In situ* technique of outer table calvarial bone harvest. **A:** Location of donor site on parietal skull. **B:** Saucerization of bone around graft. **C:** Cross-sectional view of saucerization. **D:** Calvarium split with angled saw. **E:** Calvarium split with reciprocating saw.

OCCLUSION

For the masticatory apparatus to function properly, stable reproducible occlusion must exist. For occlusion to occur, the cusps of the maxillary dentition must fit into the grooves of the mandibular dentition and vice versa (Fig. 78.8). This is termed intercuspation. Wear facets of opposing teeth should contact each other. The wear patterns may be the only reference when preinjury occlusion is abnormal. Normal molar occlusion in the anteroposterior (AP) dimension is defined as intercuspation of the mesial buccal cusp of the maxillary first molar with the buccal groove of the mandibular first molar. This description does not address transverse molar relationships or anterior dental relationships. A normal transverse relationship exists when the buccal cusps of the mandibular molars are between the buccal and palatal cusps of the maxillary molars. Normal anterior dental relationship occurs when the maxillary anterior dentition is 1 to 3 mm anterior to the mandibular anterior dentition with central incisal overlap of 1 to 3 mm. Increased distance horizontally between the incisors is overjet. Increased vertical distance is overbite or deep bite. Anterior crossbite and anterior open bite are the respective converse conditions.

Because preinjury occlusion is frequently not normal as defined previously, it is useful to question the patient or family about the preinjury occlusion. Dental records are also quite helpful. In the absence of this information, wear facets are the main occlusal guide. When the preinjury occlusion is unclear, then anatomic reduction of the fractures before interdental fixation may be more accurate. There should be no reluctance to open interdental fixation if it is preventing anatomic reduction of bone segments. The interdental fixation and skeletal reduction should correlate. If they do not, a preexisting malocclusion should be suspected.

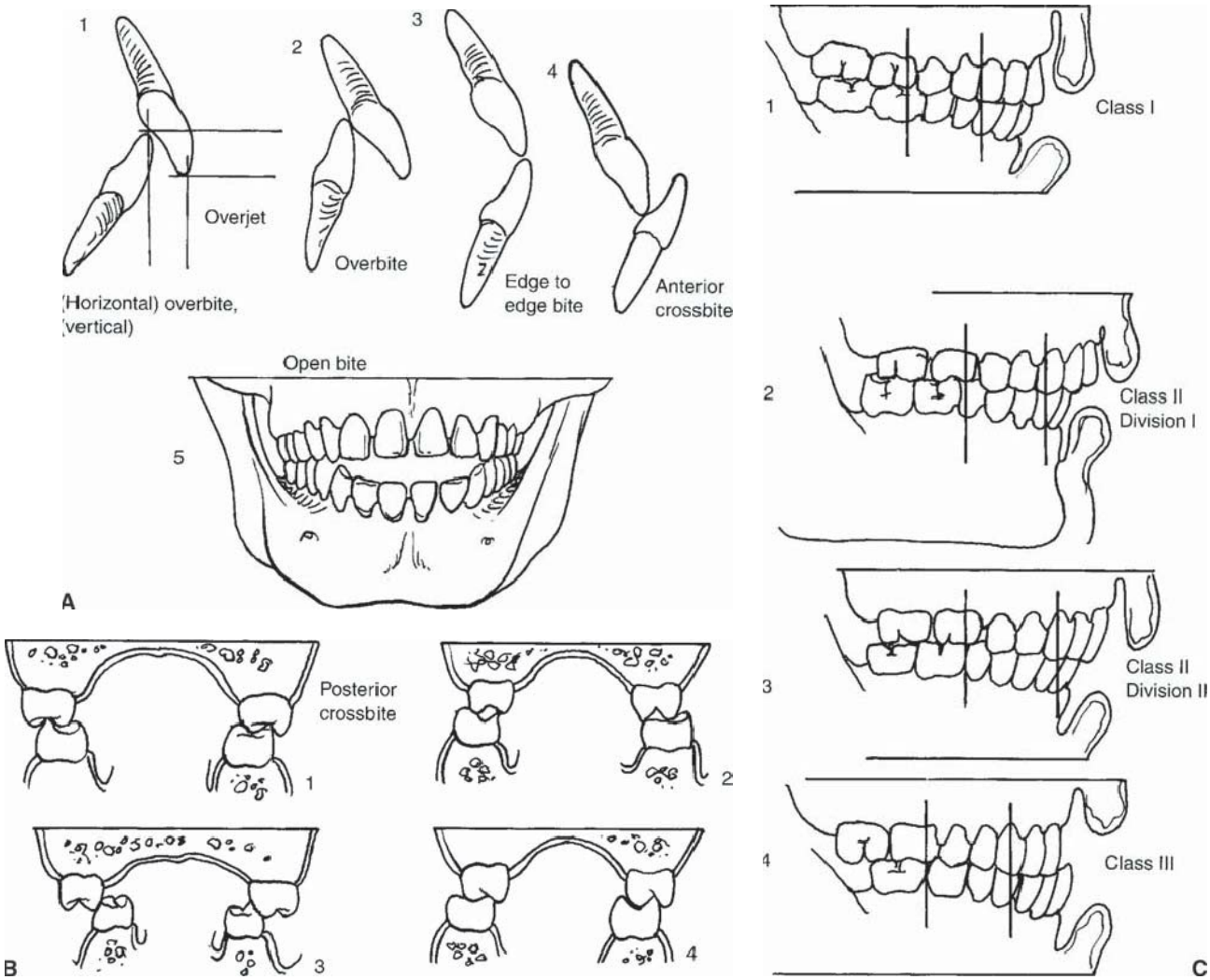


Figure 78.8 **A:** Various anterior incisal relationships. *1*, normal; *2*, overjet and overbite; *3*, edge to edge; *4*, anterior crossbite or underbite; *5*, anterior open bite. **B:** Transverse relationships. *1*, normal; *2*, bilateral lingual crossbite; *3*, bilateral buccal crossbite; *4*, unilateral lingual crossbite. **C:** Sagittal molar class relationships. *1*, class I; *2*, class II, division I; *3*, class II, division II; *4*, class III.

INCISIONS AND EXPOSURE

Adequate anatomic reduction requires wide exposure to view fractures from several angles. Lacerations may provide some exposure, but frequently more is needed. The entire craniofacial skeleton can be exposed through a combination of hidden or well-camouflaged incisions (24) (Fig. 78.9). The entire mandible except for the condyles can be exposed through intraoral vestibular sulcus incisions (25) (Fig. 78.10), and now, with the addition of endoscopic techniques, even the condylar area can be adequately exposed transorally for endoscopic-assisted repair (26). Small stab incisions through the cheek may be necessary for plating posterior fractures and subcondylar fractures; however, angulated instrumentation promises to reduce the need for even these incisions. Pitfalls associated with the mandibular vestibular sulcus incision include damage to the mental nerve, failure to achieve a watertight closure of the incision, and failure to resuspend the mentalis muscle if the chin is degloved. Intraoral incisions for the mandible are not recommended with comminuted fractures, severe periodontal disease, or hygiene problems. Because of the tangential view achieved when approaching posterior fractures transorally, it can be very difficult to contour a heavy plate to the outer cortex. It is our recommendation that any situation requiring a heavy plate placed posteriorly on the mandible should be approached extraorally through a Risdon and/or submandibular neck incision. Low subcondylar fractures needing repair can be approached transorally, but this requires specialized equipment. Unless endoscopic techniques can be utilized, high subcondylar fractures needing repair will require either a Risdon, retromandibular, or a preauricular incision (27–29).

The inferior maxilla can be exposed through a superior circumvestibular incision. The superior exposure can be extended by elevating the nasal floor mucosa between the inferior turbinate root and maxillary crest. Even further superior exposure can be obtained by incising the nasal mucosa along the cephalic border of the lower lateral cartilage and piriform aperture in a full midface degloving approach. Pitfalls include damage to the infraorbital nerve, nostril stenosis, and leaving inadequate oral vestibular mucosa for wound closure.

Upper facial access can be obtained through a coronal incision elevated in the subgaleal or subperiosteal plane. This incision provides access to the medial, superior, and lateral walls of the orbit; the zygomatic arch; and the bony pyramid of the nose. It additionally uncovers donor sites for cranial bone grafting. Pitfalls include damage to cutaneous sensory innervation and motor innervation to the

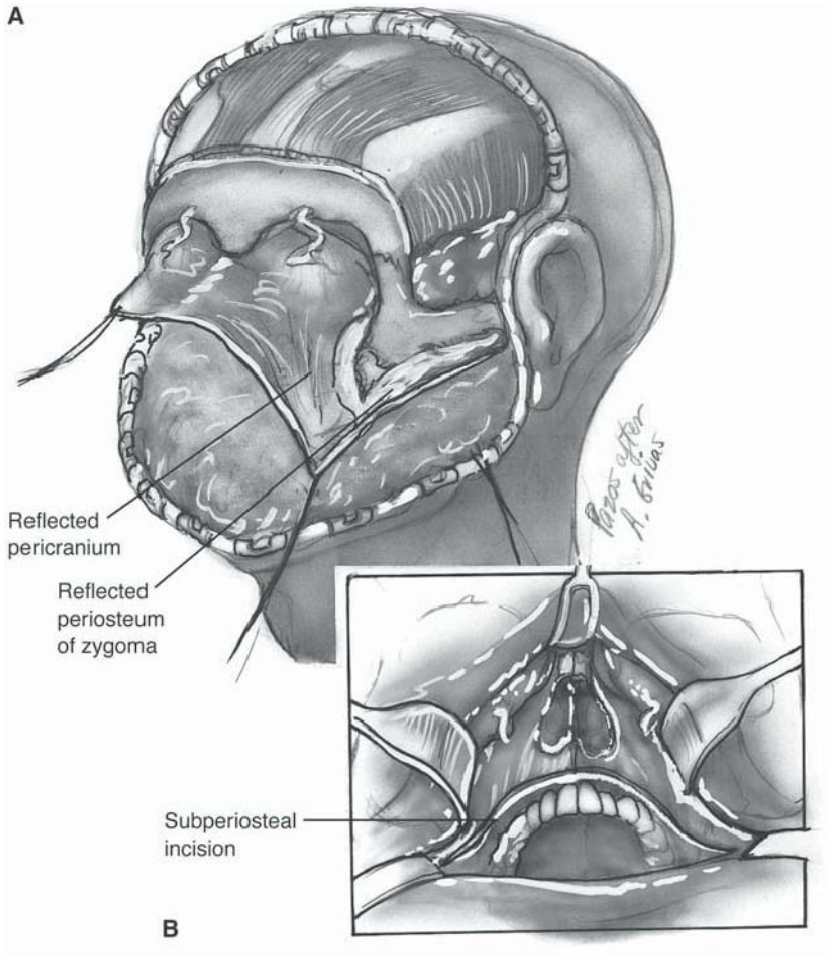


Figure 78.9 **A:** Cranioorbital exposure through bicoronal flap. **B:** Midface exposure through circumvestibular incision.

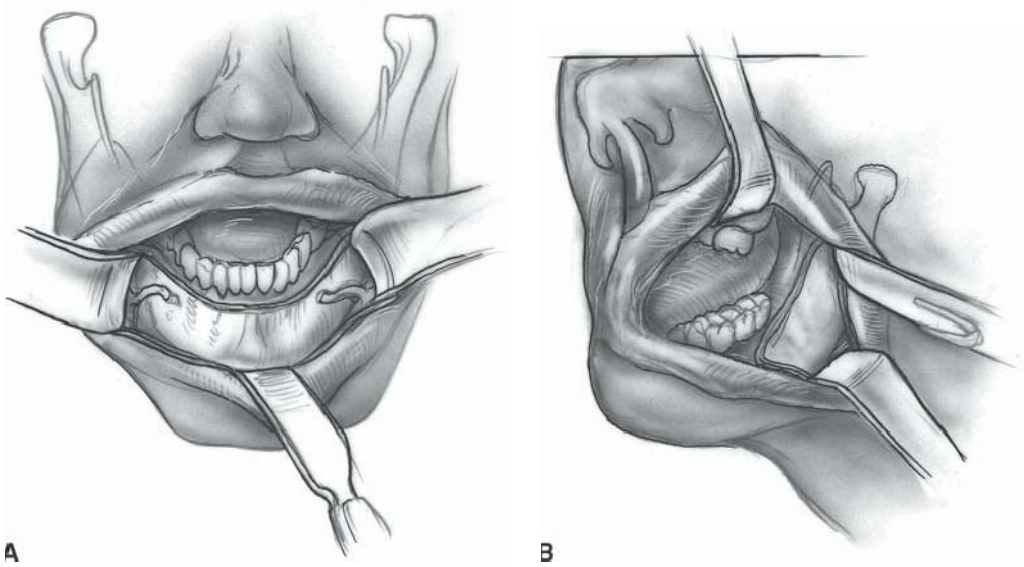


Figure 78.10 **A:** Intraoral approach to the anterior mandible. **B:** Intraoral approach to the angle of the mandible.

frontalis muscle or inadequate closure of the galea, both of which can lead to brow ptosis.

Infraorbital rim and orbital floor exposure is still limited, however, and a lower lid incision is required for that exposure. We prefer either a subciliary incision or a transconjunctival incision with or without a lateral canthotomy and inferior cantholysis for increased exposure when necessary. Inferior lid crease and rim incisions are other options in this area, although they are rarely used today. Careful closure of these incisions and canthal repair are critical to reduce lid complications of entropion or ectropion.

If a coronal incision is not performed, then access to the frontozygomatic region can be obtained through a lateral brow incision or a superior lid crease incision (12). Medial orbital wall and nasoethmoid exposure can be obtained through a broken external ethmoid-type incision. Some people use a gull-wing incision, but the scar can sometimes be quite unacceptable. If the nasal dorsal skin between the incisions is sufficiently elevated and mobilized, then adequate exposure can usually be obtained by retracting the skin without having to make the transverse incision across the nasal dorsum. A transcaruncular incision may provide adequate access to the medial orbit (30).

APPROACH TO PANFACIAL FRACTURES

Severe and complex facial disruptions represent difficult challenges for the craniomaxillofacial surgeon, because usually few reference points are available to help the surgeon determine how to reposition the multiply fractured fragments. Nonetheless, the principles of repair remain the same, and careful attention to the procedures described previously will lead to the best possible outcomes.

Emergencies related to massive facial trauma must be attended to first (Table 73.2). The airway can be threatened by anatomic obstruction, blood, or both and must be secured. Gross hemorrhage must be controlled, preferably with direct pressure. Definitive control should be obtained in the operating room to prevent damage to important nonvascular structures. Occasionally, partial reduction of severely displaced fractures is necessary to aid in the control of hemorrhage. A few interdental wires can be placed emergently to stabilize this gross reduction and alleviate some of the pain associated with mobility of the fractures. Soft tissue injuries should be irrigated and repaired if the patient is not planned for immediate fracture repair in the operating room. Dental avulsions and fractures through the pulp cavity should be treated urgently if the damaged teeth are to be salvaged, and other dental injuries should be identified and appropriate consultations obtained (31). Preoperative antibiotics have been shown to reduce infectious complications (32). Tetanus should be considered in grossly contaminated wounds.

History and physical examination can provide some initial indication of the extent of facial injuries. Historical information such as mechanism of injury and energy of impact is useful in assessing the extent of the injury. Ecchymosis patterns including raccoon eyes and Battles' sign can be indicative of skull base fractures. Other soft tissue findings such as the bowstring lid test can indicate canthal detachments. Palpation of bone surfaces will allow detection of step-offs and mobility. Documentation of cranial nerve function is critical to distinguish injury-associated deficits from iatrogenic deficits occurring after fracture repair. Other factors such as neurologic and visual function are frequently impaired with panfacial fractures. Neurologic and ophthalmologic assessments are necessary (33).

TABLE 78.2 EMERGENCIES FACIAL TRAUMA

Situation	Intervention
Airway obstruction	Intubation, tracheotomy, bronchoscopy
Hemorrhage	Fluid resuscitation, direct pressure, temporary reduction of severely displaced fractures, control in operating room, fluid resuscitation
Central nervous system injury	
Cervical spine	Immobilize
Brain	Neurosurgery evaluation
Reimplantable avulsions	
Tooth	Reimplant and stabilize
Large areas of soft tissue	Reimplant ± microvascular reanastomosis ± hyperbaric oxygen treatment
Globe rupture	Ophthalmology evaluation, repair or enucleation
Optic nerve compression	Medical management Surgical decompression

Radiologic evaluation is key to the full assessment of massive facial trauma (34,35). In our institution, axial computed tomography (CT) is obtained as part of the initial trauma protocol when head and facial injuries are present. Because of cervical spine clearance issues, acute direct coronal CTs are rarely obtained. If complex periorbital fractures are present, then when the patient's condition permits, direct coronal CT is obtained. The mandible is separately evaluated with plain radiographs and panoramic radiography if the patient's condition permits. CT evaluation of the mandible provides additional information as well (36). With severe injury, 3-D reconstructions may be helpful.

With severe craniofacial injuries, there is a high risk that injuries may involve the eyes, dura, and neural structures of the skull base and cervical spine. It is essential that the surgeon be attuned to these possibilities, because failure to recognize these associated injuries could have dire consequences for the patient. Globe injuries must be evaluated by ophthalmology. Ruptured globes often require enucleation, although occasionally minor ruptures may be repaired, and this situation may mandate postponement of the repair of the orbital/periorbital fractures. Similarly, a retinal detachment may require a period of healing before surgical manipulation of the surrounding bones.

It is critically important to identify optic nerve compression, because rapid and aggressive management of this injury may preserve or even salvage vision. When optic nerve compression is associated with frontonasal fractures of the anterior skull base, the subcranial approach as advocated by Raveh et al. (37,38) provides excellent access to the optic nerve canal(s) for decompression. In the subcranial approach, the nasal bones and front wall of the frontal sinus are removed en bloc and saved for later replacement. The posterior wall is then opened, allowing full visualization of the anterior cranial fossa without olfactory compromise or significant brain retraction. This approach also allows for the repair of associated skeletal injuries in the anterior skull base, medial orbits, frontal area, and nose. Rigid fixation allows for the dependable repositioning of the bone fragments and thereby makes the subcranial approach possible. Without rigid repair of the completely removed nasofrontal bone fragments, there would be a high probability of malposition and/or resorption of the bone. Most authors advocate a trial of very high-dose steroids before optic nerve decompression is attempted (39). An eye that shows no light perception from the moment of impact is probably irretrievable, and the value of decompression in this situation is controversial at best. On the other hand, if a patient has progressive visual loss or if a seeing eye progresses to no light perception after trauma to the area of the posterior orbit and/or anterior skull base, and if steroids are not effective in restoring vision within 24 to 48 hours, then most authors would agree that the potential benefit of optic nerve decompression probably outweighs the risks. If the subcranial approach is not appropriate (or desired), then the optic canal can be approached endoscopically through the sinuses or from above via an intracranial approach (40). Recently, some periorbital endoscopic approaches have been described that show promise.

When the floor of the anterior fossa is disrupted, then it is convenient to perform the repair at the time of facial fracture reduction. Here again, the subcranial approach provides excellent access to this area (38). It allows for repair of the anterior fossa dura with a fascial patch or a pericranial flap, without the need to significantly elevate or retract the frontal lobes. This is a very desirable feature of the technique. In most of these panfacial fracture cases, the brain has been injured and is likely to be swollen.

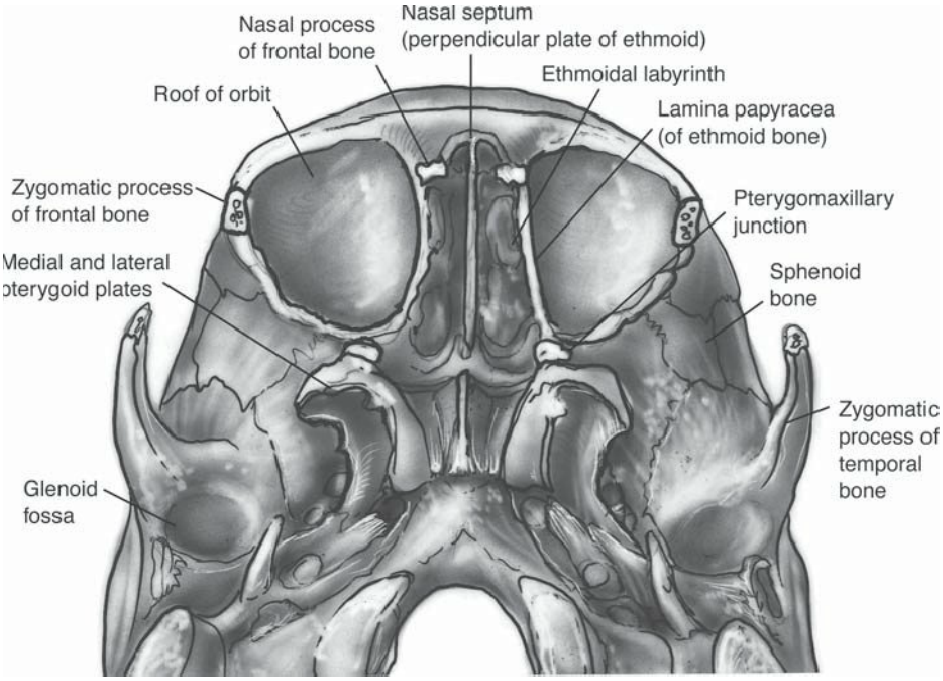


Figure 78.11 Skull base detail showing major areas of attachment of the facial skeleton to the cranial skeleton. These include the nasal and zygomatic processes of the frontal bone, the zygomatic process of the temporal bone, the nasal septum, and the pterygomaxillary junction.

Therefore, acute repair should be considered to decrease the likelihood of cerebrospinal fluid leakage and thereby decrease the risk of later development of meningitis. The subcranial approach avoids brain retraction due to the inferior and direct angle of approach, making early intervention a feasible option in this circumstance.

With regard to timing of repair of fractures, unless a patient's overall condition prevents it, immediate repair has been advocated as the best approach (41). Immediate repair allows visualization of facial structures before the full development of injury edema, which generally occurs 24 to 48 hours after the injury. However, associated injuries frequently require several days for stabilization of the patient (42). Delaying repair may lead to increased bacterial contamination and therefore increased risk of infection. With further delay, the soft tissue envelope around the fractured skeleton begins to fibrose and contract, increasing resistance to anatomic reduction. With increased delay, callus formation and resorption of some of the fine detail of the fracture edges increases the difficulty of mobilization and reduces the ability to achieve an accurate reduction.

As previously stated, one of the major problems with massive facial trauma is a lack of reference points for anatomic reduction. Approaches yielding wide exposure are preferred (43) although there has been a recent trend toward less invasive approaches (44–47). With maximal exposure of the facial skeleton, repair should begin at the periphery, including recreating the contours of the skull and the mandible. The ultimate reference for facial skeletal position is the skull base (Fig. 78.11). For the mandible, this reference is through the condyles. Therefore, the importance of open reduction of subcondylar fractures in this situation cannot be overemphasized. For the middle and upper face, the vertical reference points are the lateral and medial orbital rims, the nasal radix, the piriform apertures, and the posterior maxillary buttresses. Often underutilized is the important horizontal AP reference along the zygomatic arches. Anterior skull fractures can obscure some of these reference points, but then, the next higher point of skeletal stability becomes the new reference point. Once anterior skull fractures are repaired, facial fracture repair can proceed. A systematic approach working from areas of stability toward areas of instability is required. All fractures that are to be repaired should be exposed and reduced before any final fixation. Vertical, horizontal, and sagittal facial dimensions must be restored (Fig. 78.12). We often prereduce complex fractures with wires or sutures initially, withholding more rigid fixation until all fractures have been adequately reduced. Maxillomandibular interdental fixation should be achieved before skeletal fixation as well. Release of maxillomandibular fixation may be required to effect anatomic reduction of bony segments, particularly when preinjury occlusion does not appear to have been normal. Cutting an arch bar over an area where a fracture proceeds between teeth may also be required to achieve anatomic bony reduction. The split arch bar is then repaired once reduction is obtained.

Typically, fracture fixation proceeds centripetally toward the nasal region (centripetally) (Fig. 78.13), although some advocate starting with the nasoorbitoethmoid region (centrifugally). Skull fractures, frontal sinus fractures, and any intracranial injuries are addressed first. A subcranial approach as previously mentioned through the nasofrontal region is our preferred method to access the anterior cranial fossa and medial orbits when the anterior skull base is involved. The mandible should be repaired, and

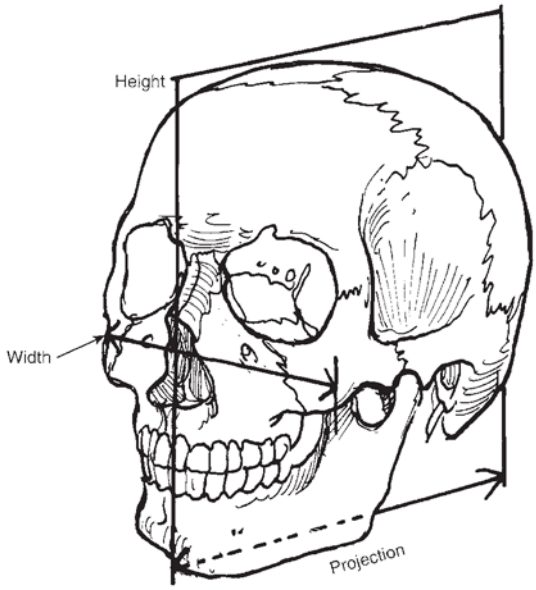


Figure 78.12 Important dimensions of the facial skeleton to be reestablished during reconstructive efforts.

if necessary defects should be bridged with reconstruction plates. Whether the mandible is severely comminuted or partially absent, the occlusal relationship remains the priority concern and the best indication of the premorbid shape. When the dentition is lost or absent, occlusion becomes less critical and obviously unusable as a landmark. Mandibular height should be reconstituted, using a costochondral graft to reestablish the condylar position if the condylar head has been lost. In the case of bilateral displaced subcondylar fractures and midface fractures, at least one of the subcondylar fractures will need to be opened and internally fixated to provide a reference for lower third facial height. If necessary, zygomatic arch fractures are then fixated to provide an AP reference for the malar eminence (48). Arch repair is performed using wires whenever possible, because even small plates on the arch may create some broadening of the cheek. If plate fixation is needed, the smallest (thinnest) plates available should be used. In rare cases, this may require bone grafting of one or both malar eminences to reestablish the proper facial projection. The maxilla and its dentition can then be suspended rigidly from the zygomas, using plates and/or bone grafts to ensure fixation and bony continuity. Lateral maxillary buttress, piriform aperture, and lateral orbital rim fractures are then repaired. Then the orbital rim contours are reconstructed, trying to recreate the natural shape of the orbits with bone grafts or implants while making sure that the globes are returned to their proper position with a 2- to 3-mm overcorrection to allow retropositioning as swelling decreases. Note that the vertical position of the globe should not be overcorrected. Any buttresses with segmental defects after appropriate reduction of the skeletal structures are bone grafted. The bone grafts are stabilized and positioned with bridging plates and/or screws. Once buttress continuity has been reestablished, remaining lamellar bone defects are addressed as needed. The bimalar diameter can usually be reestablished based on the posterior buttresses after occlusal relationships have been reestablished. With severe comminution, however, repair of the nasoethmoidal complex provides additional reference information for restoration of the bimalar diameter. Recent advances include the use of rapid prototyping, which allows for the use of prefabricated implants (49), and the use of a sterilized skull model to allow for plate adaptation (50). In addition, the advent of image guidance systems has allowed for careful planning and carrying out of complex facial repairs (17). Surgical planning can be carried out at a workstation preoperatively, and then a wand can be used at surgery to identify the positioning of bone fragments and grafts relative to the desired positions (17).

Orbital floor continuity must be reestablished. We prefer autogenous bone for this repair, although some prefer

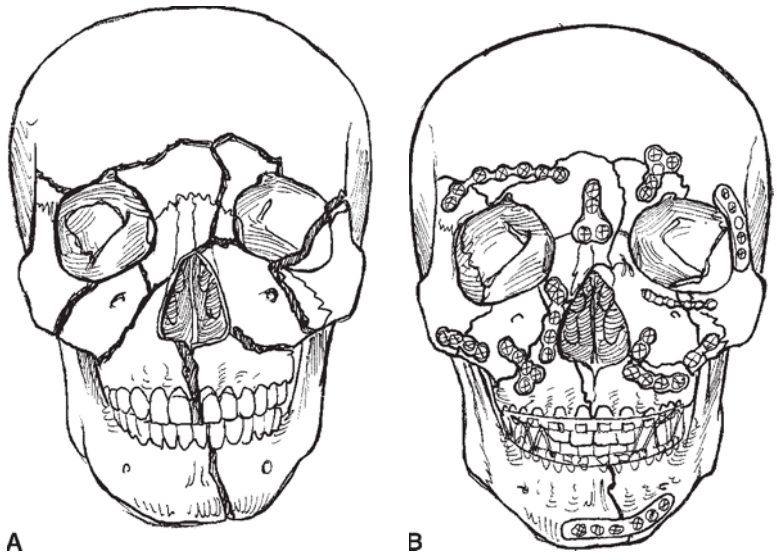


Figure 78.13 **A:** Panfacial fractures. **B:** Repair of fractures with rigid fixation. Fractures are typically repaired centripetally, working from the skull base and the mandible toward the midface and working from the lateral midface toward the medial midface.

alloplastic implants for this location; this is clearly a controversial issue. The previously mentioned titanium anatomic orbital plates and titanium polyethylene composite plates are becoming popular. Perpendicular plate of ethmoid and/or septal cartilage, if not severely fractured, can be used to replace the orbital floor, walls, or roof. Cranial bone or the nonfractured anterior face of the maxilla also do well here. Very small defects can be covered with absorbable plates, gelatin film, or homograft dura. The superior, medial, and lateral orbital walls need to be repaired if they are displaced enough to impinge on orbital contents or significantly alter orbital volume. A defect greater than 2 to 3 cm in diameter of the anterior face of the maxilla itself may need to be repaired; otherwise, facial soft tissue will collapse into the sinus, creating a subtle but noticeable deformity of the melolabial region.

Finally, the nasoethmoid complex is addressed. The typical telescoping collapse must be reduced and reprojected. Frequently, the lamina papyracea needs to be replaced with bone grafts to support forward projection and prevent the herniation of periorbita into the ethmoid sinuses. It is also important to create a structure against which the medial canthal ligament can reattach after fixation. The projection of the nose is reestablished by cantilevering off the frontal bone and/or fixation of the medial orbital region. If the nasal dorsum is deficient, a primary bone graft should be placed.

Once complete fracture reduction has been achieved, certain soft tissue structures that were detached traumatically or to provide exposure must be resuspended. The medial and lateral canthi should be suspended from the adjacent bone slightly posterior and superior to their original insertion sites either with wires or heavy nonabsorbable sutures. For medial canthal suspension, a permanent suture may be utilized. It is placed through the ligament; passed through the nasal septum, lamina papyracea, and/or drill holes in the medial orbital wall bone grafts; and positioned so that the ligament is pulled posteriorly and superiorly. The medial tension is then adjusted using the suture, which is fixed to the contralateral frontal bone using a plate hole, a screw, or a hole drilled through the medial supraorbital rim.

As previously mentioned, the mentalis muscle should be suspended from drill holes in the menton. Soft tissue of the midface might need to be resuspended too if it was significantly dissected. The lacrimal ducts should be cannulated if they are interrupted or do not flow freely when irrigated. Access incisions must be closed meticulously to prevent complications. Failure to close the galea in the bicoronal incision can lead to brow ptosis. Failure to obtain watertight closure of intraoral incisions can lead to dehiscence and plate exposure. Particular attention should be paid to the lower lid incision closure to prevent entropion or ectropion. A Frost stitch should be placed through the lower lid and fixed under tension to the forehead (with tape). This is left in place for 24 to 72 hours, to stretch the lower lid.

SOFT TISSUE LOSS

The acute repair of soft tissue loss remains controversial when dealing with facial injuries. Of course, whenever it is feasible, it is preferable to repair soft tissue loss and bone loss simultaneously. In years past, early attention was directed at restoring the soft tissues, with the belief that the primary repair of the facial skeleton could not be successfully performed in the absence of adequate soft tissue coverage. Unfortunately, in the absence of proper skeletal support, reconstructed soft tissues often shrank and retracted, leading to the development of contractures that frequently interfered with the ultimate hard-tissue reconstruction, and a satisfactory outcome was less likely to result.

The advent of rigid skeletal fixation has allowed for a rethinking of this approach, because rigidly fixed bony structures will generally survive even in the absence of adequate soft tissue coverage. This has proved particularly helpful in shotgun-blast injuries, which can be very destructive to both skeletal and soft tissues. An example is shown of the case of a stainless steel mandibular reconstruction plate that was placed across a shotgun-blast defect of the anterior mandible (Fig. 78.14). The defect extended from midbody to midbody. Deltopectoral skin was used to incompletely cover the steel plate. (Note that this approach could not have been considered before the introduction of rigid fixation techniques, because mobile exposed bone fragments often become infected and necrosed.) Ultimately, after release of the flap and closure of the soft tissue defect, the space (which had been maintained by the reconstruction plate) was reconstructed with an iliac corticocancellous graft that was fixed to the plate. The graft took completely, and the plate was later removed, leaving fully recontoured mandible.

The same principles have been similarly applied to midfacial defects. The availability of microvascular free tissue transfer has made it possible to perform immediate soft tissue and/or skeletal reconstruction of large defects when the patient's condition is appropriate. Restoration of the skeletal framework (or its shape) should be accomplished as acutely as possible. Although the soft tissue reconstruction is now generally performed acutely when possible, it can be delayed if necessary due to the needs of the individual patient and/or the techniques available for repair.

COMPLICATIONS AND REVISIONS

With severe injuries, it is not uncommon to obtain a less than perfect result, though an excellent reconstruction is often acceptable to patients who appreciate the severity of their initial injuries. Still, selective revision surgery can enhance an outcome and convert an acceptable result to an excellent one. The judicious use of bone grafts or alloplastic implants may be necessary to build up deficient areas or reposition a globe. Occasionally, a malunion may

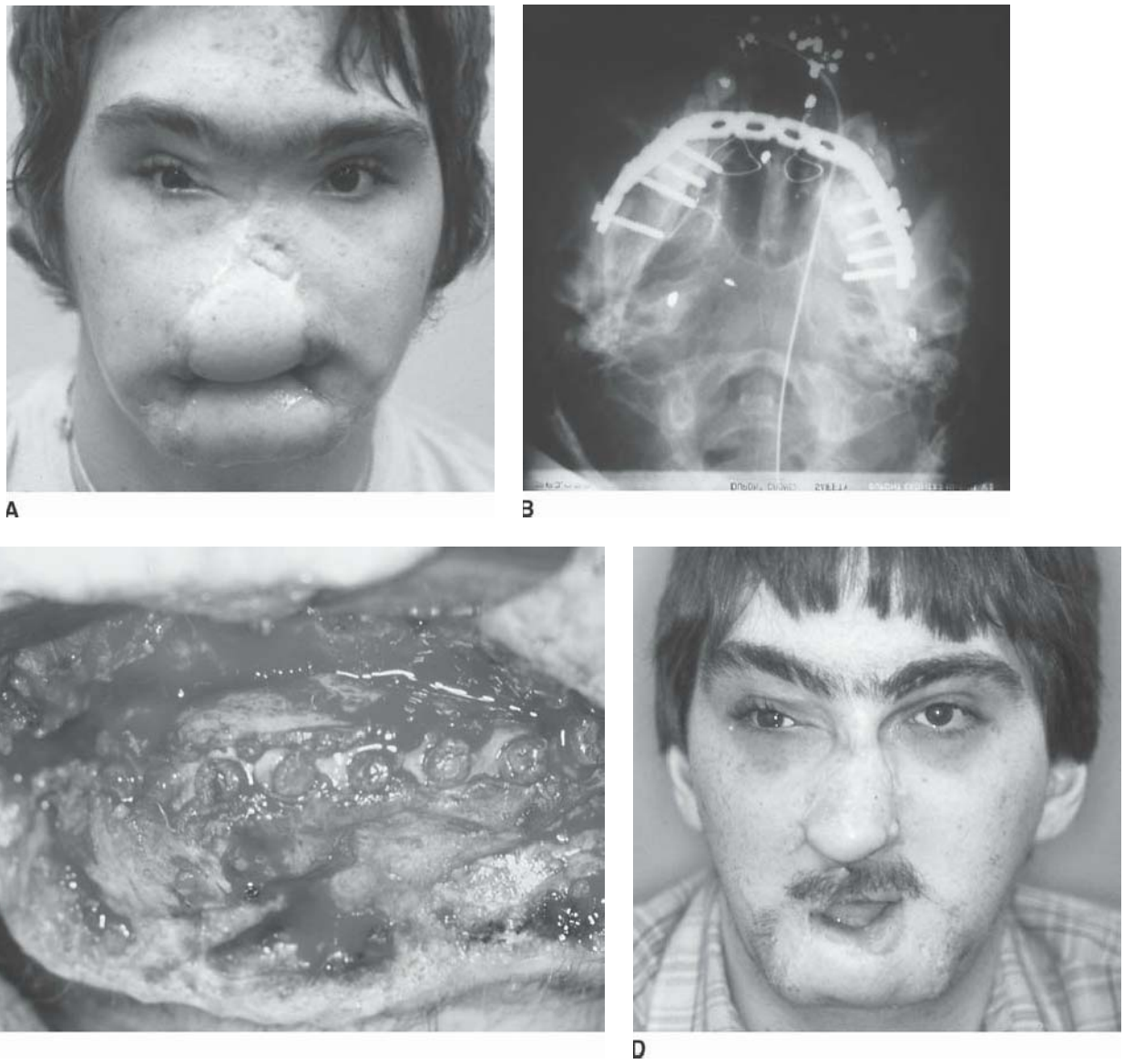


Figure 78.14 **A:** Patient with midfacial shotgun-blast injury after soft tissue repair. **B:** Initial maintenance of mandibular spacing with reconstruction plate. **C:** Bony continuity reestablished with graft, and plate removed. **D:** Result after additional soft tissue surgery.

result, and one of the options available is the remobilization of facial bones via osteotomy followed by repositioning and refixation with bone grafts as needed. The techniques for this are beyond the scope of this chapter, but it is important to offer this option to a patient with a residual deformity.

It is not uncommon for craniomaxillofacial surgeons in tertiary care centers to receive referrals of patients who have already undergone initial and sometimes subsequent repairs. Occasionally, patients have not been repaired at all for a variety of reasons. It is important for the tertiary surgeon to avoid judgmental commentary and focus on what can be offered to the patient. These are challenging cases both technically and emotionally, and they should be approached with the utmost skill and diplomacy.

A host of complications may be seen, including ectropion, entropion, facial scarring, epiphora, numbness, facial nerve injuries, diplopia, malocclusion, facial asymmetry, and temporomandibular joint dysfunction (Table 73.3). Familiarity with the multiplicity of problems and outcomes that can result will make it possible for the facial plastic surgeon to offer the patient the widest variety of options for care.

TABLE 78.3 COMPLICATIONS FACIAL TRAUMA

Type	Management
Osseous	
Osteitis	Intravenous antibiotics
Delayed union	Observation, prolonged interdental fixation
Osteomyelitis	Intravenous antibiotics ± hyperbaric oxygen, debride and revise
Nonunion	Debride and revise
Malunion/malocclusion	Osteotomize and reposition
Fibrous union with poor function	Debride and revise
Bone loss	Free bone graft ± revascularized
Temporomandibular joint dysfunction	Etiology specific
Soft tissue	
Deficiency	Local/regional/distant tissue transfer
Scarring	Scar revision, laser resurfacing, etc.
Ptosis	Etiology-specific ptosis repair
Lagophthalmos	Scar revision, weights, springs
Entropion	Lid revision, free grafts
Ectropion	Lid revision, free grafts
Nasal obstruction	Septoplasty, lysis of synechiae, valve surgery
Neurosplanchnic	
Brain injury	Per neurosurgery
Globe injury	Per ophthalmology
Globe malposition	Orbital bone grafts/repositioning
Cerebrospinal fluid leak	Endoscopic or open repair
Meningocele/encephalocele	Surgical repair
Cranial nerve dysfunction	Compensatory procedures
Glandular dysfunction	Artificial tears/saliva Punctal plugs

HIGHLIGHTS

- Management of massive or complex injuries follows the same principles used for less severe injuries.
- Anatomic reduction of fractures offers the best chance of return to preinjury function and appearance.
- Rigid internal fixation stabilizes and shields a reduced fracture from biomechanical forces that would act to displace the fracture until bone healing can occur.
- Fracture repair is best achieved as early after the injury as possible with the following being considered: the patient's overall condition takes priority and maximal soft tissue swelling occurs 24 to 48 hours after the injury.
- Within limits, the stability of an internal fixation system increases with the rigidity and thickness of the material, the size and number of screws, the thickness of the underlying bone, and compression of the fracture edges.
- Application of a screw to be a successful fixation point for a plate requires maintenance of a healthy cylinder of bone lining the drill hole that "hugs" the inner shaft of the screw as it or a tap cuts threads in the bone.
- Plate type and location selection is made to provide adequate stability to a fracture while minimizing application difficulty, hardware load, and prominence through the soft tissue.
- The 3-D skeletal buttress structure and continuity must be reestablished to restore facial appearance and the ability to withstand biomechanical forces.
- Resuspension of key soft tissue structures such as the medial and lateral canthi and the mentalis muscle is necessary to obtain the best result from treatment of massive trauma.
- Minor complications are not uncommon and can usually be managed with minor revisions. Major complications from tissue loss or malposition are best prevented, but major reconstructive procedures with osteotomies and bone grafting can provide satisfactory final results.

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Surgical Approaches to the Craniofacial Skeleton

79

John F. Hoffmann

There have been three principal advances that have revolutionized the management of craniofacial trauma over the last several decades. These are advanced imaging, sophisticated internal fixation technology, and aesthetic surgical approaches. Modern computed tomography scanning allows for visualization of the craniofacial skeleton in multiple perspectives as well as in three dimensions. This enables the clinician to precisely identify fracture patterns and anatomy. Sophisticated internal fixation plating systems have evolved to allow the surgeon to precisely and rigidly fixate craniofacial fractures so that normal anatomy can be restored and stabilized against the forces of mastication. Contemporary surgical approaches to the craniofacial skeleton have also advanced to allow one to expose facial fractures in a way that provides optimal visualization for fracture reduction and placement of fixation hardware while minimizing soft tissue damage and scarring. In some instances, surgical incisions for aesthetic facial surgery have been adapted to the exposure of the craniofacial skeleton. An example would be the lateral upper lid crease incision that has been adapted from blepharoplasty procedures. The surgeon should be familiar with the relaxed skin tension lines of the face and neck and place elective incisions within these whenever possible, thereby minimizing the visibility of the final scar. Meticulous and gentle soft tissue handling techniques are paramount to obtaining rapid healing with minimal scarring. Similarly, the use of electrocautery should be judicious especially in areas of thin soft tissues and around hair follicles. Intimate knowledge of the location and course of critical nerves—such as the facial and trigeminal nerves—is essential. This chapter discusses the various options for exposing the craniofacial skeleton from the frontal sinus to the mandible. Endoscopic approaches have gained some popularity in the management of orbital, frontal sinus, zygomatic arch, and mandibular condyle fractures. These techniques are beyond the scope of this chapter, however.

UPPER FACIAL SKELETON AND FRONTAL SINUS

The workhorse approach for the upper facial skeleton is the hemicoronal or full coronal incision. This classic surgical approach enables the surgeon to expose the upper frontal and parietal skull all the way inferiorly to the superior orbital rims, orbital roof, and nasoethmoid region as well as the entire zygomatic arches (1). The coronal approach also can be employed in those instances in which cranial bone grafts will need to be harvested. In cases of unilateral fracture, a hemicoronal approach extending from the midline down to the ipsilateral pinna may be considered. It must be remembered, however, that a hemicoronal flap will have more limited inferior exposure compared to a full coronal flap due to the reduced inferior rotation of the flap. Coronal flaps typically have robust blood supplies and can be designed to include pericranial tissues as well. In the instances where the posterior table of the frontal sinus is fractured and the risk of cerebrospinal fluid (CSF) leakage is high, the surgeon should be very careful to preserve the vascularity of the pericranial tissue as a pericranial flap may be very helpful in these cases to repair dural injuries.

The coronal incision has classically been described as a straight-line incision extending from just above the pinna, coursing several centimeters behind the anterior hairline across to the contralateral side as needed. Typically, the incision is made several centimeters behind the hairline (Fig. 79.1). In men, one may need to locate the incision more posteriorly to accommodate male pattern baldness. One disadvantage of the straight-line incision, however, is that it may be more visible. This is particularly true when the hair is wet as it may part away from the incision making it very visible (Fig. 79.2). Alternatives to the straight-line incision include a curvilinear incision or a "sawtooth" design (Fig. 79.3) (2). These modifications are intended to help camouflage the parietal portion of the

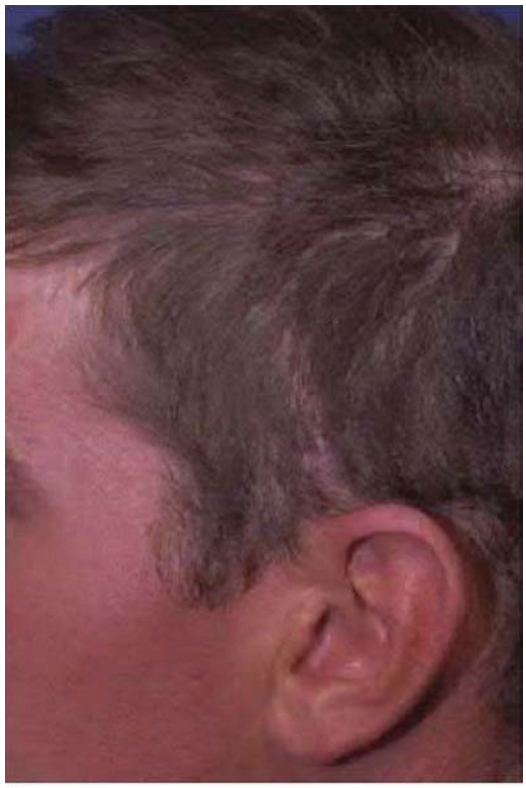


Figure 79.1 Typical coronal incision location for women and men with no significant baldness. In men with baldness, the incision is moved posteriorly as needed. (From Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, with permission.)

coronal incision. As these incisions are more irregular, wet hair will be far less likely to part away from the incision in a straight line and thereby make it less visible. A sawtooth design, however, may predispose the points of the sawtooth to some alopecia, thereby making the incision more visible. Regardless of which incision design is selected, the incision should be made parallel to the hair follicles, thereby minimizing the risk of injuring the follicles. It is also advisable to minimize the use of electrocautery along the incision line as this also may widen the area of alopecia and potentially lead to more hypertrophic scarring. Raney clips or compression sutures may be used along the



Figure 79.2 Coronal incision scarring. **A:** Highly visible strait scar, especially noticeable when the hair is wet and falls away from the scar. **B:** Intraoperative design of a curvilinear coronal incision.



C

Figure 79.2 (*Continued*) **C:** Postoperative appearance of a curvilinear incision, which is hidden since hair tends to not part in a straight line.

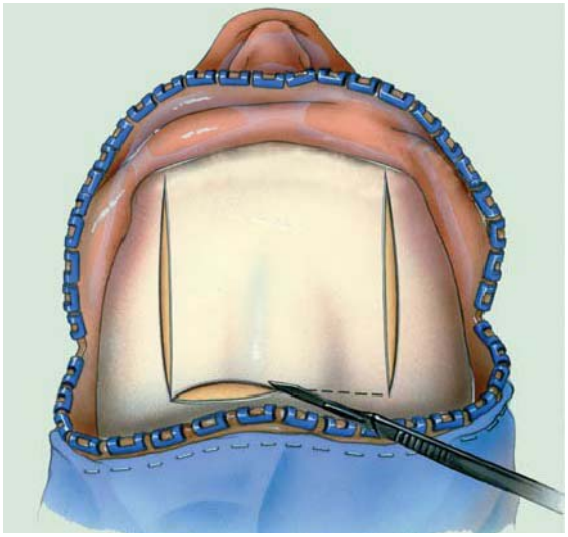
edges of the incision to aid hemostasis, but these also may lead to more alopecia due to pressure injury of the follicles. The lateral extent of the incision is normally at the apex of the ear. In cases where exposure of the zygomatic arch is anticipated, the incision may be extended inferiorly in a preauricular crease down to the tragus. Centrally, the flap may be elevated in a subgaleal or in a subperiosteal plane. If the flap is raised initially in the subgaleal plane, then a transition will need to be made through the pericranium above the fracture site itself. The surgeon must anticipate the potential need for a pericranial flap early in the flap design and plan accordingly. A pericranial flap may be developed separately or dissected off of the galea once the flap has been raised (Fig. 79.4). In the parietal and temporal aspects of the flap, the typical dissection plane is in the loose areolar tissue beneath the temporoparietal fascia and just superficial to the deep temporalis muscle fascia. Blunt dissection over the temporalis fascia allows for rapid inferior elevation of the flap in a relatively bloodless plane. One must, however, sharply release the fascia along the anterior temporal line as it is firmly affixed to the periosteum here. As will be discussed below, the lateral blunt dissection must be stopped several centimeters above the zygomatic arch in order to avoid injury to the frontotemporal branches of the facial nerve.



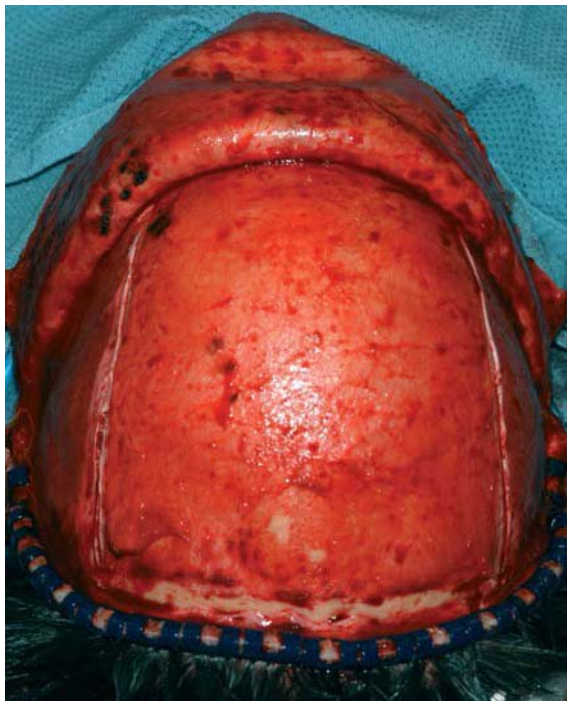
Figure 79.3 Sawtooth design alternative for a coronal incision. This may lead to alopecia at the tips of the triangular incision points.

As the flap elevation proceeds inferiorly, the surgeon should carefully identify and preserve the supraorbital neurovascular bundles. The supraorbital structures may emerge from the orbit via a notch in the superior orbital rim or from a complete bony foramen usually at the junction of the medial and central thirds of the orbital rim (3). In order to fully visualize the superior orbital rim and to extend dissection into the nasoethmoid region or the orbital roof, the supraorbital structures must be mobilized. If the flap has been raised in a subgaleal plane, then a transition through the pericranium is made several centimeters above the supraorbital rims. If the supraorbital bundles are within a notch, then the careful subperiosteal elevation will release them. If, however, these structures exit through a foramen, then an osteotomy may be necessary to fully mobilize them (Fig. 79.5). Once the supraorbital structures are released, the dissection can proceed inferiorly to expose the nasal root, the medial canthal region, the nasal ethmoid complex, and the orbital roof. The surgeon should be careful during exposure of the medial orbital wall and nasoethmoid region to not detach the medial canthal tendon from the bone as this would lead to soft tissue telecanthus, which can be quite difficult to correct. The coronal incisions will also provide excellent exposure of the lateral orbital rim and the frontozygomatic junction, a site frequently involved in facial fractures. Again one should be cautious to not detach the lateral canthal tendon during subperiosteal dissection as well to prevent postoperative malposition of the lateral canthus.

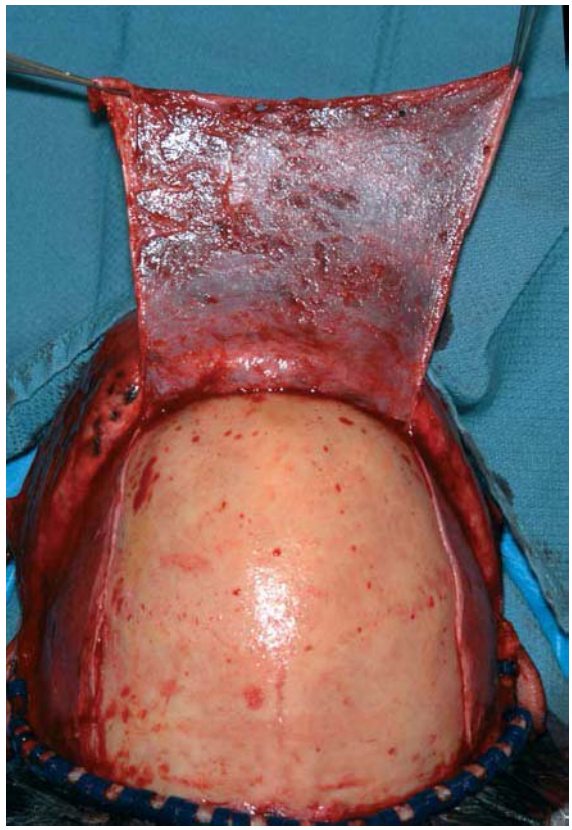
The coronal approach also provides an ideal surgical exposure of the zygomatic arches (4). Exposure of the arches may be necessary either in severely comminuted and displaced zygomaticomaxillary–orbital fractures or in LeFort III fractures. With exposure of the arches, however, the surgeon must alter his dissection plane in order to avoid injury to the frontotemporal branches of the facial nerve. Below the level of the zygomatic arch, the facial nerve travels beneath the superficial musculoaponeurotic system (SMAS) layer. At the level of the zygomatic arch, however, the fascial planes coalesce and the facial nerve branches pass over the zygomatic arch where they are quite



A



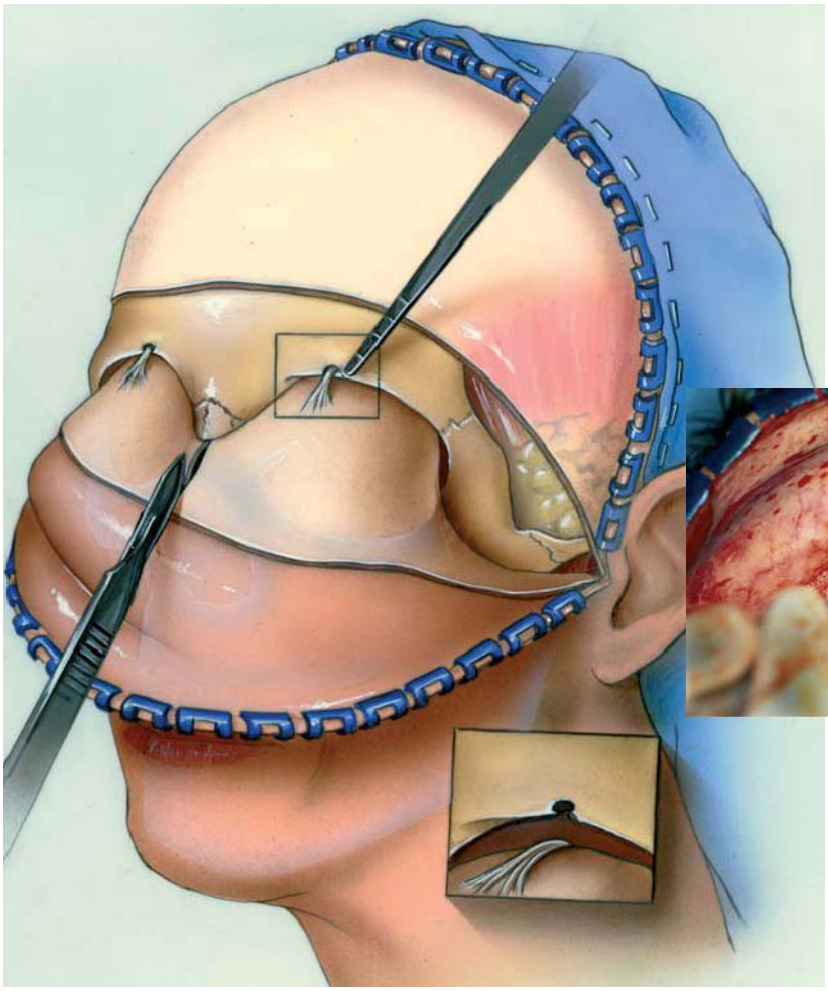
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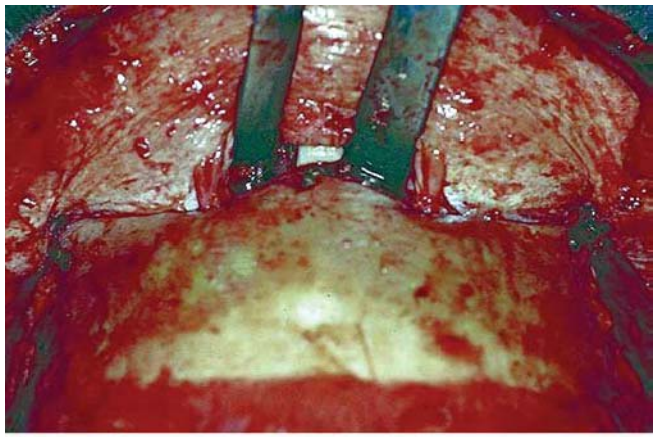
C

Figure 79.4 Pericranial flap elevated in conjunction with coronal incision. This may be needed to help seal CSF leakage in severe frontal or nasoorbital fractures. (From Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, with permission.)

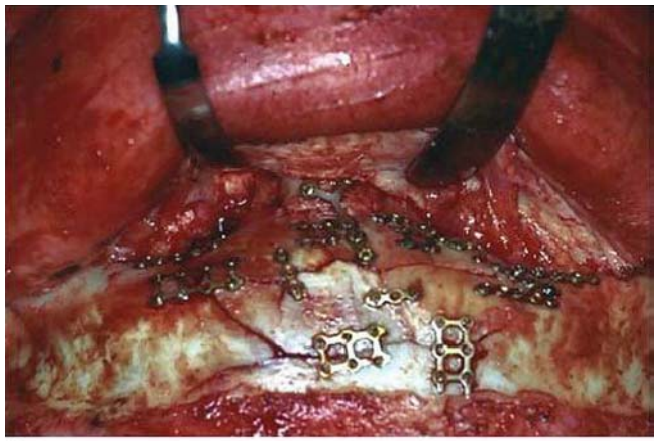
vulnerable to surgical injury. Once above the zygomatic arch, the facial nerve lies within the temporoparietal fascia on its way to the corrugator and frontalis muscles. In order to avoid injury to the facial nerve as it passes over the zygomatic arch, the surgical dissection plane must change. If dissection were to continue along the surface of the deep temporalis muscle fascia, then the facial nerve would be damaged at the level of the arch. To avoid this, the dissection plane should change several centimeters above the zygomatic arch (Fig. 79.6). An incision should be made through the superficial layer of the deep temporalis fascia, and then dissection should continue inferiorly on the undersurface of this fascia. This space contains the temporal fat pad, and one should minimize disruption of the fat pad during dissection to help minimize postoperative atrophy. Atrophy of this fat pad can lead to hollowing within the temporal fossa, which is aesthetically displeasing and is difficult to correct. The zygomatic arch should be approached along its superior border at which point the periosteum is incised and elevated. The facial nerve branches will then be contained within the soft tissues of the flap. The arch can then be exposed along its entire length from its origin at the temporal bone to its attachment to the malar eminence (Fig. 79.7). At the conclusion of the procedure, it is critical to resuspend the soft tissues to avoid ptosis of the malar tissues (5). This is typically done by suturing the mobilized fascia back to the temporalis fascia, taking care while placing the sutures to not injure the facial nerve.



A



B



C

Figure 79.5 Coronal flap exposure frontal skeleton. **A:** Mobilization of the supraorbital neurovascular pedicles with osteotomies. **B:** Intraoperative photo of coronal flap with mobilized supraorbital structures seen bilaterally. **C:** Intraoperative photo of fixation hardware in place for repair of comminuted frontal sinus fracture. (Part A from Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, with permission.)

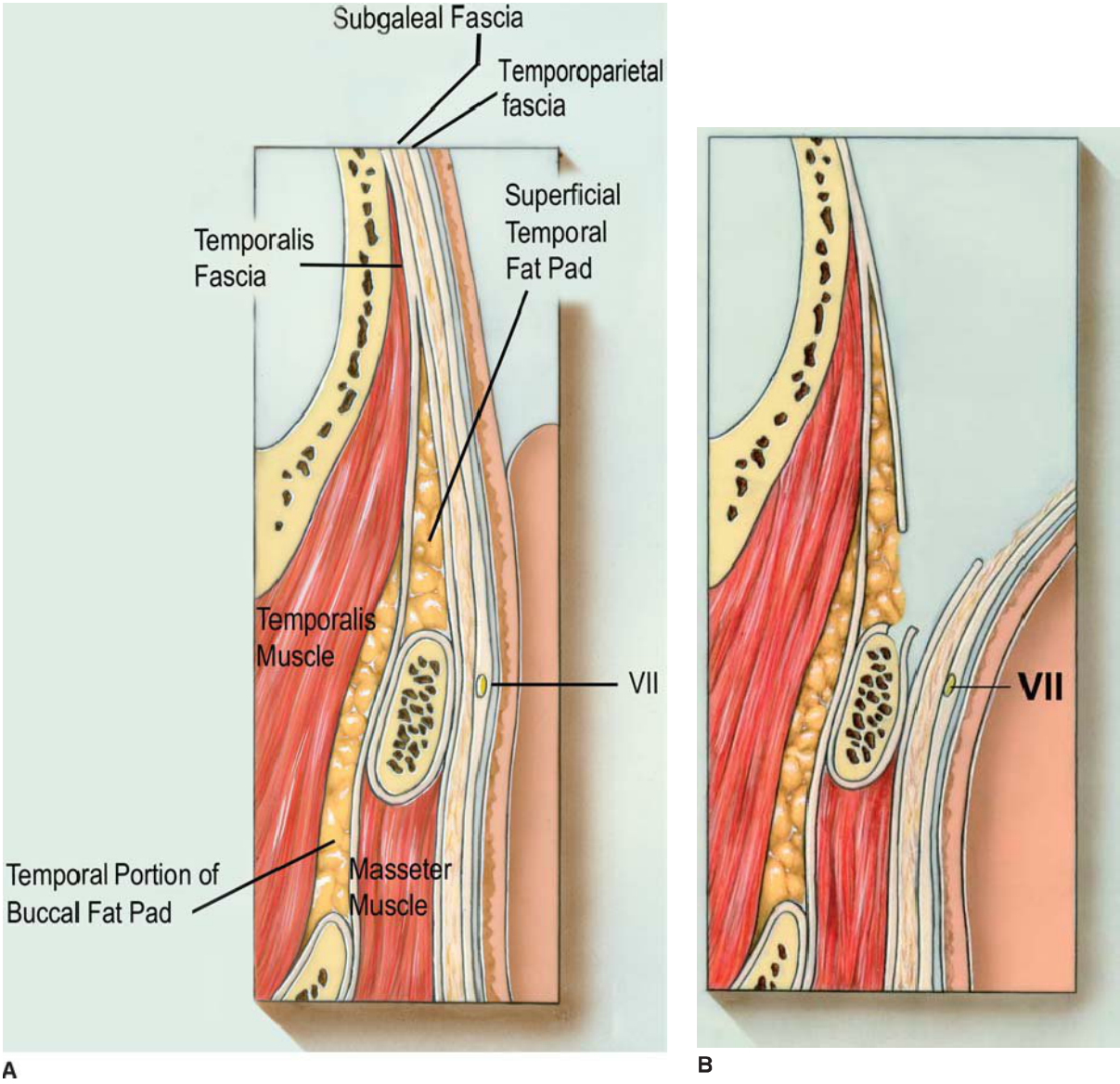


Figure 79.6 Exposure and dissection planes in temporal region and zygomatic arch. **A:** Tissue planes and location of frontal branch of facial nerve over the zygomatic arch. **B:** Dissection plane over zygomatic arch to avoid injury to the facial nerve branches. Above the arch the plane of dissection passes through the deep temporal fascia into the temporal fat pad. The periosteum in incised along the superior border of the arch and is elevated deep to the facial nerve. (From Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, with permission.)

A suction drain may or may not be required and can be used at the surgeon's discretion. The scalp incision is then carefully closed in a layered fashion. All tension on the wound should be borne by sutures placed within the galeal layer, and cutaneous closure should only be done to realign the epithelium correctly. Excessive skin closure tension will possibly lead to increased scarring and alopecia. Complications of the coronal approach include bleeding or hematoma, temporary or permanent numbness of the forehead tissues, injury to the frontal branches of the facial nerve, and excessive scarring or alopecia. Patient should be counseled that some degree of numbness is inevitable posterior to the incision.

Another alternative for exposure of fractures of the upper facial skeleton exists when there is a large laceration. This most commonly occurs in fractures of the frontal sinus as direct blows to this region will often cause lacerations. Another common location of lacerations is along the lateral brow, and occasionally these can be used to expose the frontozygomatic area and the lateral orbital wall. One should be cautioned, however, to avoid significantly lengthening a laceration to obtain appropriate



Figure 79.7 Intraoperative exposure and plating of zygomatic arch in a LeFort III fracture. Temporalis muscle is retracted to the right of the picture.

exposure of fractures. This could easily lead to unsightly scarring or possible nerve injury. In general, one should avoid the historical eyebrow or "gullwing" incision. This routinely leads to unsightly scarring and a deformity of the eyebrows (Fig. 79.8). There is significant propensity for chronic edema in this dependent flap as well as extensive numbness of the forehead. For these reasons, a coronal flap should be employed as it provides unparalleled access and a far more pleasing aesthetic result. This is true even in patients with baldness.



Figure 79.8 "Gullwing" brow incision. Note chronic edema of flap above the incision and the highly visible scar.

MIDFACIAL SKELETON

Orbit

The lateral orbital wall and frontozygomatic area can be easily approached via upper eye lid crease incisions. In essence, this type of incision is a limited lateral blepharoplasty incision. Historically, incisions adjacent to or within the lateral brow were advocated. However, these incisions frequently leave unsightly scars or may cause permanent hair loss in the eyebrow and do not offer any exposure advantage over the lid crease incisions (Fig. 79.9). Instead, placing the incision within the lateral upper eyelid crease is far more preferable aesthetically and also provides improved exposure of the lateral orbital rim and medial aspect of the lateral orbital wall. The technique is very straightforward (Fig. 79.10). The lateral aspect of the lid crease is marked prior to the injection of local anesthetic. The incision is made through the skin and the underlying orbicularis fibers are bluntly separated. The periosteum of the lateral rim is incised and elevated as needed for fracture exposure and implant placement. It is frequently beneficial to extend the subperiosteal exposure posteriorly along the lateral orbital wall. This allows the surgeon to visualize the displaced fractures and provides another perspective to evaluate accurate anatomic reduction of fracture segments. Following fracture repair, the periosteum is closed and the incision is closed in a layered fashion. It is not typically necessary to drain this incision. Although one may see some temporary orbicularis weakness postoperatively, permanent lagophthalmos should be very rare. Healing is usually rapid with an excellent aesthetic result (Fig. 79.10D).



Figure 79.9 Left lateral brow incision. This scar can be very visible and cause permanent loss of eyebrow hairs and has more limited exposure of the lateral orbit and should be avoided.

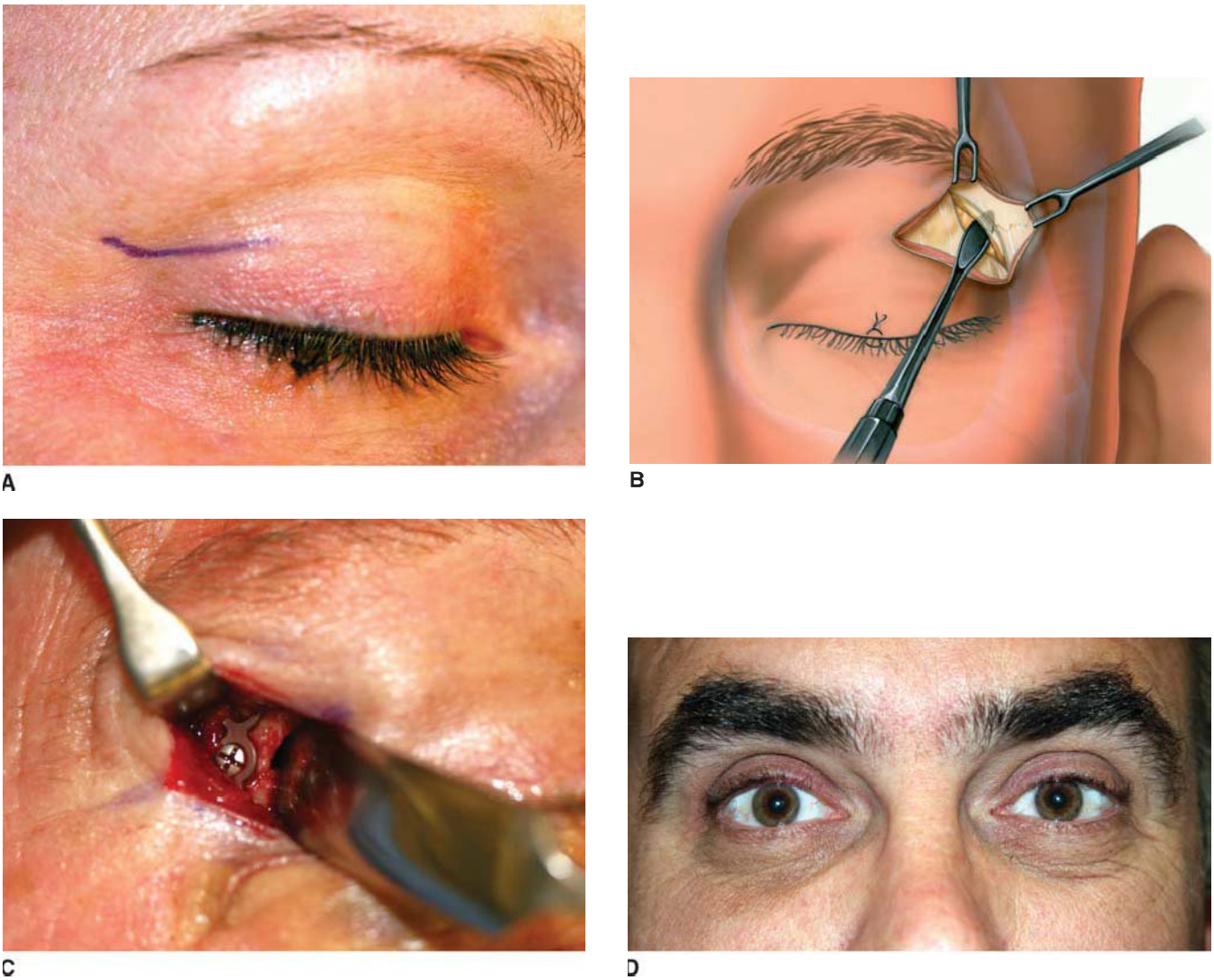


Figure 79.10 Lateral lid crease (upper blepharoplasty) approach. **A:** Incision is placed in natural supratarsal lid crease as shown and extended laterally within the crease as needed. **B:** Periosteum of lateral wall is incised and elevated to expose bone above and below the fracture to allow reduction and fixation hardware placement. The orbital aspect of the lateral wall should be exposed and visualized for accurate fracture reduction. **C:** Intraoperative photo showing hardware placement. **D:** Postoperative photo following ORIF of right malar complex fracture with inconspicuous incision healing. (Part B From Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, with permission.)

Inferior Orbital Rim, Floor, and Medial Wall

The inferior orbital rim, orbital floor, and medial orbital wall are most commonly approached through the various lower eyelid incisions. These incisions may either be transcutaneous or transconjunctival (Fig. 79.11). Both of these approaches have been long advocated in the literature, and when carefully designed and executed, both approaches will yield excellent results (6). Transconjunctival approaches have several potential advantages, however (7). Obviously, there is no visible scar unless a short lateral canthotomy incision is incorporated. A transconjunctival approach lends itself very well to extended medial exposure for fractures involving the medial orbital wall. In addition, transconjunctival approaches are completely posterior to the orbicularis muscle of the lower eyelid and therefore preserve an important structural support of the lower lid. As a result, postoperative lower lid malposition or ectropion may be less common with a transconjunctival approach (8,9). Furthermore, a transconjunctival approach can be done in some cases without any division of the lateral canthal structures and thus weaken lower lid support even less.

Transconjunctival Lower Lid Approaches

The lower eyelid transconjunctival approach is begun with an incision placed in the inferior fornix. A corneal shield can be employed if desired but may impede exposure somewhat. If a shield is used for a long case, such as a complex nasoethmoid or LeFort fracture, one should

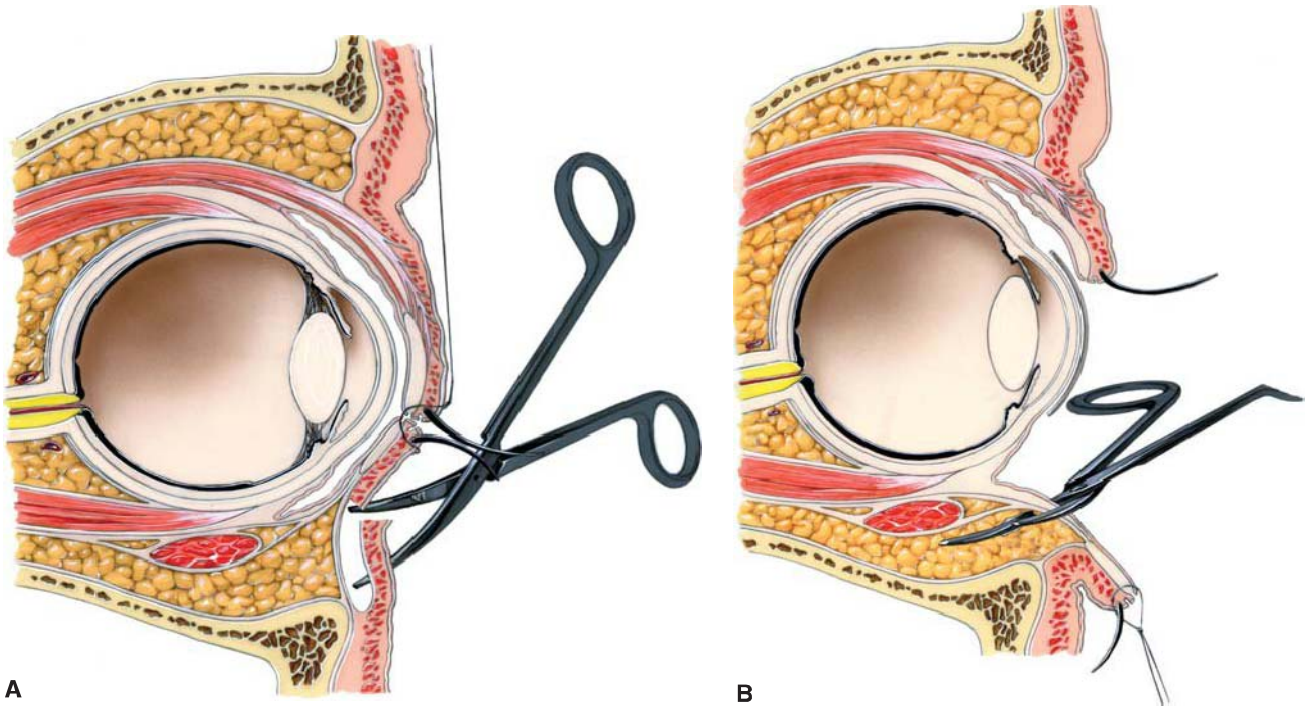
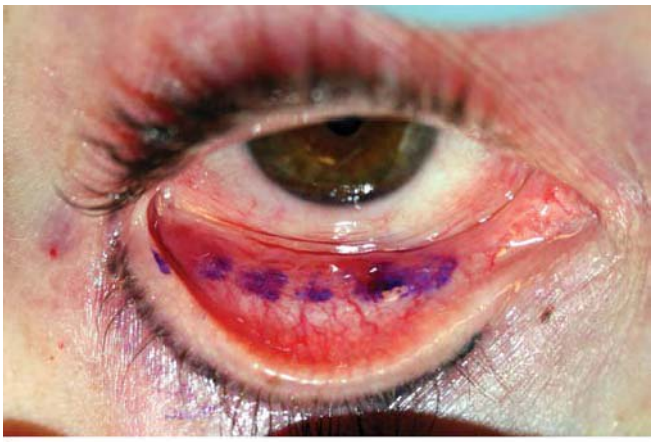
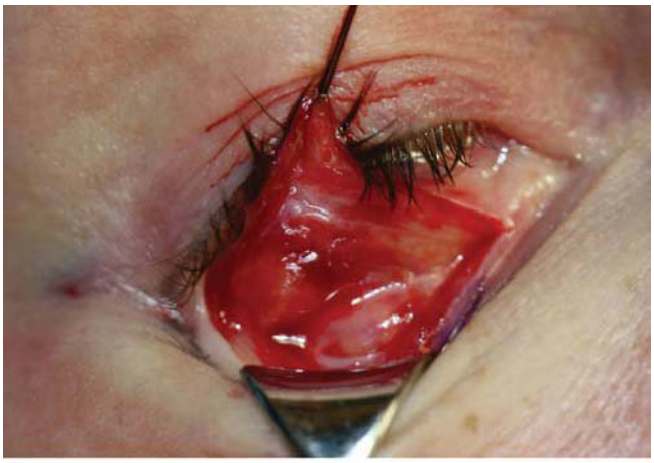


Figure 79.11 Transcutaneous and transconjunctival approaches to the orbital floor. **A:** Cross-section of eyelids demonstrating surgical planes for transcutaneous (subciliary or lid crease) approach. **B:** Cross-section of eyelids demonstrating transconjunctival approach. Following the incision in the inferior fornix, the dissection can proceed either anterior or posterior to the orbital septum (see Text and Figure 79.13).

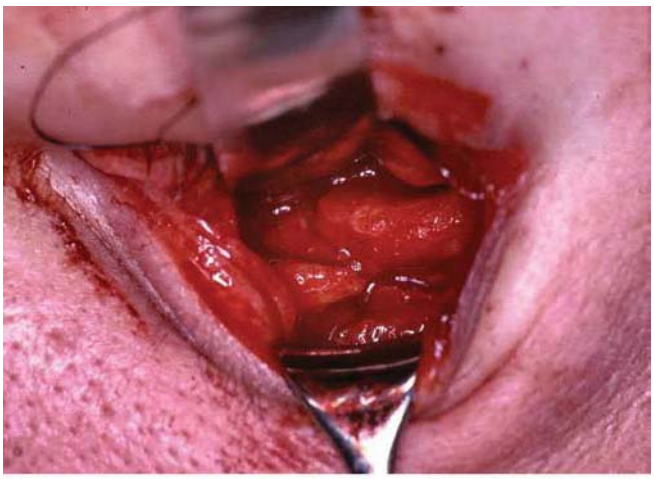
remove the shield periodically and reapply ocular lubricant to reduce the risk of corneal compromise or abrasion. Initially, the lower lid is retracted gently, and the incision is typically made several millimeters below the tarsal plate. Limited orbital floor fractures may be repaired with this incision alone without any lateral canthotomy incision. One should try and avoid a lateral canthotomy if possible as these approaches heal with the lowest incidence of lid malposition (7). If, however, the orbital floor fracture is large, the lid has little laxity, or if one anticipates the need to explore the medial orbit, a lateral canthotomy and cantholysis may be necessary (Fig. 79.14). The lateral canthotomy incision is made directly through the lateral canthus and typically extends only a few millimeters. Extending the cutaneous incision beyond this will not enhance exposure and will make the incision more visible. The lateral canthal tendon is then divided with a cantholysis, which is typically performed with small tenotomy scissors angled obliquely downward under the conjunctiva. The canthal tendon fibers are fully divided so that full mobilization of the lower lid is obtained. The conjunctival incision is then extended along the inferior fornix a few millimeters below the inferior border of the tarsus. A flap of conjunctiva and lower lid retractors is created and retracted superiorly with a traction suture (Fig. 79.12B). This provides coverage of the cornea and often eliminates the need for a corneal protector. Tension on this flap will also provide countertraction, which will aid the inferior dissection toward the rim. At this point, there are two options for surgical dissection: preseptal or post (retro) septal (Fig. 79.13). Preseptal dissection is typically done with blunt instruments in the loose areolar tissue between the orbicularis muscle and the orbital septum inferiorly until the infraorbital rim is encountered. An advantage of this approach is that the orbital fat is largely contained by the septum and therefore does not obscure visualization. A potential disadvantage is that scar contracture could occur along the orbital septum leading to some postoperative displacement or malposition of the lower lid. This may result in inferior displacement of the lower lid leading to increased scleral show or perhaps some entropion (10,11). Retroseptal dissection is also blunt but is behind the orbital septum and traverses the orbital fat. A principal disadvantage of this approach is that visualization may be more difficult as the orbital fat will protrude into the surgeon's view, and there is a somewhat greater potential for injury to the inferior oblique muscle as it is adjacent to the plane of dissection. Advocates of this approach, however, feel that the risk of lower lid malposition is largely eliminated as there is no contracture along the orbital septum. In either approach, the orbital rim is quickly and widely exposed (Fig. 79.14). The periosteum of the rim is then incised, and wide subperiosteal dissection is performed as dictated by the fracture. It is essential that the dissection along the orbital floor be complete and be carried out to fully expose the intact bony shelves along the lateral orbital floor, medial orbital floor, and especially



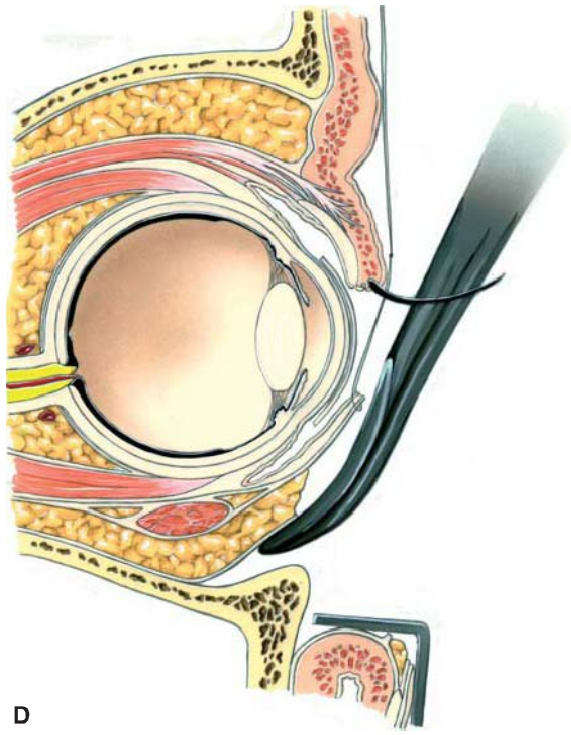
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F

Figure 79.12 Transconjunctival approach. **A:** Incision is made in inferior fornix several millimeters below the inferior border of the tarsus. **B:** A flap of conjunctiva and lower lid retractors is developed and retracted superiorly with a suture. This provides corneal protection and facilitates the dissection. A corneal shield can be employed if desired. **C:** Intraoperative photo with exposure of infraorbital rim and orbital floor fractures. **D:** Cross-section of orbit demonstrating elevation of orbital floor periosteum. **E:** Intraoperative photo demonstrating fixation hardware in place. **F:** Postoperative photo following repair of right zygomaticomaxillary–orbital fractures demonstrating healing of lower lid in excellent position. No canthotomy was performed. (Part D from Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, with permission.)

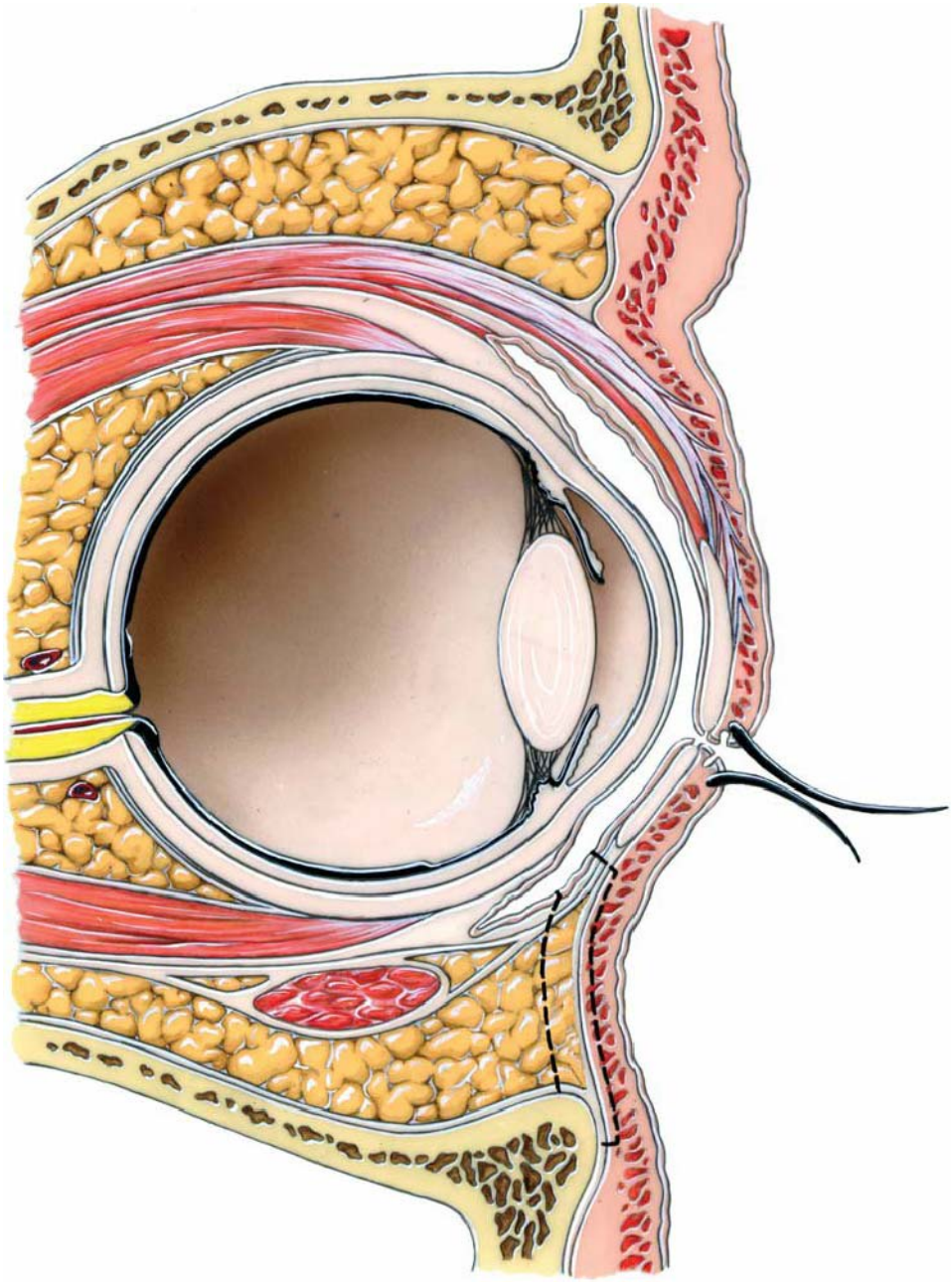


Figure 79.13 Sagittal view of orbit demonstrating preseptal versus retroseptal planes of dissection. (From Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006 with permission.)

back to the posterior orbital bony shelf. Care is taken during floor dissection to bluntly identify the infraorbital nerve and separate it from the orbital soft tissues. Repair of the fracture is then performed using the implant or graft preferred by the surgeon. At the conclusion of the repair, it is important to repair the periosteum along the infraorbital rim. This is particularly true if there has been wide elevation of the periosteum off of the face of the maxilla or malar eminence as in a malar complex or LeFort fracture repair. In those cases, closure of the periosteum will help prevent inferior displacement or ptosis of the midface soft tissues. It is not necessary to close the conjunctiva although a few sutures to realign the edges may be helpful. There is some wisdom to not closing the conjunctiva tightly as this will allow blood and serous fluid to escape from the orbit postoperatively. If a canthotomy and cantholysis have been performed, then the lateral canthal tendon segments are carefully reapproximated, and precise closure of the lateral canthus is essential. Failure to close the lateral canthus precisely could lead to rounding or webbing in this area.

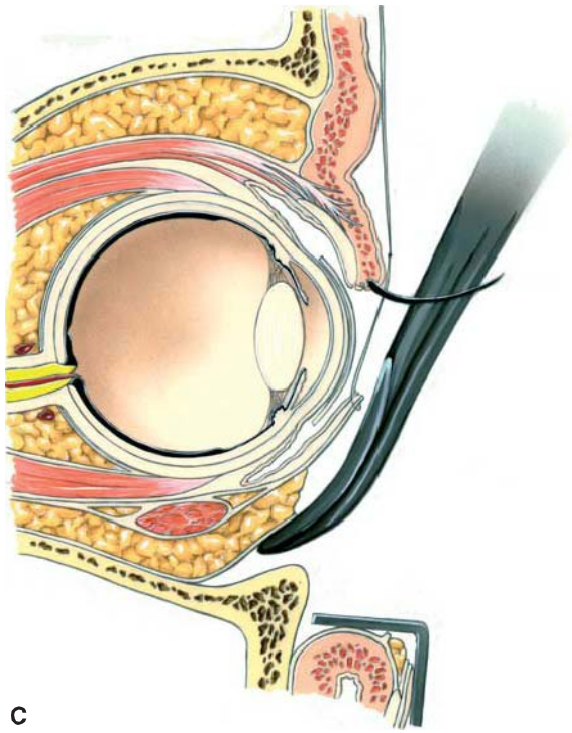
A medial extension of the transconjunctival approach provides an opportunity to fully expose the medial orbital wall as well. This is done with an extension through the caruncular area (Fig. 79.15) (12,13). The caruncle is the soft



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B



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D



E

Figure 79.14 Technique for lateral canthotomy and cantholysis. **A:** Lateral canthotomy incision. This is typically 3 to 5 mm long. **B:** Inferior cantholysis. The canthal tendon fibers are divided either through the conjunctiva or submucosally but never through the skin. The tendon fibers can usually be palpated with the scissor tip as a "bowstring." **C:** Artist's depiction of cantholysis. **D:** Complete lid mobilization is apparent after the tendon fibers are divided. **E:** Postoperative view following repair of left orbital floor fracture with canthotomy/cantholysis and transconjunctival approach. (Part C from Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, with permission.)

tissue collection in the conjunctiva, which lies posterior and lateral to the medial canthus and just anterior to the semilunar fold of the conjunctiva. Deep to the caruncle are the attachments of the medial orbital septum and Horner muscle and portions of the medial canthal tendon. The common canaliculus is immediately medial to the caruncle as well. The caruncular approach can be performed as an isolated incision to gain access to the medial orbital structures as in an isolated medial wall fracture. More often, it is combined with the lower lid transconjunctival approach to provide wide access for the entire inferior and medial orbital structures. Typically, the lower lid portion is executed first and the dissection is then extended medially. A lateral canthotomy and cantholysis, as discussed above, may facilitate better exposure in this instance. Orbital retractors are employed to retract the globe laterally and the medial canthus medially.

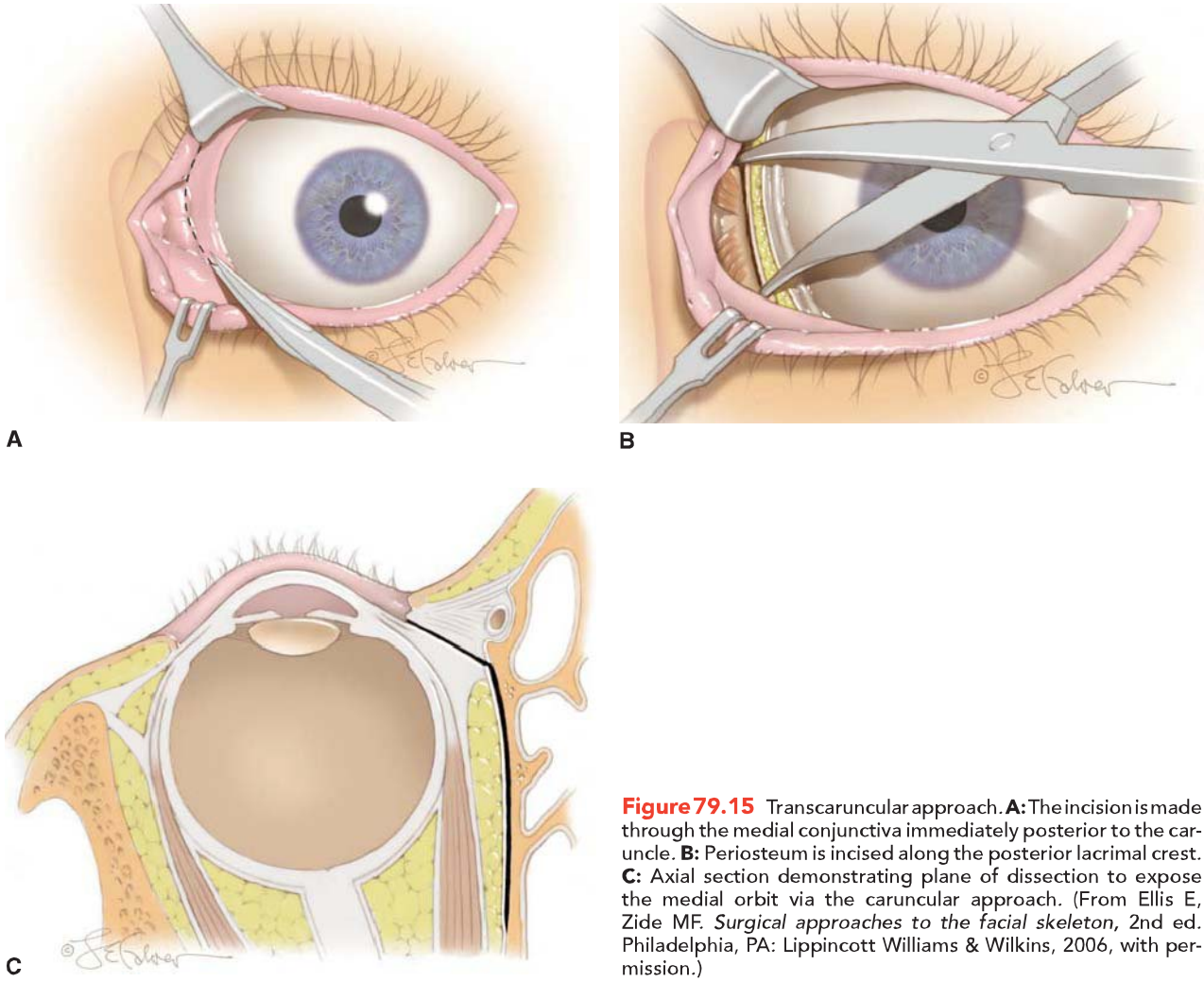


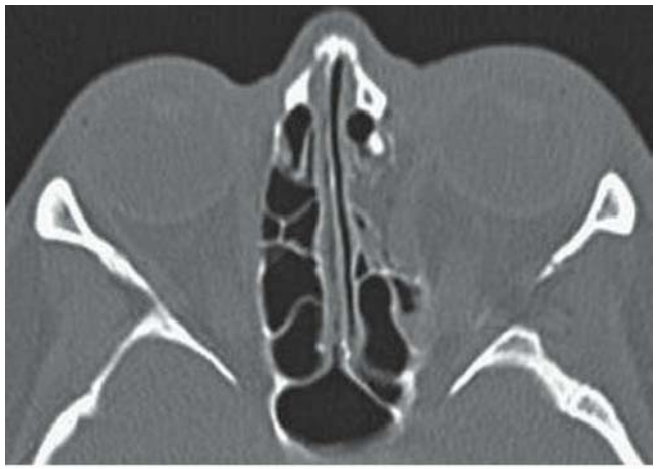
Figure 79.15 Transcaruncular approach. **A:** The incision is made through the medial conjunctiva immediately posterior to the caruncle. **B:** Periosteum is incised along the posterior lacrimal crest. **C:** Axial section demonstrating plane of dissection to expose the medial orbit via the caruncular approach. (From Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, with permission.)

The incision is made between the caruncle and the semilunar fold of the conjunctiva. Dissection with a small tenotomy scissor or periosteal elevator extends posteriorly until the posterior lacrimal crest is palpated. The periosteum is incised along or just posterior to the posterior lacrimal crest, and the exposure is extended posteriorly and superiorly as indicated. It is essential to only dissect posterior to the lacrimal fossa in order to avoid damaging the lacrimal sac and canaliculi. This transcaruncular approach will allow visualization from the lacrimal fossa up to the frontoethmoid suture and the ethmoid arteries and even the medial orbital roof. When more extensive superior exposure is required, the ethmoid arteries can be cauterized or ligated and divided while remaining cognizant of the nearby optic nerve location. Once the surgical repair is complete, the conjunctiva is closed near the junction of the wall and floor boundary as this will help to prevent webbing between the medial wall and lower lid conjunctiva. The patient may have some chemosis and edema postoperatively, but the healing is rapid and the final result is aesthetically excellent and far superior to the transcutaneous medial wall, "Lynch," incisions that often heal with unsightly scarring that is hard to camouflage (Fig. 79.16). The Lynch incision is simple to execute, and the dissection is direct to the medial orbital wall. However, the inferior dissection is limited by the lacrimal structures, and there is more risk of detaching the medial canthal tendon. More importantly though is the fact that the scar is potentially quite visible and somewhat prone to webbing as it heals and contracts. If one insists on using a transcutaneous medial orbital incision, a Z-plasty should be incorporated into the design of the incision to minimize webbing of the scar as it heals, and this will help to camouflage the final scar. Overall, the caruncular approach through the conjunctiva is far superior and it is strongly recommended.

In general, transconjunctival approaches heal predictably well (6,8,9,11). Prolonged chemosis may occasionally occur. Eyelid malpositions are uncommon and may result either in increased scleral show from vertical contracture or perhaps entropion if there is contracture of the posterior lamellar tissues (10). Most of these will improve with time and massage but occasionally will require corrective surgery with scar release and perhaps mucosal grafting to the posterior lamella. If there is significant lateral canthal webbing or scarring, then secondary canthoplasty may be needed.



A



B



C

Figure 79.16 **A:** Postoperative view following repair of large fracture left medial orbital wall via caruncular approach. **B:** Axial C/T scan of patient shown in (**A**). **C:** Postoperative view of a medial orbital fracture repaired through a Lynch incision. Note the highly visible scar as well as a visible subciliary incision on the left.

Transcutaneous Lower Lid Approaches

There are several options for cutaneous incisions in the lower lid (Fig. 79.17). The subciliary incision is perhaps the most commonly employed and is typically placed 2 to 3 mL below the eyelashes. A good alternative is to place the incision within a natural lower lid crease (subtarsal), which is below the subciliary line (8,14). Placing the incision directly over the infraorbital rim should usually be avoided as this location is more prone to visible scarring and may lead to prolonged lower lid edema above the incision and sits in thicker cheek skin (Fig. 79.18). With transcutaneous approaches, corneal protection is provided by placing a temporary tarsorrhaphy suture from the lower lid up to the upper lid, taking care that the suture does not penetrate the conjunctiva (Fig. 79.20A). If one chooses the subciliary approach, the incision is made through the skin only a few millimeters below the lashes and typically stair-stepped preserving a cuff of orbicularis muscle along the tarsus as this helps to support the lower lid position while healing. Below the tarsus, the orbicularis is penetrated and the skin–muscle flap is then bluntly raised off of the underlying orbital septum down to the infraorbital rim (Fig. 79.19). If a lower lid crease (subtarsal) is chosen for the incision, then a skin–muscle flap is immediately developed as the crease is typically below the level of

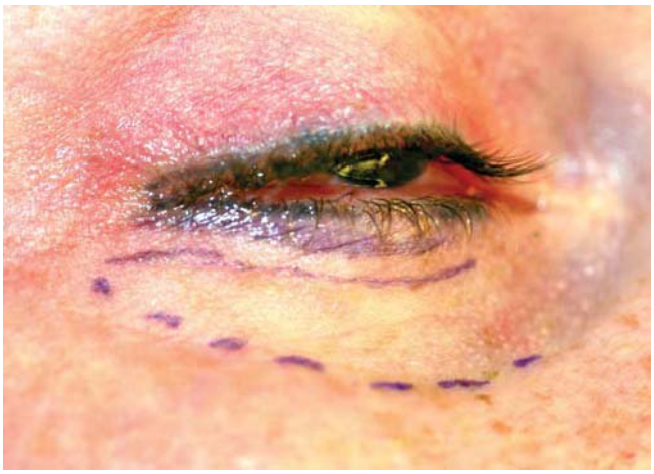


Figure 79.17 Transcutaneous lower eyelid incision. From superior to inferior: subciliary, lid crease, and infraorbital rim.



Figure 79.18 Postoperative appearance of an inferior rim incision. Note the visibility of the scar, the chronic edema, and the lower lid malposition.

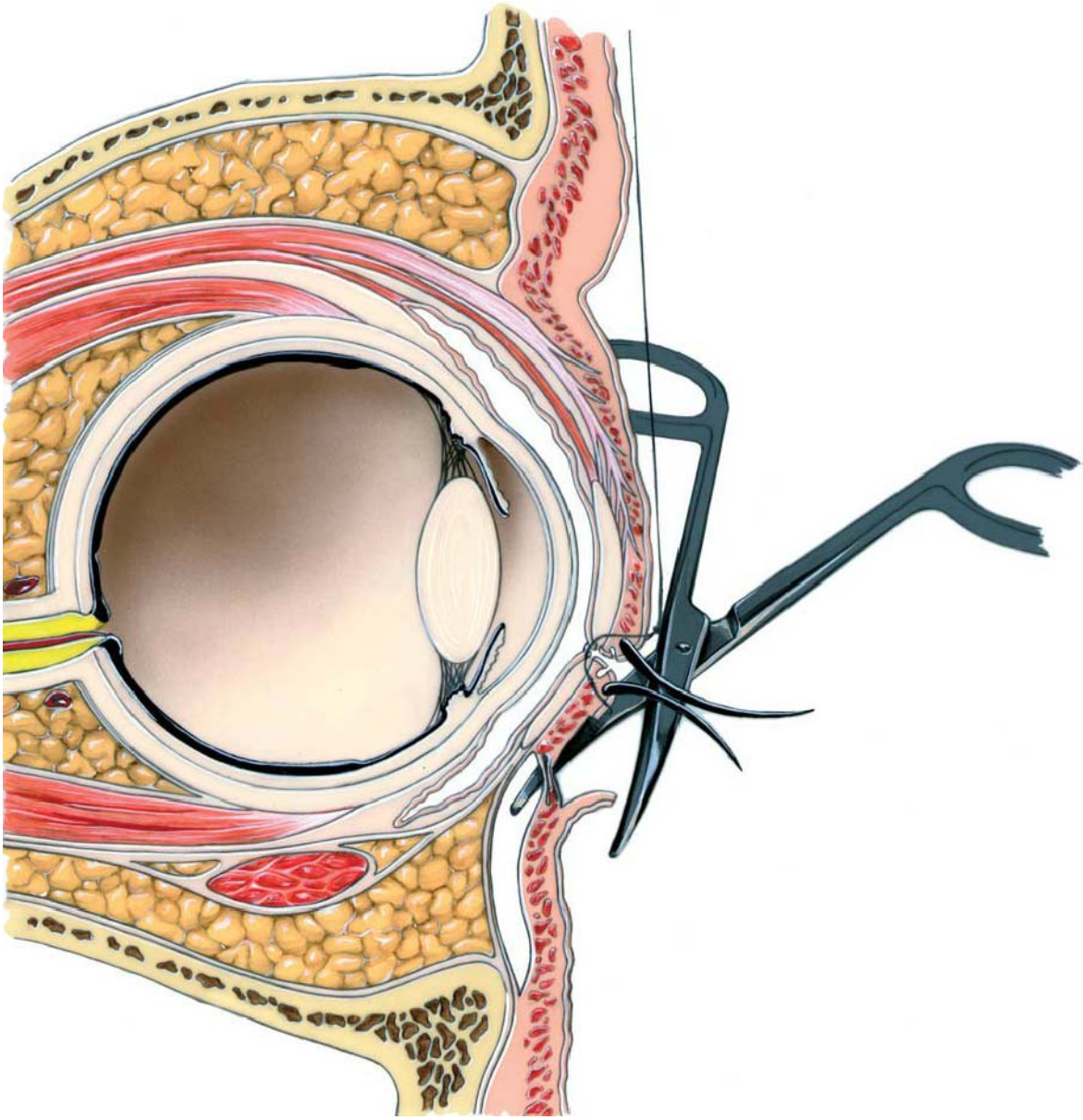


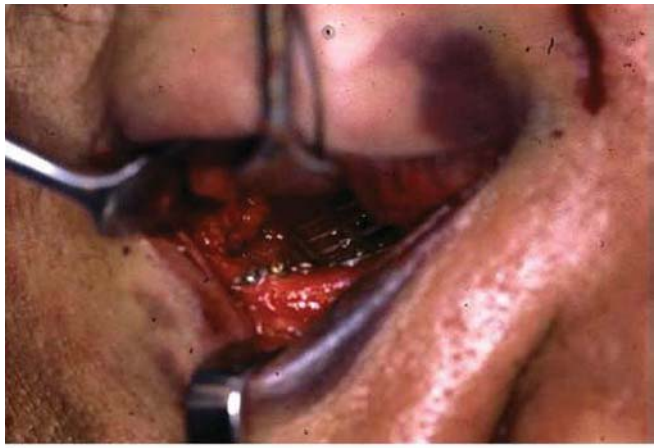
Figure 79.19 Sagittal view of plane of dissection with transcutaneous approach. (From Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, with permission.)

the tarsus. Dissection is again between the orbicularis and orbital septum. The infraorbital rim is exposed and the periosteum is incised, and dissection continues along the floor as needed for fracture repair (Fig. 79.20). At the conclusion of the repair, it is important to close the periosteum along the rim to help suspend the elevated premaxillary soft tissues and to provide soft tissue coverage over the fixation hardware. During closure of the skin–muscle flap, it is critical that the flap be resuspended to the periosteum of the lateral orbital rim near the lateral canthus. This is important because the skin–muscle flap weakens the support of the lower lid by dividing and partially denervating the orbicularis muscle, which is a critical support of the lower lid. The suspension suture, typically a 5-0 slowly resorbing suture material, is placed from the orbicularis of the flap to the lateral orbital rim periosteum. The suspension suture should be tightened so that the skin edges are brought together with no tension along the incision line. If the periosteum is lacking or has been elevated during fracture repair, then one can drill a small hole in the bone of the lateral rim and pass the suture through that. Elderly patients frequently have some preexisting laxity of the lower lid, and in these patients, some tightening of the lateral canthal structures at the time of wound closure will help prevent lid malposition.

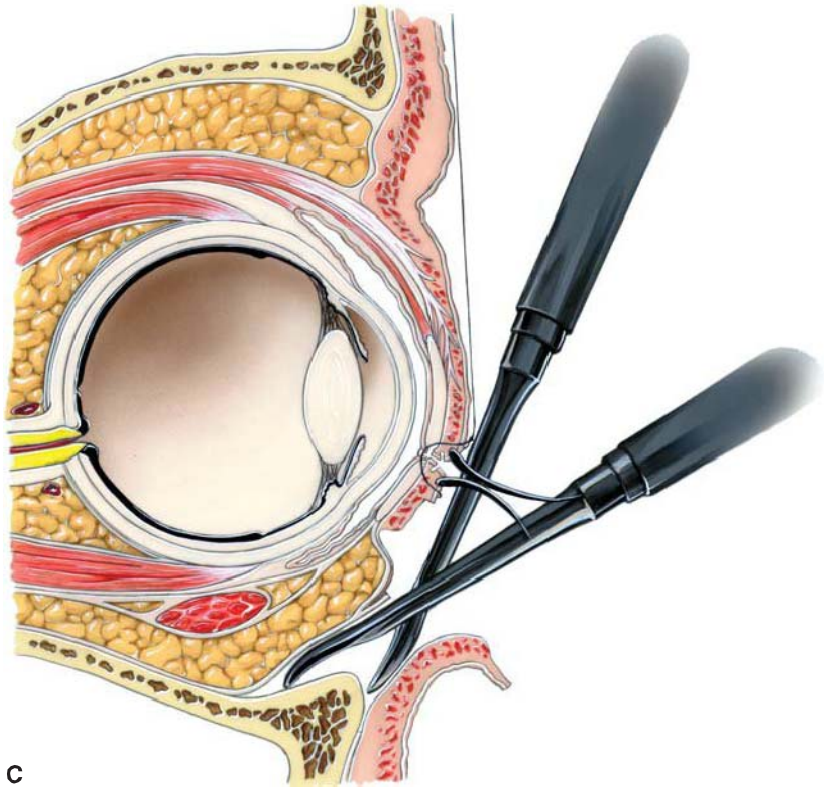
A major criticism of the transcutaneous approach—particularly the subciliary approach—is that it is potentially more prone to cause malposition of the lower lid, particularly ectropion (Fig. 79.21) (6,8,9). This is thought to be due to contracture along the orbital septum or anterior lamella (i.e., skin and orbicularis) combined with weakening of the lower



A



B



C



D

Figure 79.20 Transcutaneous exposure of the orbital floor. **A:** Subciliary incision has been made and skin–muscle flap has been developed. A temporary tarsorrhaphy suture has been placed to provide corneal protection. **B:** Sagittal view of dissection planes with orbital floor and rim exposure. **C:** Exposed orbital floor with hardware in place. **D:** Postoperative view of patient following repair of left malar complex and orbital fractures with a subciliary approach and lateral upper lid crease incision. It is critical to resuspend the skin–muscle flap to the lateral orbital rim periosteum to prevent lower lid malposition. (From Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, with permission.)



Figure 79.21 Malposition of right lower eyelid following repair of right orbital fracture through a transcutaneous approach. This may be due to unrecognized lid laxity, failure to resuspend the skin–muscle flap, or excessive scar contracture.

lid orbicularis. It has been suggested that a lower lid crease, or subtarsal, incision may have a lower incidence of malposition presumably because the pretarsal orbicularis sling is not traumatized (6,15). Lower lid malposition can lead to corneal exposure, epiphora from a displaced puncta, and aesthetic deformity, which may need complicated surgical repair. If an ectropion is seen in the early postoperative period, one should initially treat it with massage and perhaps judicious corticosteroid injections. On occasion, corrective surgery with scar release, skin or mucosal grafting, and lateral canthal tightening may be necessary. Proper suspension of the skin–muscle flap as described and closure of the incision under no tension will help to limit this outcome and can allow for excellent aesthetic and functional results (Fig. 79.20).

LOWER MIDFACE AND MAXILLA

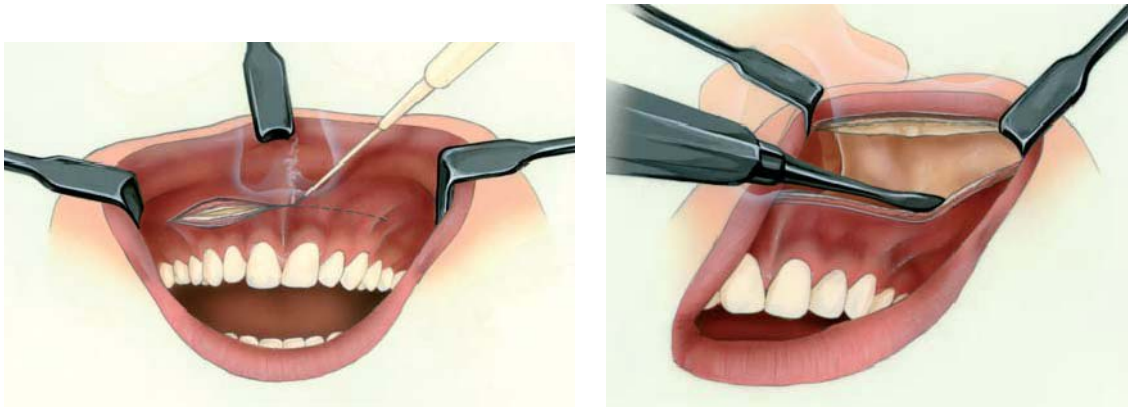
The upper labial sulcus approach provides for exposure of the lower midface including the pyriform aperture, medial maxillary buttresses, and lateral maxillary buttresses (Fig. 79.22). This approach allows the surgeon to visualize the midface from the maxillary alveolus up to the infraorbital rim and from the malar eminence to the nasal bones (16). The incision is placed 5 to 10 mL above the gingiva and extended from the midline to as far lateral as needed based on the needs of the fracture exposure. One must be certain to place the incision high enough to not devitalize the gingiva around the teeth. The incision is made sharply down through the periosteum and subperiosteal elevation is begun. The infraorbital nerve must be identified early and carefully preserved. Release along the pyriform aperture can be done taking care to avoid perforation into the nasal cavity. Laterally, the periosteum is firmly adherent to the bone where the masseter muscle attaches to the lateral maxilla and malar eminence, and this will need to be sharply released in order to visualize the superior lateral buttress and medial zygoma. The dissection can continue upward to expose the infraorbital rim as needed. If the labial sulcus approach is needed bilaterally, one should try to maintain some of the soft tissue attachments of the alar bases as these will tend to lateralize if fully released and may cause some flaring of the nostrils. If wide release is needed across the midline, then this flaring should be corrected at the time of closure with cinching sutures (Fig. 79.23). Once the repair is complete, the incision is closed with interrupted resorbable sutures taking care to incorporate the periosteum to help prevent wound dehiscence.

Complications of the sublabial approach are uncommon. They include wound dehiscence and implant exposure. This is most likely to occur laterally over the lateral maxillary buttress hardware. If the incision is placed too low, then some necrosis of the gingiva can occur leading to periodontal disease. Injury to the infraorbital nerve can result in permanent facial and dental anesthesia as well as prolonged facial pain. Careful incision placement, careful dissection around the infraorbital foramen, and meticulous wound closure should minimize these problems.

Mandibular Exposure

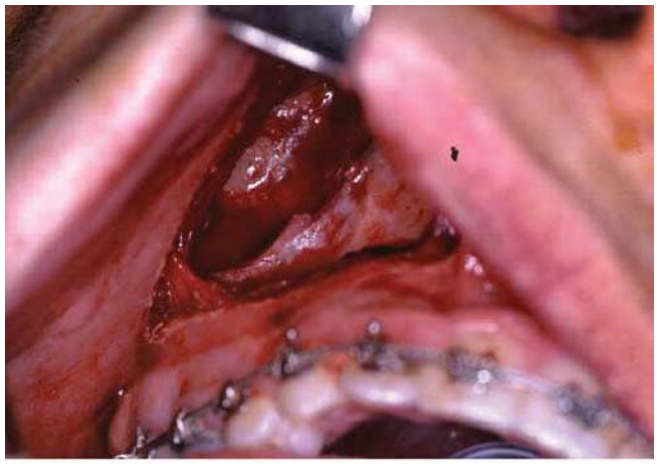
Transoral Approaches

The majority of mandibular fractures can be exposed through the oral mucosa. This includes symphyseal and parasymphyseal fractures, noncomminuted body fractures,



A B

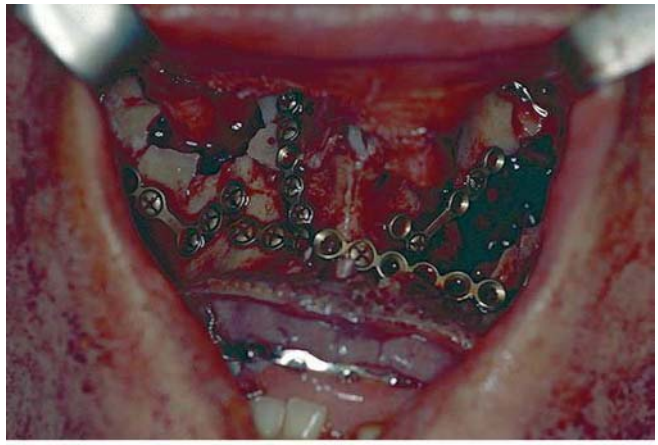
Figure 79.22 Upper labial sulcus approach. **A:** The incision is made leaving a cuff of gingival above the teeth. **B:** Subperiosteal elevation is performed to widely expose the fracture, taking care to identify and preserve the infraorbital nerve.



C



D



E

Figure 79.22 *(Continued)* Upper labial sulcus approach. **C:** Intraoperative photo of labial sulcus exposure of maxillary fractures. **D:** Intraoperative view of lateral maxillary buttress hardware placement. **E:** Extensive bilateral maxillary hardware placement for LeFort fractures via bilateral labial sulcus approach. (Parts A and B from Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, with permission.)

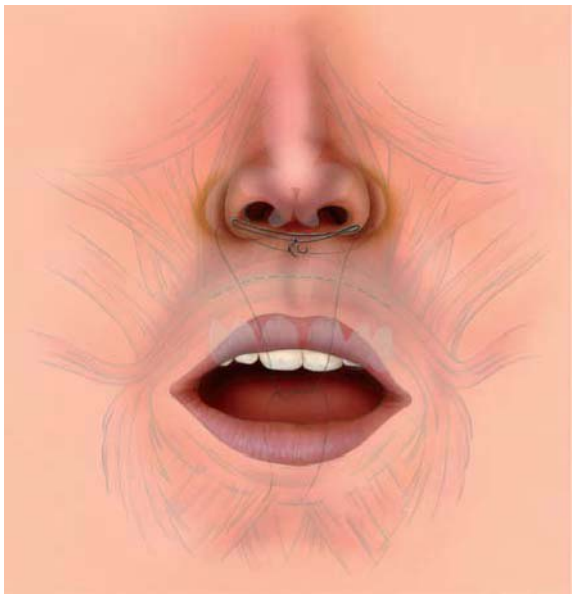


Figure 79.23 Technique of alar cinching suture to prevent flaring or widening of the alar base following bilateral labial sulcus exposure. (From Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, with permission.)

ramus and subcondylar fractures, and some condylar fractures. A transoral incision eliminates a visible scar, allows identification and preservation of the inferior alveolar nerve, and provides wide exposure of the fractures. A major disadvantage of intraoral incisions is that the lingual cortex is not easily seen, and thus, three-dimensionally accurate reduction of fractures may not occur since this cortex is not visualized. This is particularly true in the case of symphyseal and parasymphyseal fractures that are prone to lateral splaying. If the lingual cortex is not fully reduced, then posterior widening of the mandible may occur. In addition, since most fixation plates are placed along the inferior border of the mandible, the alveolar nerve may be at more somewhat greater risk as the dissection is from above and must extend below and around the nerve.

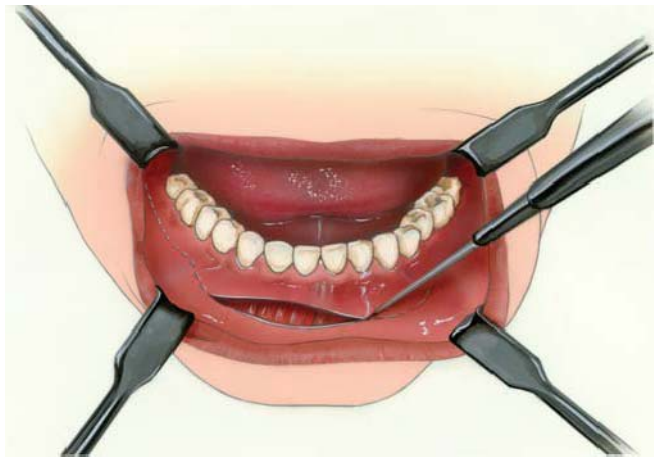
Most intraoral incisions are made in the labial sulcus and should preserve a viable cuff of gingiva. Sharp dissection extends under the periosteum and is extended as need to fully expose the fracture and to allow room for placement of the fixation hardware (Fig. 79.24). The alveolar nerve is carefully identified and preserved. In the symphyseal region, the dissection can extend under the inferior border of the mentum to allow some visualization of

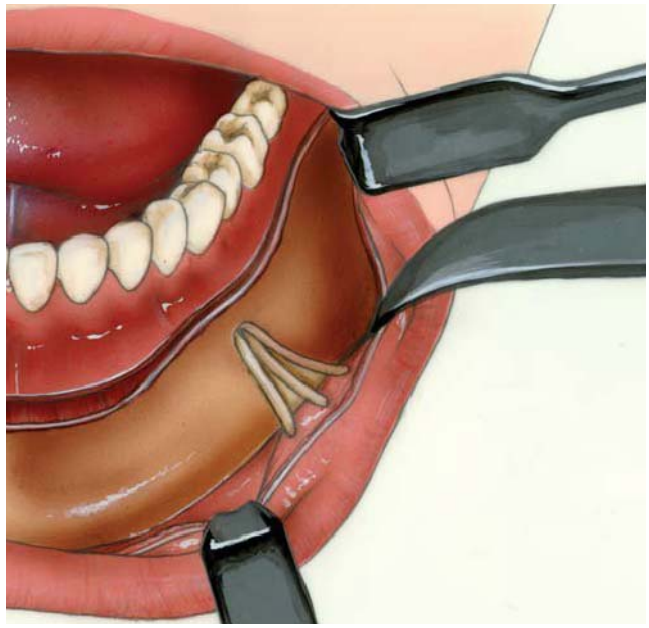
the inner cortex reduction. Following the fracture reduction and hardware placement, the incision is closed with interrupted resorbable sutures that should include the periosteum for strength.

In the region of the angle and ramus, the incision is placed along the anterior border of the ramus (Fig. 79.25). Subperiosteal elevation is done as needed and can be done on both the inner and outer surfaces to allow visualization for accurate fracture reduction. This approach can also be combined with endoscopic visualization, which can assist reduction and fixation of subcondylar fractures (17,18).

Transcutaneous Approaches to the Mandible

Some mandibular fractures may be better approached through the neck or facial skin rather than transorally. Severely comminuted fractures may require large reconstruction hardware and primary bone grafting and are usually best treated through a cutaneous approach. This is especially


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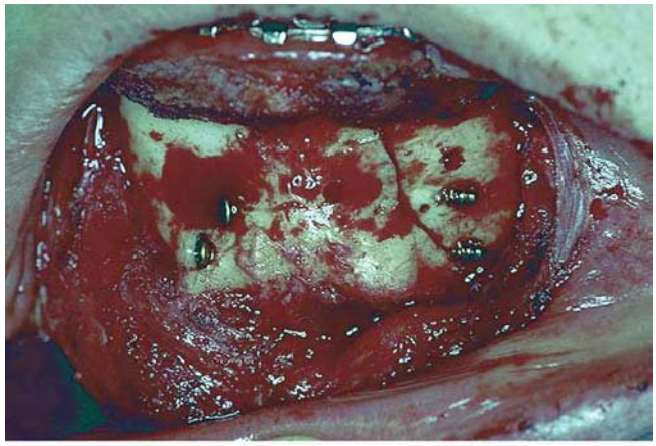

E

Figure 79.24 Transoral exposure of the mandible with labial sulcus approach. **A:** Incision placement. **B:** Subperiosteal exposure with identification of the mental nerve. **C:** Intraoperative exposure of left anterior body fractures. **D:** Intraoperative view of hardware placement. Note placement of plate along inferior border of the mandible with preservation of the mental nerve. **E:** Intraoperative view of repair of parasymphyseal fractures with lag screws placed via bilateral sulcus approaches. (Parts A and B from Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, with permission.)

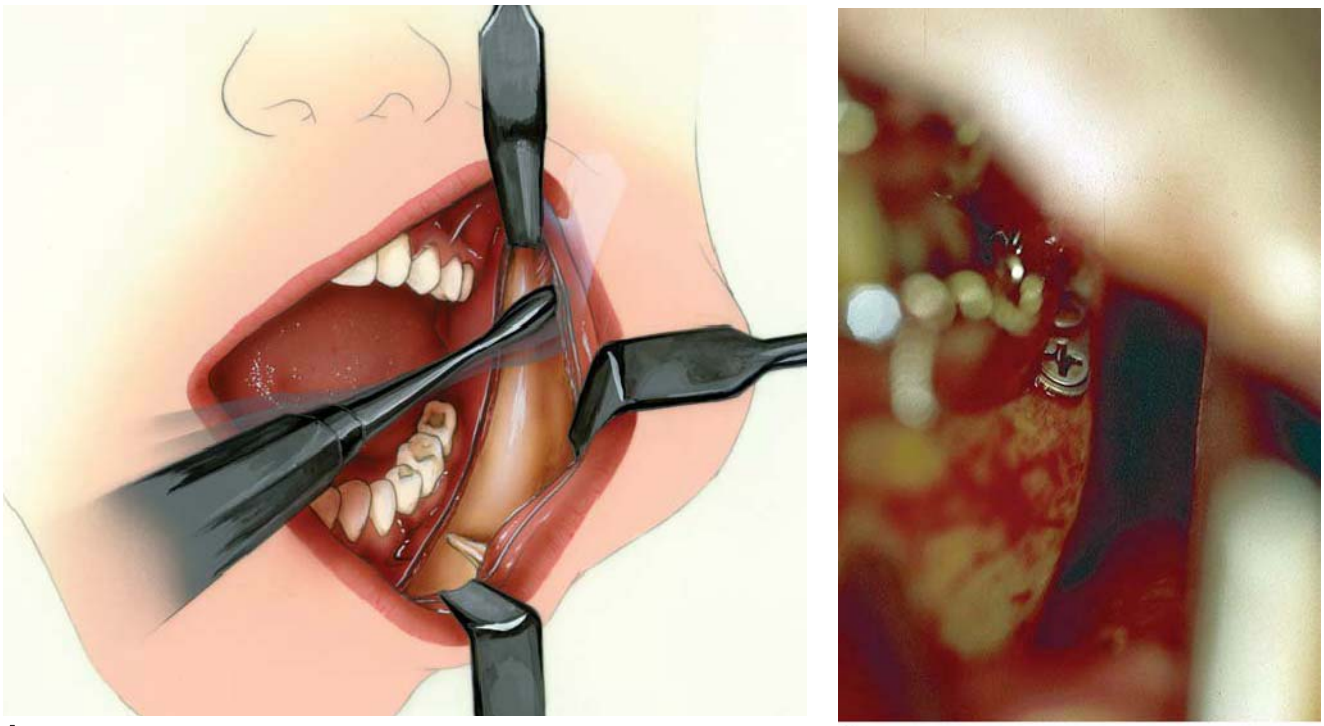


Figure 79.25 Transoral exposure of mandibular angle fractures. **A:** Artist's depiction of incision along anterior border of the ramus and wide subperiosteal exposure. **B:** Intraoperative view of hardware placed along superior border of the angle and ramus. (Part A from Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, with permission.)

true in the body and angle regions. On occasion, a large laceration may be employed for exposure. However, one should avoid the temptation to significantly enlarge existing lacerations unless they are optimally located and extension will not endanger nerves or worsen the cosmetic outcome.

The symphysis can be approached through an extended submental incision placed in the submental crease. This is similar to that used in chin augmentation but typically is longer as wider exposure is needed. Sharp dissection is carried down to the bone and subperiosteal dissection is extended as needed. This is quite straightforward with few risks except for potential injury to the alveolar nerve. The principle advantage compared to an intraoral approach is that the inner cortex can be well visualized from below and that may assist accurate fracture reduction. The majority of symphyseal and parasymphyseal fractures are well managed with the intraoral approach.

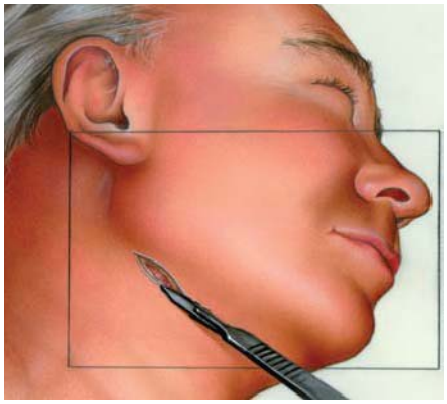
The course of the marginal mandibular nerve must be well understood to perform transcutaneous exposure of the mandible. After the marginal mandibular branches of the facial nerve exit the substance of the parotid, they course anteriorly where they innervate the lower lip depressor muscles. Early anatomic studies (19) demonstrated that the marginal branch dropped below the inferior border of the mandible behind the facial artery in less than 20% of people. More recent studies have found, however, that in approximately half of people, the nerve dips up to 1.2 cm below the mandible until it crosses over the facial artery (20). In front of the facial artery, however, the marginal nerve is virtually always above the inferior border. Injury to the nerve will denervate the lower lip depressors resulting in elevation of the affected side with animation (Fig. 79.26). This deformity is permanent and very difficult to correct or camouflage. For this reason, most have advocated placing the incision at least 1.5 cm, or approximately two fingerbreadths, below the inferior border of the mandible usually following a natural skin crease



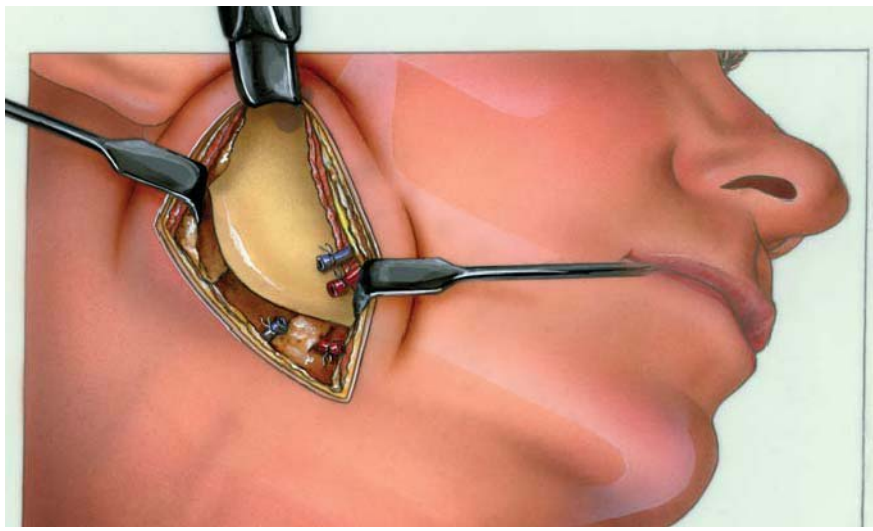
Figure 79.26 Clinical example of deformity caused by injury to the right marginal mandibular nerve. This injury weakens the depressor muscles of the lower lip, which causes the lower lip to rise leading to a crooked smile.

(Fig. 79.27). Dissection is carried through the skin, the subcutaneous fat, and the platysma. Blunt dissection under the platysma muscle extends up to the inferior border of the mandible, and if needed, the facial artery and vein can be ligated and divided for exposure. The cervical fascia is opened at least 1.5 cm below the inferior border of the mandible especially posterior to the mandibular notch again to avoid injuring the marginal nerves. The submandibular gland will usually be seen and is gently retracted inferiorly. The periosteum is opened and elevated, and the masseteric fibers are released as needed for exposure of the angle and ramus. This approach will allow exposure from the posterior ramus, across the angle and up to the anterior body. This approach can also be extended across the midline to the contralateral side in those unusual cases where complete exposure of the mandible is needed. Following the repair, the wound is closed in layers including the fascia and platysma. A passive drain can be placed if desired, but suction drains should be avoided as they can pull oral contaminants down into the wound and may encourage the development of oral–cutaneous fistulae.

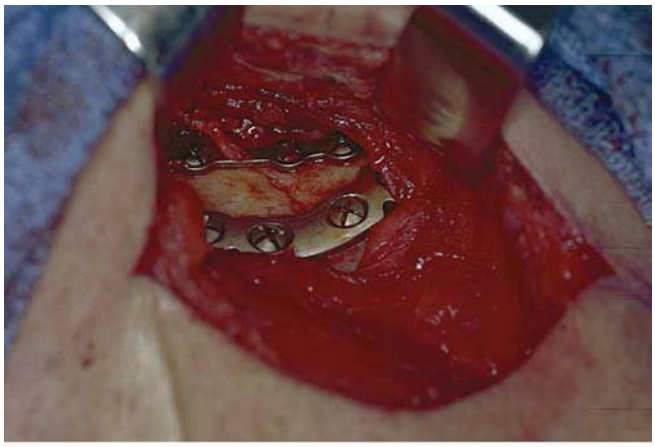
A retromandibular or preauricular approach can also be employed for extended exposure of the mandibular ramus and condylar region (Fig. 79.28) (21–23). The retromandibular approach typically employs a vertical incision placed directly over the posterior border of the ramus below the ear. The preauricular approach employs a curvilinear incision along the preauricular crease, around the lobule, and



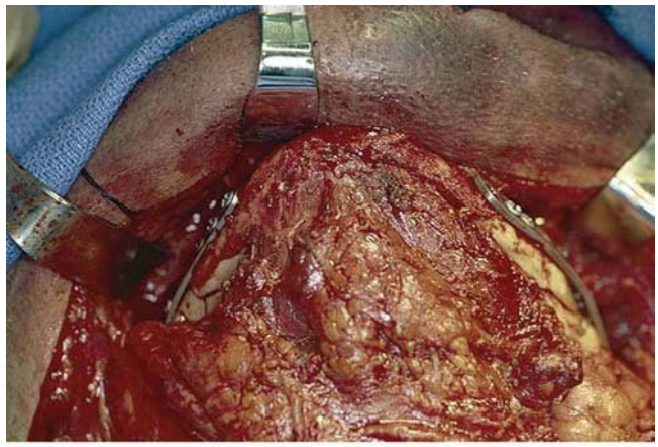
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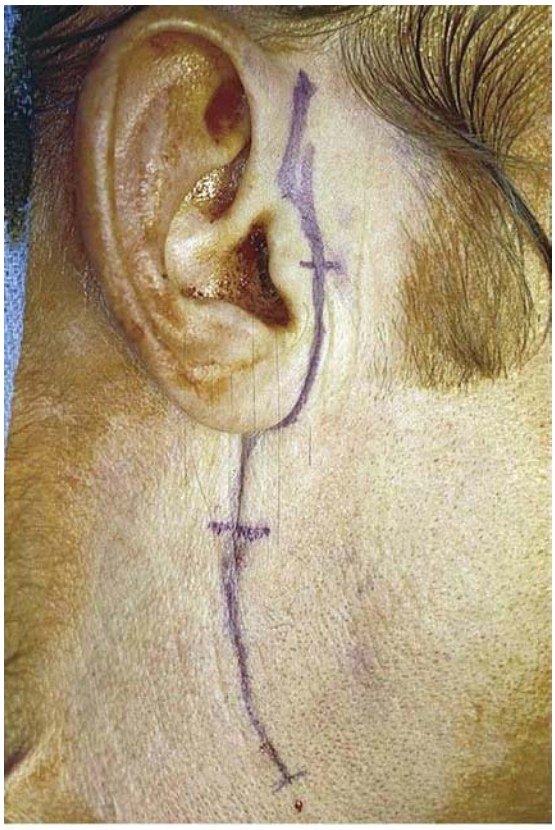


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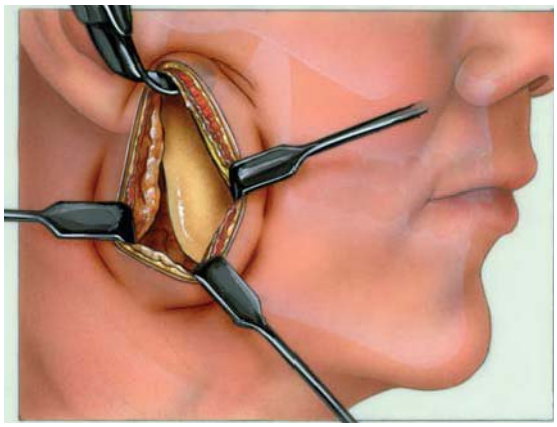


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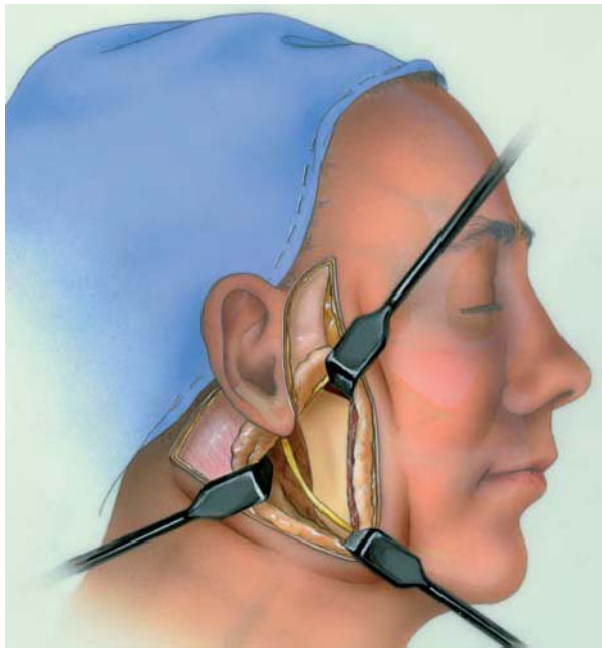
Figure 79.27 Submandibular approach to the mandible. **A:** Incision placement. Incision is oriented to follow relaxed skin tension lines in the neck typically 1.5 to 2 cm below the mandible. The platysma is incised along the length of the incision. **B:** Exposure of mandible is accomplished but dividing the superficial and deep layers of the cervical fascia. The fascia is opened at least 1.5 cm below the inferior border of the mandible to avoid the marginal branches of the facial nerve. The facial artery and vein may be ligated if needed. **C:** Intraoperative view of mandibular angle fracture repair with hardware in place. **D:** Extensive bilateral exposure of the mandible for severe bilateral comminuted body fractures with extended submandibular approach. (Parts A and B from Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, with permission.)



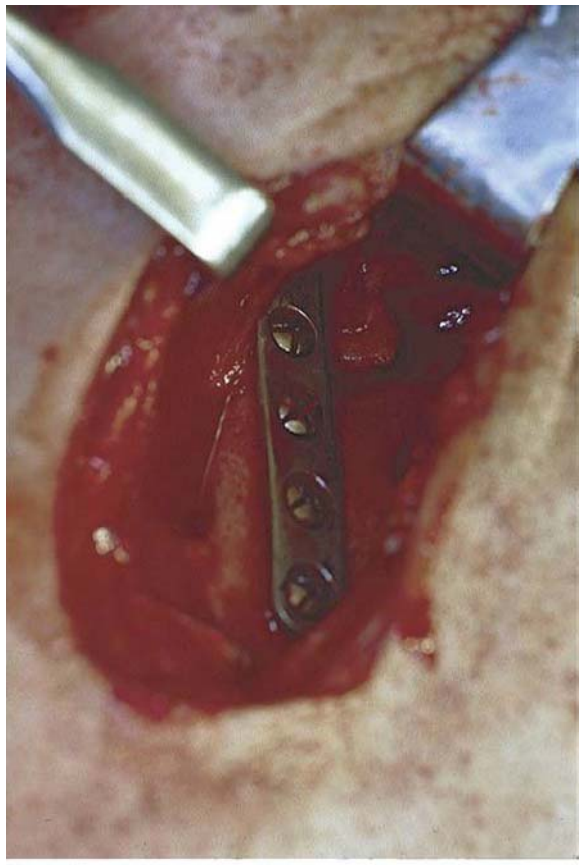
A



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C



D

Figure 79.28 Retromandibular and rhytidectomy approach. **A:** Modified preauricular retromandibular incision for exposure of the ramus and subcondylar area. **B:** Exposure of the ramus with retromandibular approach. **C:** Rhytidectomy incision approach for ramus and subcondylar areas. **D:** Intraoperative view of hardware in place through a retromandibular approach. (Parts B and C from Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, with permission.)

extending up the postauricular sulcus as one would use in a face-lift or rhytidectomy. The advantage of the face-lift incision is that it leaves a more aesthetically pleasing scar. However, the subcutaneous dissection is more extensive and closure is more involved. The incision extends through the skin and subcutaneous tissues and flaps are raised as needed. Dissection continues down through the SMAS and the parotid fascia. At this point, dissection is done with purely blunt technique with spreading of the parotid tissues toward the posterior border of the ramus of the mandible. The marginal nerve branches may be seen and should be meticulously protected with gentle retraction either superiorly or inferiorly as needed. The retromandibular vein is identified and ligated as needed. The masseter muscle fibers are incised and elevated to gain exposure of the posterior border of the ramus, and then subperiosteal dissection is extended as dictated by the fracture repair. The greatest concerns of this approach are the risks to the facial nerve and the potential for a salivary fistula from the divided parotid tissues. The marginal nerve is at greatest risk, but typically the marginal nerve can be identified and protected. Temporary paresis or weakness of the marginal nerve is common and likely is due to retraction of the nerve during exposure during the fracture repair. Closure is done in layers including the periosteum, masseteric fibers, SMAS, and skin. A passive drain may be used, but again active suction drains should be avoided.

SUMMARY

Contemporary management of facial skeletal trauma demands that the surgeon carefully diagnose, expose, and repair the facial skeleton with precision and anatomic accuracy. Surgical exposure should be performed with careful soft tissue handling techniques and with aesthetic surgical concepts in mind. The incisions should be carefully designed and placed and should follow relaxed skin tension lines whenever feasible. Dissection should follow proper anatomic planes. The surgeon should have a thorough understanding of the anatomy of the facial and trigeminal nerves and carefully avoid and protect them. Meticulous wound closure and tissue resuspension should minimize postoperative soft tissue deformities. If these basic concepts are observed, the facial trauma victim can expect an excellent recovery—hopefully with few long-term soft tissue consequences and minimally visible incisions.

HIGHLIGHTS

- Thoroughly counsel patients preoperatively regarding the exact location of all planned incisions, the risks of each approach, and postoperative care and the possible need for future scar revision.
- Incisions should be planned with relaxed skin tension lines and natural skin creases in mind.
- Gentle soft tissue handling and judicious electrocautery will minimize scarring and hair follicle damage.
- The surgeon must be intimately familiar with the location, course, and depth of the facial and trigeminal nerves.
- Consider camouflaging the scalp coronal incision with curvilinear design in the parietal regions and bevel incisions parallel to the hair follicles.
- Preserve or enhance lower eyelid support and utilize techniques that will suspend the lower lid tissues during healing to prevent lower lid malposition and ectropion. Transconjunctival approaches may be less prone to postoperative lid malposition.
- Preserve an adequate cuff of viable gingival tissue when making intraoral incision to expose the maxilla or mandible. Identify and preserve the mental nerve.
- Consider transoral approaches for all mandible fractures except those that have severe comminution that will require extensive hardware or bone grafting.
- Be cognizant of the anatomy of the marginal mandibular nerve with all transcutaneous approaches to the mandible.
- Endoscopic visualization may assist the repair of orbital floor, frontal sinus, zygomatic arch, and mandibular condylar fractures.

RECOMMENDED READING

Ellis E, Zide MF. *Surgical approaches to the facial skeleton*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006. This is an excellent, comprehensive text, which covers the topic of approaches to the craniofacial skeleton in great detail. The text is enhanced by clear illustrations, cadaver dissections and intraoperative photographs. This text is highly recommended for all facial trauma surgeons both novices and experts.

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Mandibular Fractures

80

Brett A. Miles *Jesse E. Smith*

Mandibular fractures represent common injuries and are second only to nasal fractures with regard to frequency. The central role of the mandible in mastication, swallowing, and speech makes the surgical management and rehabilitation of mandibular fractures challenging. In addition, complications related to the management of mandibular fractures, while seldom life threatening, often result in significant morbidity for patients with these injuries. Therefore, accurate assessment of the injury and the appropriate application of the priniciples of the management of mandibular fractures is critical for sucessful outcomes.

ANATOMY

The mandible articulates with the skull base at the paired temporomandibular joints (TMJs) and is suspended by a complex ligamentous and neuromuscular apparatus. Because of this unique, bilateral articulation with the skull base and the vector of forces contributing to mandibular trauma, a bilateral fracture pattern is commonly observed. The anatomic components of the mandible include the symphysis, parasymphysis, body, angle, ramus, coronoid process, condyle, and alveolus (Fig. 80.1). Anatomic locations with an increased propensity for fracture include the third molar area (especially if the third molar is impacted), the mental foramen region, and the condylar neck. Edentulous, atrophic mandibles are inherently susceptible to fracture in multiple anatomic locations. Additionally, pediatric patients in the deciduous phase of dentition are prone to mandibular fracture, the result of weakening of the mandible due to the presence of unerupted teeth.

Knowledge of dental occlusion is integral to the diagnosis and management of all facial fractures. In the Angle classification of occlusion, the mesiobuccal cusp of the maxillary first molar is used as a reference (Fig. 80.2). Class I occlusion is the most commonly observed pattern. Class II represents retrognathism, and class III represents prognathism. Cognizance of the three classes of occlusion and careful examination of the cuspal interdigitation and wear facets allow accurate restoration of the patient's preinjury occlusion. Restoration of the patient's occlusion is the primary goal during the surgical management of mandibular fractures as well as during postoperative rehabilitation. The universal dental numbering system is useful in describing the location of mandibular fractures and reporting associated dental injuries (Fig. 80.3).

BIOMECHANICS OF THE MANDIBLE

Biomechanically, the mandible can be considered a cantilever beam. The beam is suspended at two points, which represent the TMJ attachments. In the mandibular body and angle, occlusal forces produce zones of relative tension along the superior border and compression along the inferior border. Mandibular tension–compression stress distribution is complex, and stress distribution can vary dramatically, depending on the magnitude and point of force application. In the symphyseal area, the situation is more complicated when the mandible is viewed and tested as a three-dimensional model. Compression is produced at the upper border, and tension and torsional forces exist along the lower border. These three-dimensional stress relationships are important to understand, because tension and compression forces dictate the type of fixation applicable to a particular fracture.

Angle and body fractures can be classified as either vertically or horizontally favorable or unfavorable (Fig. 80.4). Fractures are classified as favorable when muscles tend to draw the fragments toward each other, thus, reducing the fracture. Fractures are described as unfavorable when the

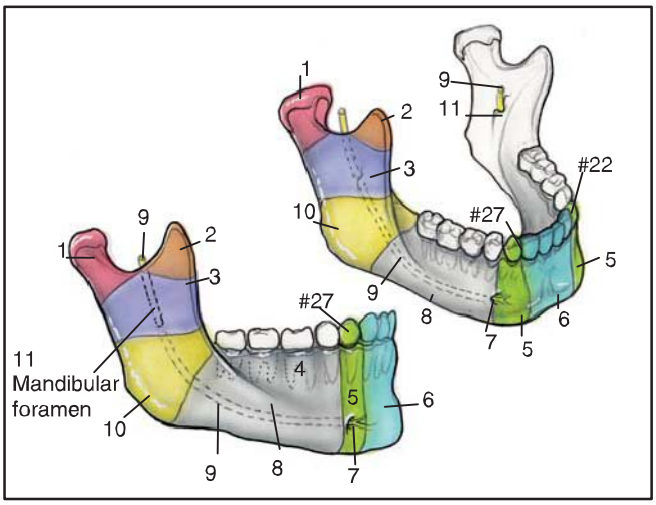


Figure 80.1 The anatomic components of the mandible include the symphysis, parasymphysis, body, angle, ramus, coronoid process, condyle, and alveolus. *1*, Condylar process; *2*, Coronoid process; *3*, Ramus; *4*, Alveolar process; *5*, Parasymphysis; *6*, Symphysis; *7*, Mental foramen; *8*, Body; *9*, Inferior alveolar nerve; *10*, Angle.

fragments tend to be displaced by muscular forces. The majority of mandibular angle fractures are horizontally unfavorable as the masseter, medial pterygoid, and temporalis muscles contribute to the superior and medial displacement of the proximal segment. Vertically unfavorable angle fractures result in medial displacement of the proximal segment by the pterygoid musculature. Vertically unfavorable fractures of the body of the mandible are distracted by the mylohyoid and suprahyoid musculature. A careful assessment of the biomechanical pattern of the fracture is paramount to guide surgical management in order to prevent displacement of fragments due to inadequate fixation techniques.

EVALUATION AND DIAGNOSIS

History

Pain and malocclusion after a blow to the lower face strongly suggest mandibular fracture. Additional symptoms include anesthesia or paresthesia of the lower lip and chin caused by trauma to the inferior alveolar nerve as it courses through the mandibular canal (Table 80.1).

Physical Examination

Fractures of the symphysis–parasymphysis and body can be accompanied by malocclusion, palpable tenderness, altered sensation, gingival lacerations/dental trauma, hematoma in the floor of the mouth, or loss of normal facial contours. Mobility of fractures in these locations is often identified with manipulation. Trismus is a relatively common finding with mandibular fractures, but it also occurs after zygomaticomaxillary complex fractures and with facial contusions without evidence of fracture. The maximal interincisal opening (MIO) of a patient with a mandibular fracture can be markedly reduced secondary to pain, muscle splinting, or impinging fragments. The normal MIO in a healthy adult is approximately 40 to 50 mm.

Fractures of the condyle and condylar neck are associated with impaired translational movement of the condyle along the articular eminence. Although limited rotation may also occur, this lack of translation produces a characteristic deviation of the chin toward the side of such a fracture when opening as well as reduced interincisal distance (Fig. 80.5). Fractures of the neck of the condyle tend to be displaced anteromedially in response to the action of the lateral pterygoid muscle. This displacement produces a loss in the functional height of the ramus, resulting in

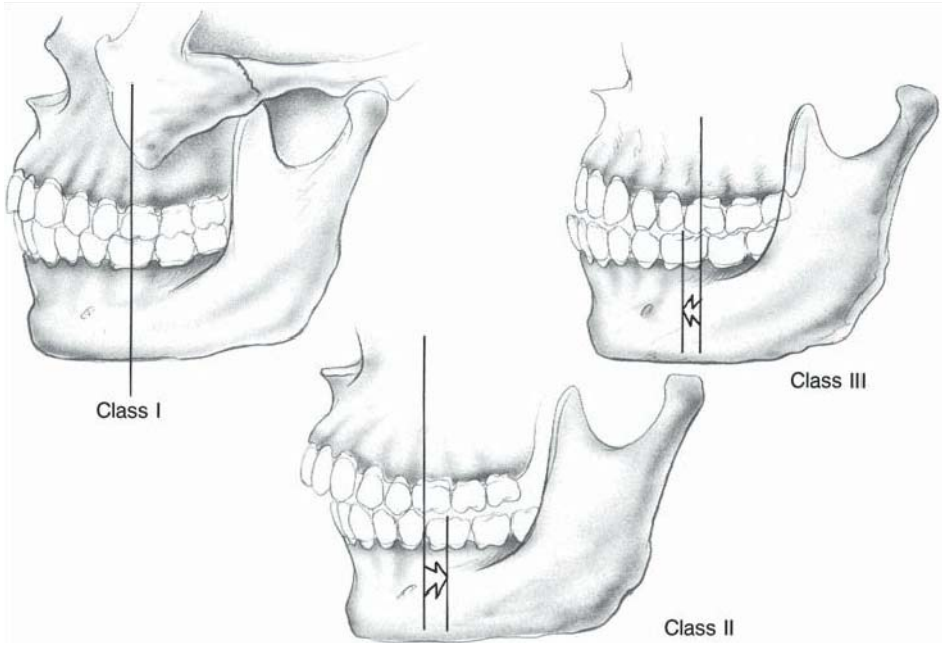


Figure 80.2 The Angle classification of occlusion is based on the relation of the mesiobuccal cusp of the maxillary first molar to the buccal groove of the mandibular first molar.

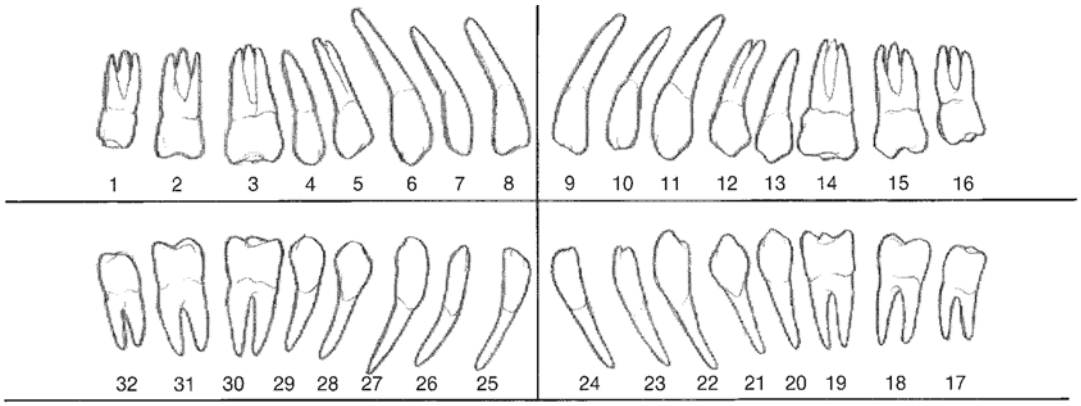


Figure 80.3 The universal numbering system for the permanent dentition begins with the maxillary right third molar. Similarly, the 20 teeth of the deciduous dentition are lettered from *A* to *T*, beginning with the maxillary right second deciduous molar.

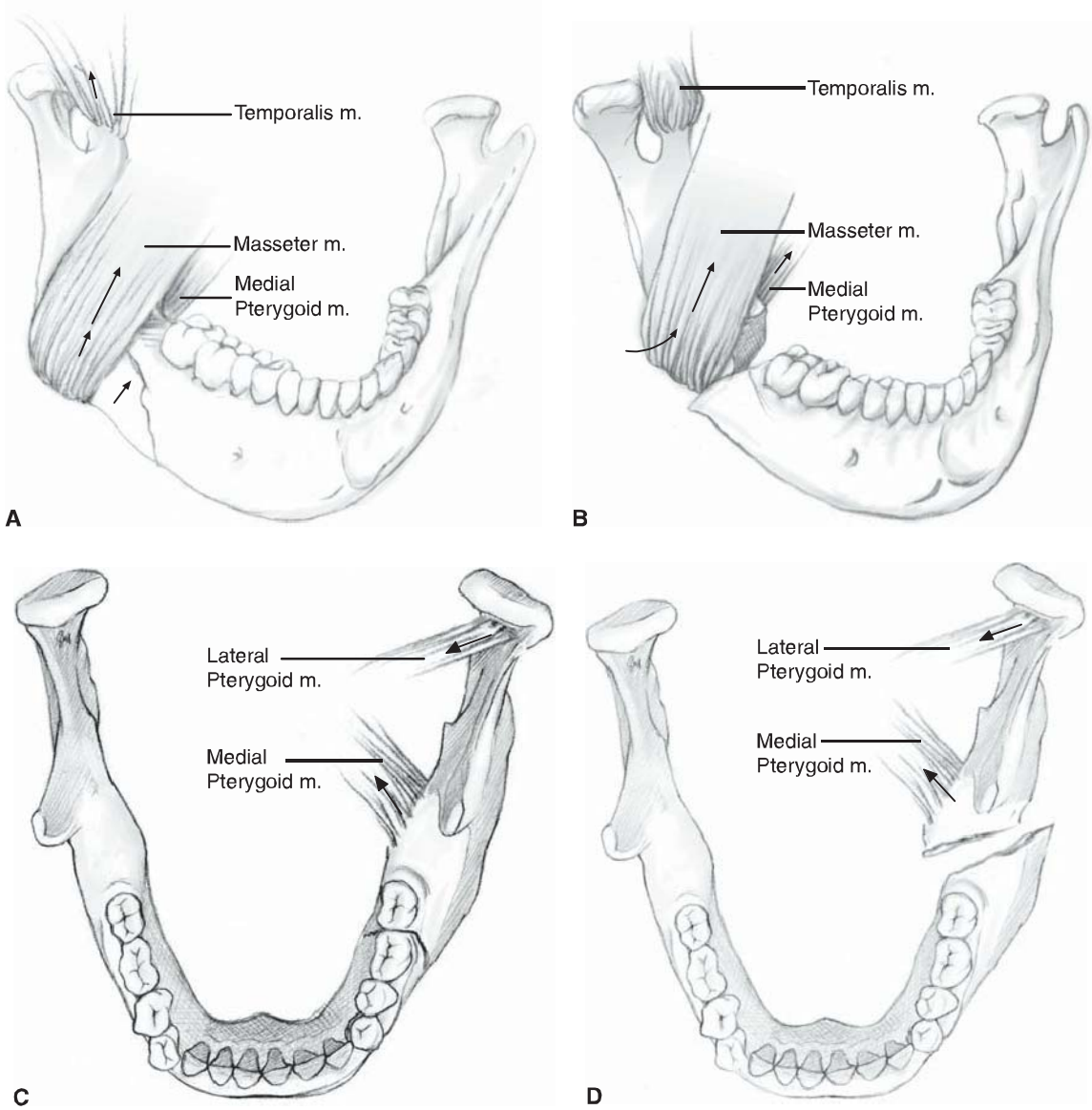


Figure 80.4 **A:** Horizontally favorable fracture. **B:** Horizontally unfavorable; the masseter, medial pterygoid, and temporalis muscles contribute to the superior and medial displacement of the proximal segment. **C:** Vertically favorable fracture. **D:** Vertically unfavorable angle fractures result in medial displacement of the proximal segment by the medial and lateral pterygoids.

TABLE 80.1 DIAGNOSIS MANDIBULAR FRACTURE

Malocclusion
Fragment mobility
Trismus
Deviation on opening toward side of fractured condyle
Anterior open bite contralateral to side of fractured condyle
Radiographic evidence of fracture
Hematoma in floor of mouth
Laceration of attached gingiva overlying fracture site

premature contact of the ipsilateral molar teeth. The point of contact acts as a fulcrum and produces a characteristic open bite on the side opposite the fracture (Fig. 80.6). Bilateral condylar/subcondylar fractures often produce a symmetric anterior open bite due to the loss of vertical height of the posterior mandible.

Radiographic Evaluation

The single best radiograph for evaluation of mandibular fractures is the panoramic view (Fig. 80.7A–C). Historically, mandibular series of plane radiographs (posteroanterior view, a Townes anteroposterior axial view, and bilateral oblique views) were used to provide additional information; however, presently, computed tomography (CT) is used in many centers (Fig. 80.7D and E). CT scans, while not required, have become standard in the evaluation of mandibular fractures due to increased accuracy, and are useful in determining the fragment location and size, degree of displacement, as well as undiscovered associated fractures. Helical CT scans have been shown to accurately diagnose 100% of mandibular fractures, whereas initial panoramic imaging was sensitive in 86% of cases (1). Cone-beam technology offers extremely high-resolution, three-dimensional images of the mandible for the diagnosis of mandibular fractures as well as for evaluation of postoperative results (2,3).

MANAGEMENT

General

The primary goals when treating mandibular fractures are to establish and maintain the preinjury occlusion and provide appropriate stabilization for bone healing. Surgical management of mandibular fractures varies based on the location of the fracture and severity of the injury. In general, fractures involving the tooth-bearing portion of the mandible with communication to the oral cavity are considered open. Displacement of jaw fragments is uncomfortable, impairs oral hygiene and alimentation, and contaminates exposed bone with bacterial flora from the oral cavity. These features warrant antibiotic prophylaxis starting as soon as possible after the injury as well as intraoperatively; however, the benefit of perioperative antibiotics has been questioned recently (4). Postoperative antibiotics are unnecessary in the majority of cases (5). Topical chlorhexidine rinse may also help minimize the bacterial contamination of the fracture site. Temporary partial reduction via the use of wire fixation may alleviate some mobility at the fracture site in severely displaced fractures, prior to surgical management. Although delay of fracture repair for a short duration does not markedly increase the infection or complication rate, consideration of patient comfort and prolonged environmental exposure warrants timely intervention. It should also be noted that nonmobile, nondisplaced, or incomplete fractures may be treated with careful observation and soft diet, provided the occlusion is stable and there is no mobility at the fracture site.

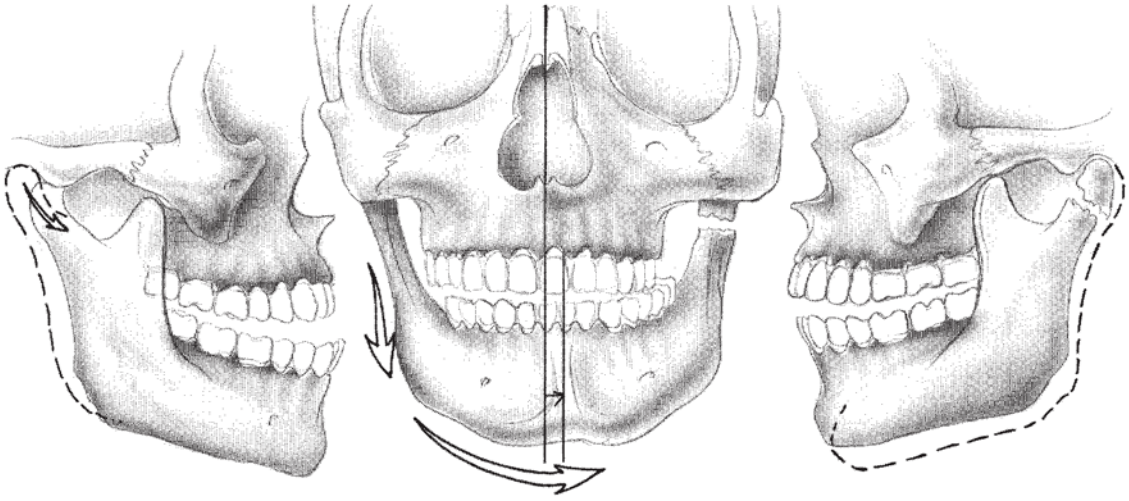


Figure 80.5 Fractured condyle does not translate down the articular eminence during jaw opening. The unopposed translational movement of the opposite condyle deviates the chin toward the side of the fractured condyle.

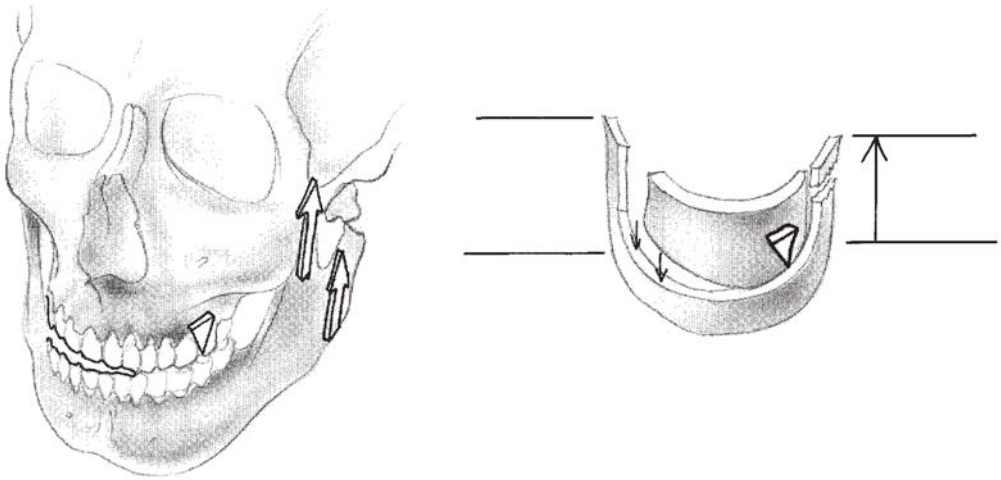


Figure 80.6 Fractured condyle distracted anteromedially by the lateral pterygoid muscle. This produces a shortened functional height of the ramus as the masseter, medial pterygoid, and temporalis muscles draw the ramus closer to the skull base. The ipsilateral molar teeth act as a fulcrum to produce a slight contralateral open bite.

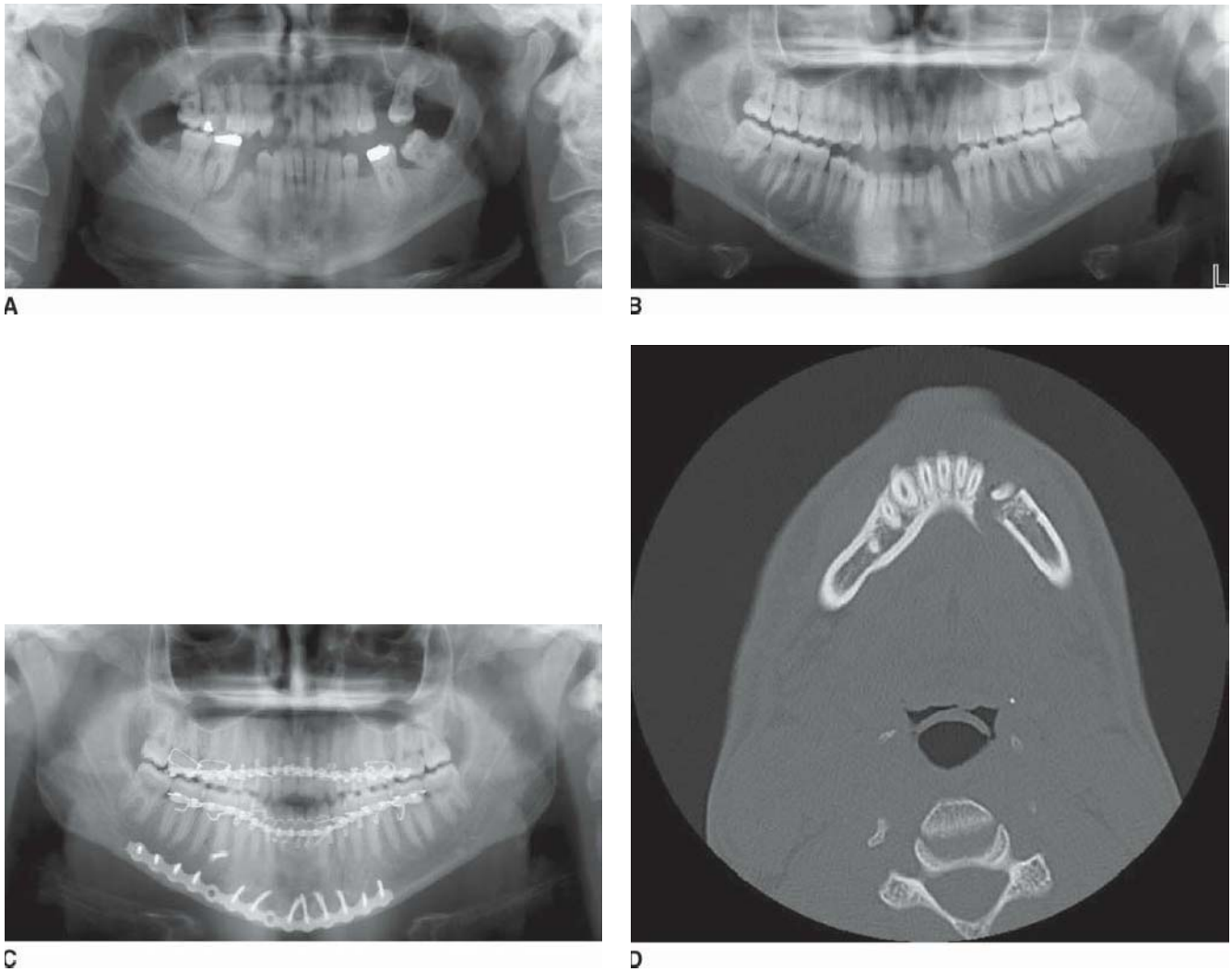


Figure 80.7 **A:** Panoramic radiograph of symphyseal fracture and left subcondylar fracture. **B:** Panoramic radiograph of right body fracture and left parasymphyseal fracture. **C:** Postoperative panoramic radiograph after open reduction internal fixation of fractures in B. Note the location of the reconstruction plate along the inferior border. Small lag screw was also used in this case for oblique section of the body fracture. **D:** Axial CT scan of moderately displaced left mandibular body fracture. *(Continued)*



E

Figure 80.7 *(Continued)* **E:** Coronal CT of laterally displaced right subcondylar fracture.

Closed Reduction

Many favorable fractures in adult patients can be managed by means of closed reduction with arch bars, bone screws, or other means of intermaxillary fixation (IMF). Four to six weeks of IMF is generally considered appropriate for the symphysis, angle, and body. Considerable variation among experts exists regarding the duration of IMF for condylar fractures to optimize condylar mobility while achieving osseous union. Longer periods of IMF (4 to 6 weeks) have been associated with poor range of motion, ankylosis at the TMJ, muscle atrophy, and loss of interincisal opening (6). Nevertheless, many condylar fractures are successfully managed with closed techniques (7). Closed reduction techniques are still commonly used for fractures in children involving the developing dentition and in nonmobile, nondisplaced fractures. The indications for closed reduction vary widely; however, closed techniques should be utilized for cases in which an open reduction is either unnecessary or contraindicated.

Open Reduction

Table 80.2 summarizes treatment options for open reduction with internal fixation (ORIF) for mandibular fractures in adult patients according to fracture location. Internal fixation can be classified as being rigid (reconstruction plates, lag screws), semirigid (miniplates), or nonrigid (interosseous wires). Most rigid and semirigid techniques obviate the use of postoperative IMF, and the occlusion may be guided with postoperative dental elastics when

TABLE 80.2 OPEN REDUCTION INTERNAL FIXATION OPTIONS FOR ADULT DENTATE PATIENTS

Fracture Location	ORIF
Symphysis and parasymphysis	Inferior plate and arch bars Inferior locking or nonlocking reconstruction plate Inferior locking or nonlocking 2.0-mm mandible plate and superior border monocortical tension band Two 2.0-mm miniplates (8) Two lag screws (9)
Body	Inferior plate and arch bars Inferior locking or nonlocking reconstruction plate Inferior locking or nonlocking 2.0-mm mandible plate and superior border monocortical tension band Two 2.0-mm miniplates (8) Multilag screw technique, if oblique
Angle	Single malleable superior border miniplate (11) Two biplanar or monoplanar miniplates (12) Inferior locking or nonlocking reconstruction plate with superior tension band
Ramus and condyle	One 2.0-mm miniplate Two 1.5/2.0-mm miniplates

required. This is an especially important consideration among patients with epilepsy, diabetes, alcoholism, psychiatric disorders, or severe disability, who may not tolerate IMF. The classic indication for open reduction and rigid internal fixation is inability to reduce or stabilize the fracture with a closed technique. Other indications include associated midface fractures, associated condylar fractures, IMF is either contraindicated or not possible, to preclude the need for IMF for patient comfort, and to facilitate the patient's return to work or other activities. The fundamental principles of rigid internal fixation include accurate anatomic reduction, stable internal fixation, early mobilization, and careful tissue handling with preservation of the neurovascular supply. The application of appropriately stable fixation varies depending on the location and severity of the fracture. Internal fixation is the application of sufficient hardware to prevent movement across the fracture site during function; however, this is not necessarily rigid internal fixation in many situations. Thus the concept of *load-bearing* versus *load-sharing* fixation merits review. *Load-bearing* fixation is the application of hardware of sufficient rigidity to resist all functional forces until osseous union is achieved. When treating comminuted mandibular fractures, atrophic mandibular fractures, and those with segmental defects, load-bearing fixation is generally required. In contrast,

load-sharing fixation refers to the application of hardware that allows the functional load to be shared between the hardware and the apposed mandibular cortices after fracture reduction is achieved along the fracture site. The majority of mandibular fractures are adequately treated with load-sharing fixation.

Comminuted fractures are defined as a fracture pattern in which a single anatomic region is broken into pieces. Comminuted fractures of the mandible have been treated in a variety of fashions, including closed reduction, external pin fixation, internal wire fixation, and ORIF with titanium plating systems (8–10). Most nonunions in these fractures result from inadequate immobilization of comminuted fragments. Investigations have revealed that periosteal stripping during ORIF does not lead to increased infections as long as fragments are properly stabilized (9,10). Comminuted mandibular fractures treated with formal ORIF using reconstruction plates exhibit lower complication rates and decreased recovery time when compared to external pin fixation and closed reduction techniques (Fig. 80.8) (9,10).

In terms of soft tissue approaches, similar complication rates have been observed when comparing transoral versus extraoral reduction of mandible fractures (11). The majority of mandibular fractures may be treated via the transoral approach, which allows direct occlusal visualization during reduction and internal fixation, eliminates facial scarring, and limits the risk of facial nerve injury. In many instances, posterior body, angle, ramus, and condyle fractures can be addressed through combined intraoral and extraoral approaches utilizing trocars to reduce external scars. The main advantage of the extraoral approach is enhanced visualization and access for complex or comminuted fractures. Extensive comminution or fractures in the severely atrophic mandible often require an external approach to appropriately address the fracture.

Selection of Hardware

In comminuted, segmental, and infected fractures, when load-bearing fixation is required, large reconstruction plates using 2.4 or 2.7-mm screws are advised (Fig. 80.8). In general, these reconstruction plates require placement of at least three to four screws on either side of the fracture within stable portions of the mandible. Locking reconstruction plates retain their yield load, yield displacement, and stiffness even when imprecise contouring to the bone has occurred, whereas nonlocking reconstruction plates demonstrate significant differences in these factors even with as little as 1 mm of displacement from the bone (12). For this reason, many now prefer the use of locking reconstruction plates in these situations. The benefit of locking technology may be less apparent in load-sharing fixation schemes and nonlocking plates are often sufficient (13).

Miniplates (1.5 to 2.0 mm) are commonly used for mandibular fracture repair (13–15). Generally, a six-hole plate is positioned at the inferior border and bicortical screws are placed; a four-hole plate is placed at the upper border with either bicortical or monocortical screws to provide a tension band. Careful attention to the location of the mental nerve and tooth roots is required. Sagittal and oblique fractures may be amenable to repair with lag screw techniques. To achieve optimal compression without displacement, the lag screw hole must be drilled perpendicular to the fracture (Fig. 80.9). The most common indication for the lag screw technique is the symphyseal fracture. It should be noted that dynamic compression plates, which produce interfragmentary compression of bone, were historically thought to offer an advantage over standard reconstruction plates. Investigations have revealed that dynamic compression may introduce unwanted forces resulting in difficulty with hardware application, oblique fracture displacement,

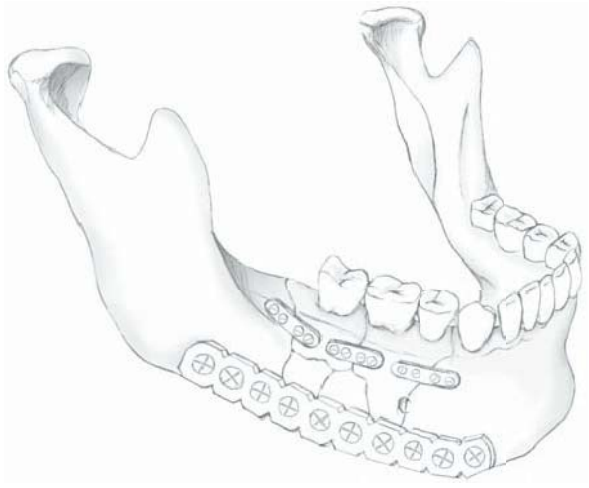


Figure 80.8 Reconstruction plates (2.4 or 2.7-mm) are used in comminuted, gap, and infected fractures. Small fragments may be reduced and stabilized with smaller (2.0-mm) plates prior to application of the reconstruction plate.

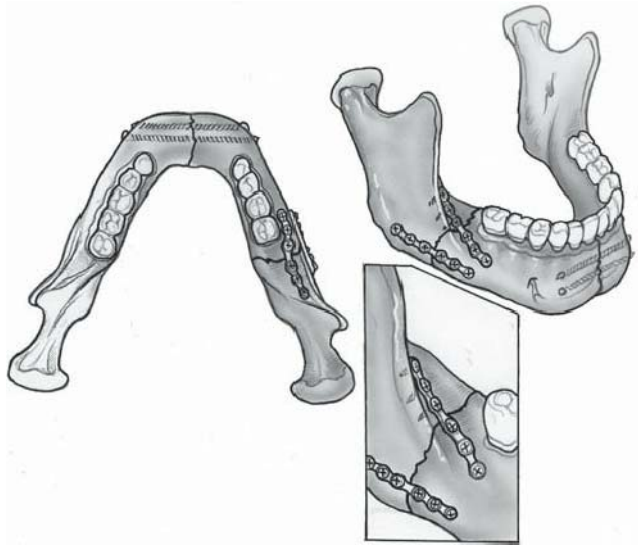


Figure 80.9 Reduction and fixation of a symphyseal fracture and angle fracture with lag screw technique in the symphyseal region and superior border plate (2.0-mm) for the angle fracture.

and malocclusion (16). In addition, dynamic compression does not follow physiologic principles as bone tends to resorb under compression and therefore this technology is rarely indicated.

Symphysis–Parasymphysis

Symphysis and parasymphyseal fractures are those fractures located between the canines (see Fig. 80.1). Vertically unfavorable symphyseal fractures tend to collapse the mandibular arch in response to the medial pterygoid and mylohyoid musculature. A rigid technique necessitates application of arch bars and temporary intraoperative interdental wiring to establish the proper occlusion. Open reduction with rigid internal fixation of symphyseal fractures may be accomplished with a variety of hardware configurations. These include an inferior border contoured mandibular fracture plate with mandibular arch bar, an inferior locking or nonlocking reconstruction plate, an inferior locking or nonlocking 2.0-mm mandible plate and a superior border monocortical tension band, two lag screws, or two properly placed 2.0-mm miniplates (Fig. 80.10) (15,17–20). Inferior border plates placed in these regions should be slightly overbent to prevent lingual splay of the fracture resulting in widening at the mandibular angles and transverse occlusal discrepancies. Recent biomechanical investigations indicate that the lag screw technique addresses the issue of lingual cortex reduction and likely provides the most stable construct for symphyseal fractures (17,18). Nevertheless, knowledge of multiple techniques is required to address the variety of fracture patterns of the mandibular symphysis for predictable outcomes.

Body

Fractures of the body are located between the canine and the last molar (Fig. 80.1). Fixation of body fractures is accomplished by the same means as fractures of the symphysis; however, special attention must be directed to the inferior alveolar/mental nerve and dentition. In addition, the marginal mandibular branch of the facial nerve is at risk when an external approach is utilized. Rigid fixation can be easily applied to body fractures using a retromandibular or submandibular approach, or via an intraoral approach with or without transbuccal trocars.

Hardware configurations for mandibular body fractures are similar to those for the fixation of symphyseal fractures with the exception of lag screws, which are less commonly indicated. Anterior body fractures coursing through the mental foramen can be managed by placing an inferior bicortical mandibular plate (2.0 to 2.4 mm) and a superior border monocortical tension-band plate. If the fracture occurs in an edentulous area of the body, or an atrophic situation exists, consideration of load-bearing fixation is recommended due to the increased leverage produced by any remaining anterior dentition on the hardware construct.

Angle

Fractures of the mandibular angle occur posterior to the second molar within the retromolar triangle (Fig. 80.1). Fractures of the angle are associated with a high incidence of infection and often require ORIF due to the relatively small cross-section of bone in this region, and the

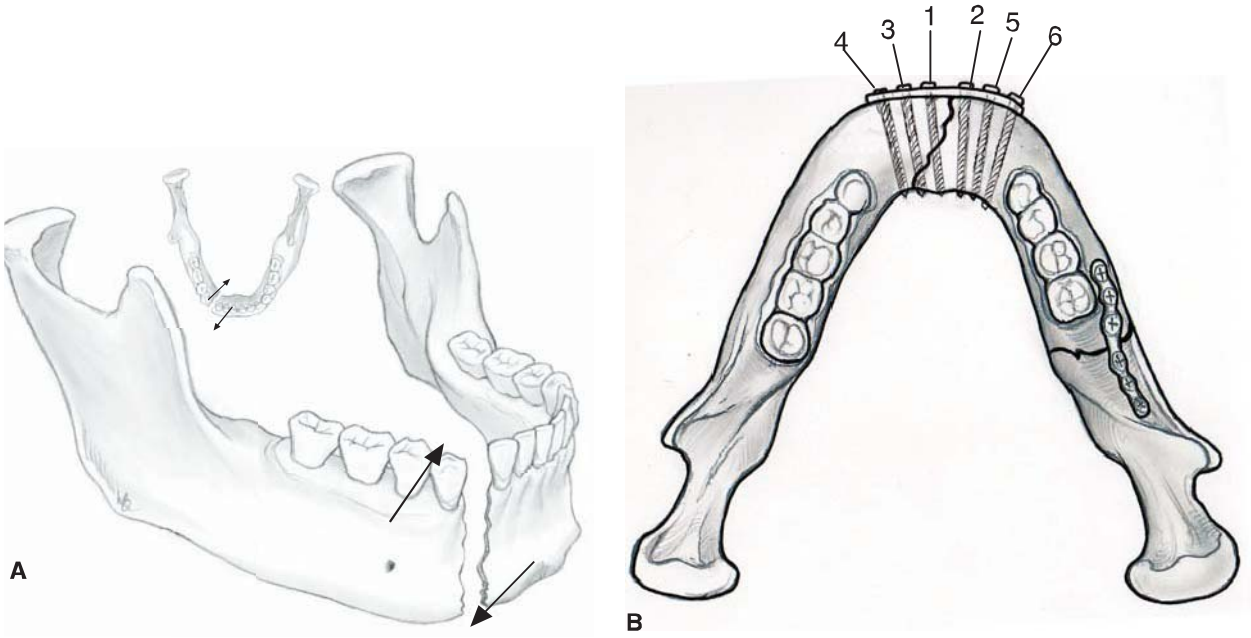


Figure 80.10 **A:** An oblique symphyseal fracture. **B:** Initial compression and reduction at the superior mandibular border provided by the arch bar. The 2.0- or 2.4-mm mandibular reconstruction plate is slightly overbent and is applied with bicortical screws. The screws are numbered in the order that they should be placed.

oblique and irregular fracture configuration. Additionally, impacted wisdom teeth in this area increase the risk of fracture, complicate treatment, and may require removal in the event reduction is not possible or the tooth is loose (21,22). Transoral placement of a single malleable miniplate (noncompression with 2.0-mm monocortical screws) along the superior border of the angle has been commonly used with excellent results (Fig. 80.11A and B) (21,23,24). Two-miniplate rigid fixation of the angle also produces acceptable results and can be accomplished thorough an intraoral approach. These two miniplates can be placed in either a biplanar or monoplanar manner, although studies confirm that the biplanar method is more stable (Fig. 80.11A and C) (25).

The external approach can also be used to apply a variety of hardware configurations: an inferior border locking or nonlocking reconstruction plate with or without a monocortical superior tension plate, an inferior bicortical dynamic compression plate with neutral screw placement and a superior monocortical tension plate, or two monoplanar miniplates. These systems can be applied using an intraoral approach with the aid of transbuccal trocars as well. Although many technical variations for ORIF of mandibular angle fractures are effective, selection should be based on the availability of equipment and the experience of the surgeon.

Condyle

The condyle is classified as the area superior to the line extending from the sigmoid notch to the posterior border of the mandible (Fig. 80.1). The goals of treating condylar fractures include normal range of motion without pain, preinjury occlusion, and symmetry of the mandible. The treatment of fractures of the mandibular condyle include open and closed techniques; however, considerable controversy exists regarding optimal management (7,26–28). Generally, nondisplaced condyle fractures are treated conservatively with arch bars and guiding elastics. Brief periods of IMF have been advocated; however, no consensus exists regarding the optimal duration (7,29). As noted previously, long periods of IMF can result in TMJ ankylosis and limited opening and are therefore not recommended. Early mobilization with guiding elastics to support the occlusion allows for return to preinjury range of motion and increased patient comfort (6,7). The indications for open reduction of condylar fractures remain debatable; however, the classic indications summarized in Table 80.3 provide a framework for treatment consideration. Nevertheless, there are many advocates for ORIF of mandibular condylar fractures, as several investigations have demonstrated faster recovery with improved occlusion, excellent function, and improved facial symmetry (30,31). Condylar, subcondylar, and ramus fractures can each be stabilized with a single 2.0-mm mandibular miniplate with at least two screws on each side of the fracture line. Complications that can occur with open treatment of condyle fractures include hematoma, facial nerve damage, infection, auriculotemporal nerve dysfunction, Frey syndrome, and scarring. Recent transoral endoscopic treatment of condylar fractures offers an excellent approach and avoids facial nerve injury (28,32,33). The technique requires specialized equipment and can be technically challenging until significant surgical experience is achieved (23,25–27). It should also be noted that the transoral technique is not without complications (34).

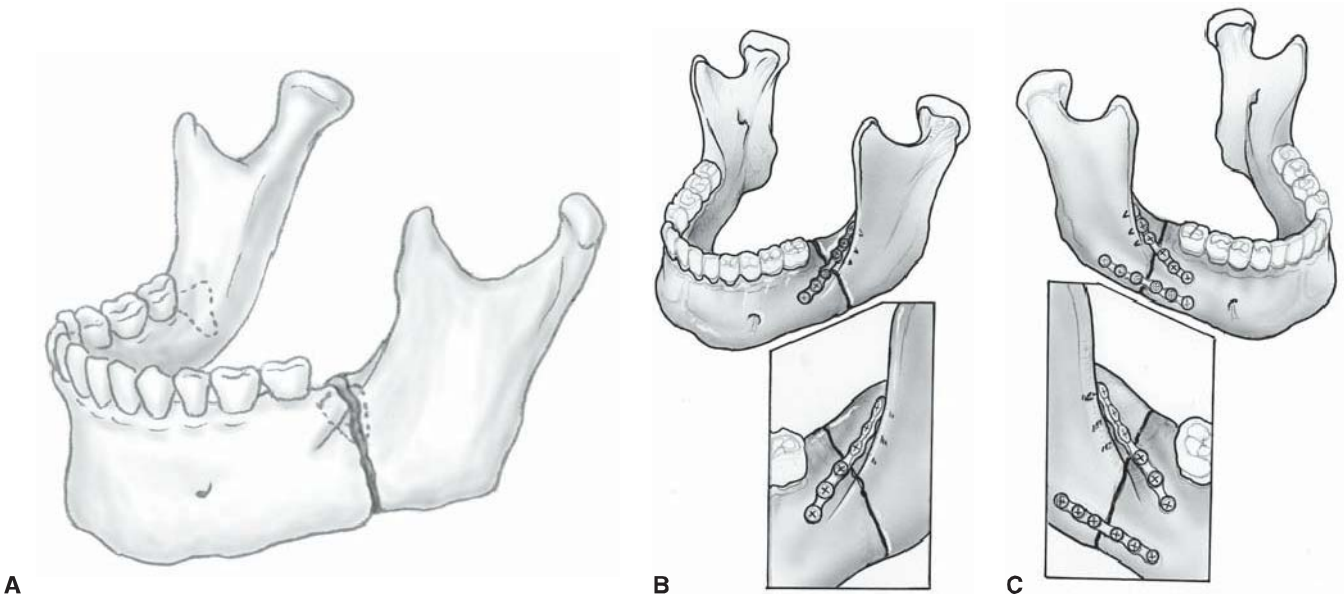


Figure 80.11 **A:** Transverse angle fracture with minimal displacement. **B:** Transoral placement of a single malleable 2.0-mm miniplate with monocortical screws near the superior border of the angle. **C:** Two 2.0-mm miniplate rigid fixation of the angle fracture placed in a biplanar manner.

TABLE 80.3 INDICATIONS FOR OPEN REDUCTION OF MANDIBULAR CONDYLE FRACTURES

Absolute Indications
- Displacement into the middle cranial fossa
- Foreign body in the joint capsule (e.g., gunshot wound)
- Lateral extracapsular deviation of the condyle
- Inability to open mouth or achieve occlusion after 1 week
- Open fracture with the potential for fibrosis

Relative Indications
- Unilateral or bilateral condylar fractures associated with comminuted midfacial fractures
- Comminuted symphysis and condyle fracture with loss of teeth
- Displaced fracture resulting in an open bite or retrusion in medically compromised, mentally unstable or retarded adults
- Displaced condyle with edentulous, or partially edentulous, mandible with posterior bite collapse

Adapted from Zide MF. Open reduction of mandibular condyle fractures. Indications and technique. *Clin Plast Surg* 1989;16(1):69–76, with permission.

Although intracapsular condylar fractures have been traditionally managed with closed techniques due to the risks of necrosis and TMJ arthrosis, open techniques have been applied to these situations with reasonable results, and the optimal management remains elusive (26,27,35).

Ramus

The ramus is the area superior to the angle and inferior to an angle formed by two lines with the apex at the sigmoid notch (Fig. 80.1). In many situations, ramus fractures may be treated closed when they occur in isolation as they are seldom displaced and splinted by the pterygomasseteric sling. Traditional techniques of internal fixation may be used in situations of displacement or comminution of the mandibular ramus.

SPECIAL CONSIDERATIONS

External Fixation

Historically, stabilizing mandibular defects and fractures by external fixation was frequently used in contaminated gunshot wounds or infections resulting in the loss of mandibular continuity (Fig. 80.12A). Although current locking reconstruction technology addresses many of these situations (Fig. 80.12B), external fixation provides the advantage of fragment stability and allows wound debridement and stabilization prior to rigid internal fixation and is appropriate in some situations. Following the resolution of infection and the healing of the soft tissue envelope, reconstruction can be accomplished using a traditional reconstruction plate with bone grafting or free tissue transfer.

Management of Teeth in the Line of Fracture

It is generally agreed that previously healthy teeth can be left in the line of fracture if the tooth is stable and the periodontal ligament associated with the tooth is reasonably intact. Conversely, teeth that have suffered structural damage, periodontal ligament damage compromizing the blood supply, or which prohibit proper fracture reduction should be removed. Removal of previously healthy third molars in the line of angle fractures can contribute to fracture instability and distraction and, therefore, are retained but monitored for infection in the postoperative period (22).

Edentulous Fractures

Edentulous fractures are more common in older patients (Fig. 80.13). Historically, the management of an edentulous mandibular fracture was often closed reduction in which arch bars are applied to the dentures or Gunning splints to allow IMF. This technique has several disadvantages including poor mandibular segment control and poor reduction of the fracture. Current treatment of edentulous mandible fractures is performed with open reduction internal fixation using a reconstruction plate in the majority of cases. Locking reconstruction plates are generally recommended; however, multiple options have been used with success provided load-bearing fixation is achieved (36–38). Severely atrophic mandible fractures (less than 10 mm vertical height) have the greatest risk of complications, and consideration to primary bone grafting should be entertained provided there is no evidence of active infection (39). A variety of bone grafting techniques have been used in the treatment of atrophic mandibular fractures, including corticocancellous iliac crest and free tissue transfer (39–42).

Pediatric Fractures

Pediatric mandibular fractures represent a somewhat unique situation due to the presence of the unerupted dentition and the growth potential in this population. In addition to providing areas of weakness prone to fracture, unerupted tooth buds also present challenges for fixation and screw placement. When compared to the adult situation, a significantly larger proportion of pediatric mandibular fractures can be managed by means of closed reduction. Some scenarios such as nondisplaced, stable fractures may be managed with soft diet and observation. Placement of standard archbars during the mixed dentition stage can be problematic, and involvement of the dentist/orthodontist to provide anchorage devices to facilitate closed management is recommended. Functional appliance therapy with guiding elastics, begun immediately after the injury, is useful in maintaining proper occlusion and restoring mandibular position. Rigid and open techniques are considered

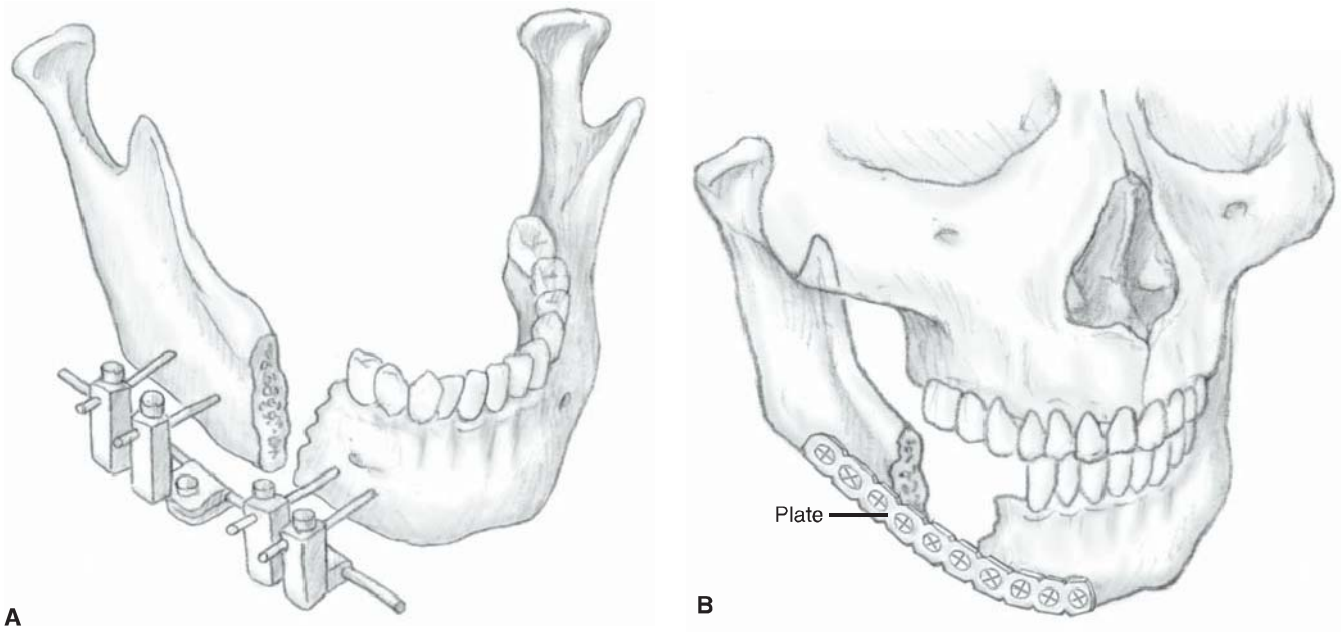


Figure 80.12 **A:** Application of an external fixation system allows alignment of the fracture or defect, appropriate for some situations in which rigid internal fixation is contraindicated. **B:** 2.4- to 2.7-mm reconstruction plate (generally locking) used to bridge a mandibular defect.

in situations of severe displacement, occlusal instability, and comminuted fractures. The selection of hardware is similar to the adult situation; however, consideration for monocortical techniques to avoid the developing dentition, inferior border placement of hardware, and resorbable technology is warranted to avoid complications. The most dreaded complication of pediatric condyle fractures is the development of ankylosis of the TMJ, which can result in growth disturbances producing facial asymmetry/deformity. Consideration for open reduction of severely displaced, bilateral subcondylar fractures is warranted to prevent loss of facial height, mobility, and anterior open bite if closed techniques fail. Regardless of whether closed or open techniques are utilized, early mobilization reduces the risk of limited mobility due to fibrosis/ankylosis, and should be a tenet of treatment.

Removal of Hardware

The need for hardware removal has been somewhat controversial historically; however, current titanium fixation systems are extremely biocompatible and form an intimate association with bone that makes plate removal technically difficult and probably unnecessary in the majority



Figure 80.13 The atrophic, edentulous mandible often fractures at the midbody, in the area of minimal bone height.

of situations. Mandibular fractures require hardware removal more commonly when compared to midface fractures. Infection and mobility of the hardware are the most common indications for hardware removal after ORIF of mandibular fractures (43). In the pediatric situation, controversy continues regarding titanium plate removal with concerns of long-term growth disturbances, systemic titanium absorption, and "false migration" of hardware during growth (44,45). Nevertheless, while hardware removal is often recommended, the literature indicates that long-term retention of titanium hardware has minimal effects on mandibular growth with the possible exception of the condylar growth center (46,47).

COMPLICATIONS

Table 80.4 lists complications of mandibular fractures. Total complication rates have been reported at approximate rates of 15% to 40% (16,25,34,48–50). The most common factors contributing to poor outcomes in fracture repair are the absence of teeth, medical comorbidities, poor patient compliance, delay in presentation, and trauma severity. The infection rate after ORIF of mandibular fractures is about 6% to 10% provided appropriate preoperative antibiotics are administered. As noted previously, postoperative antibiotics are likely unnecessary in the majority of cases (5). Marked malocclusion immediately after rigid fixation is usually caused by an error in fragment alignment and is permanent unless corrected by prompt revision surgery. Standard orthognathic surgical techniques can be used to correct malocclusion caused by late malunion of jaw fractures. Although posttraumatic TMJ ankylosis is rare with mobilization, the true incidence of TMJ dysfunction after mandibular fracture is difficult to establish. There are, however, fracture patterns related to the condyle, which likely result in significant joint disturbance (51). Sensory disturbances of the inferior alveolar nerve are relatively common after mandibular fracture, but traumatic neuroma formation is rare.

EMERGENCIES

Emergencies related to mandibular fractures are relatively rare and are listed in Table 80.5. Bilateral fractures of the mandibular body can cause posterior displacement of the anterior mandibular arch owing to the presence of the suprahyoid musculature. This can precipitate airway compromise, especially when the patient is in the supine position. Immediate intervention is required to establish a stable airway and includes patient repositioning, wire stabilization, intubation, or tracheotomy. Cerebrospinal otorrhea can herald displacement of a condylar head into the middle cranial fossa. Such an injury can be associated with a dural tear; neurosurgical consultation and prompt ORIF is recommended. Concomitant injury to the adjacent internal carotid artery occasionally occurs in conjunction with fractures of the condylar neck. A severely displaced fracture can prompt further radiologic investigation of the adjacent carotid artery. Gross hemorrhage rarely accompanies mandibular fracture, but troublesome bleeding occasionally arises from the inferior alveolar artery within the mandibular canal. Ligation of this vessel is difficult, and temporary reduction of the fracture effectively tamponades the bleeding site.

FUTURE CONSIDERATIONS

Further improvements in endoscopic and hardware technology will drive improvements in the treatment of facial fractures (28,32,34,52). Resorbable fixation systems for internal fixation are an attractive option in the treatment of adult and pediatric mandibular fractures and is currently under investigation (53,54). Improved imaging modalities, stereotactic image guidance, and medical modeling will likely improve the treatment of acute fractures and the correction of late deformities. Improved biotechnology, such as bone morphogenetic protein, will likely contribute to improved bone healing in these situations (55–58).

TABLE 80.4 COMPLICATIONS MANDIBULAR FRACTURES

Infection
Malocclusion, malunion, nonunion
TMJ ankylosis
TMJ dysfunction
Sensory disturbances of inferior alveolar nerve
Trismus
Tooth loss
Facial nerve damage
Poor cosmetic outcome

TABLE 80.5 EMERGENCIES MANDIBULAR FRACTURES

Airway obstruction
Condylar displacement into middle cranial fossa
Adjacent injury to internal carotid artery
Hemorrhage
Severed facial nerve
Anesthesia or paresthesia of lower lip and chin

HIGHLIGHTS

- Fractures of the condylar neck are associated with anteromedial displacement of the condyle owing to the action of the lateral pterygoid muscle.
- Unilateral condyle fractures produce a characteristic open bite on the side opposite the fracture.
- During opening, the chin deviates toward the side of a fractured condyle.
- Bilaterally displaced fractures of the condyles are associated with a symmetric anterior open bite.
- Almost all fractures of the mandibular angle are unfavorable and necessitate open reduction.
- Vertically unfavorable angle fractures result in medial displacement of the proximal fracture segment.
- Normal maximal interincisal opening is approximately 40 to 50 mm.
- The majority of stable teeth in the line of a mandibular fracture are preserved.
- Posttraumatic ankylosis of pediatric condylar fractures produces severe functional disturbances and developmental facial asymmetry.
- Bilateral fractures of the mandibular body, especially in edentulous patients, can allow the anterior arch of the mandible to fall posteriorly and may obstruct the airway.
- When malocclusion is detected immediately after open reduction with rigid fixation, revision surgery is indicated to correct errors in fracture alignment.

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Midface Fractures

81

Brendan C. Stack Jr *Francis P. Ruggiero*

ANATOMY

Buttresses

The structure of the midfacial skeleton is related to its mechanical adaptation to forces generated by mastication. Forces of up to 200 pounds per square inch are developed during chewing. Additionally facial contours result from paranasal sinus pneumatization. These sinuses are involved in voice resonance, act as shock absorbers, and account for an approximate lightening of the head of 1 kg if they have otherwise been solid bone. The concept of *buttresses* describes the relatively stronger areas of the midfacial skeleton that bear the bulk of the vertically oriented forces produced during mastication. These forces are absorbed and transmitted to the base of skull (Fig. 81.1) (1).

The vertical buttress system has seven components, including three paired pillars and one unpaired structure: (a) The *nasomaxillary* (NM) (aka medial, nasofrontal) buttresses extend from the anterior maxillary alveolus along the pyriform aperture and medial orbit, through the nasal and lacrimal bones to the frontal bone. (b) The *zygomaticomaxillary* (ZM) (aka lateral) buttresses extend from the lateral maxillary alveolus along the lateral maxilla to the malar eminence of the zygoma, then superiorly along the lateral orbital rim to the frontal bone. (c) The *pterygomaxillary* buttresses extend posteriorly from the maxilla to the pterygoid plates of the sphenoid bone. (d) A midline buttress, consisting of the vomer and perpendicular plate of the ethmoid bone, connects the palatine process of the maxilla to the frontal bone (2).

The mostly curved, vertical buttresses are reinforced by a number of horizontal buttresses. These include the frontal bar (superior orbital rims plus the frontal bone), the inferior orbital rims, and the maxillary alveolus, among others (3).

Maxilla

The maxilla consists of paired bones also called maxillae. Each has a hollow body that is the maxillary antrum. Projections from the maxillary body extend superiorly and medially to the frontal and nasal bones, and laterally to the zygoma. The inferior and medial palatine process of the maxilla forms the bulk of the primary hard palate. The alveolar process of the maxilla extends inferiorly and holds the roots of the upper teeth (4).

The bone of the maxilla is for the most part quite thin. The lateral wall of the maxillary antrum however includes a wedge of thicker, compact bone. It is in this area that the ZM buttress arises. It appears that the greatest occlusal load is borne by this buttress.

Zygoma

The zygoma is a relatively sturdy bone that is important structurally, as an integral component of the buttress system, and also forms the aesthetically vital malar prominence. It is related to the surrounding facial bones via articulations with four bones—the frontal, maxillary, temporal, and sphenoid bones.

The superficial projections of the zygoma define two critical external arcs of facial contour (Fig. 81.2). The vertical arc follows the course of the ZM buttress (concave), running from the zygomatic process of the frontal bone, over the zygoma itself to the lateral antral wall of the maxilla (convex). The horizontal convex arc runs from the maxilla in the area of the lacrimal fossa, across the zygoma, to the zygomatic process of the temporal bone. The point of intersection of the vertical and horizontal arcs defines the location of the malar prominence.

The deep projections of the zygoma are the sphenoid projection, which articulates along the lateral orbital wall with the orbital plate of the sphenoid bone, and the orbital floor projection, that articulates with the orbital surface

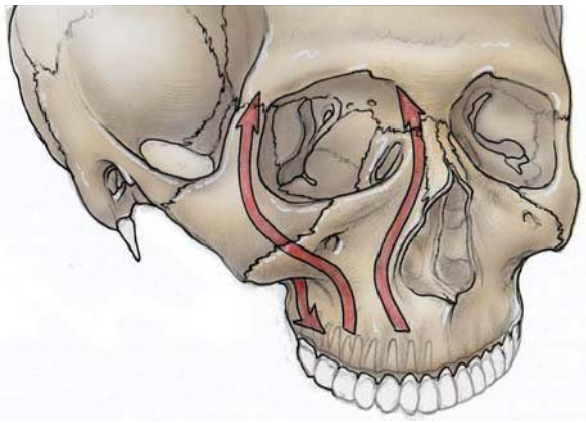


Figure 81.1 Vertical buttresses of the facial skeleton: The NM (medial), ZM (lateral), and pterygomaxillary buttresses of the facial skeleton are illustrated.

of the maxilla along the lateral aspect of the orbital floor. The zygoma therefore constitutes the majority of the lateral orbital rim and wall, and a portion of the inferior rim and the orbital floor.

PATHOPHYSIOLOGY/MECHANISM OF TRAUMA

With the midfacial skeleton adapted to the vertical forces of mastication, it is the force delivered at other vectors that cause the bulk of midface fractures. Common etiologies of midfacial fractures include motor vehicle accidents, assaults, and sporting events (5).

Maxilla

Le Fort Fractures

Rene Le Fort introduced a classification of midfacial fractures on the basis of cadaver experiments he performed in the early part of the 20th century (6). He noted that fractures tend to occur at characteristic locations, which correspond with relatively weak areas of the facial skeleton.

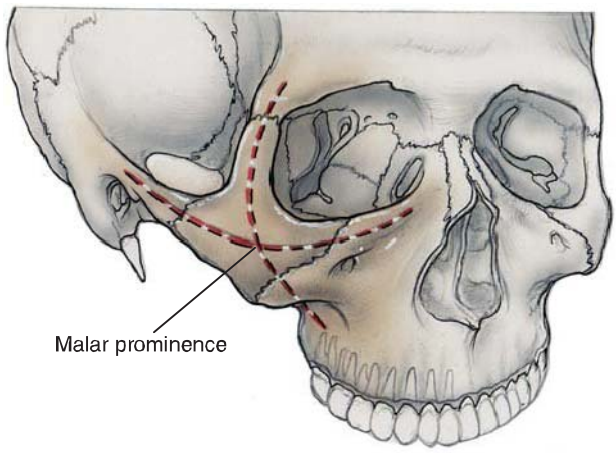


Figure 81.2 Vertical and horizontal projections of the zygoma. Their intersection defines the location of the malar prominence.

Le Fort Level I fractures are transverse fractures separating the maxillary alveolus from the rest of the midfacial skeleton (Fig. 81.3).

These injuries generally result from anterior force directed at the lower midface. The *NM* and *ZM buttresses* are disrupted (7). The fracture line then extends transversely through the maxillary sinus and nasal septum and posteriorly across the pyramidal process of the palatine bone and pterygoid processes of the sphenoid bone (2).

Le Fort Level II fractures create a pyramidal NM fragment separate from the upper craniofacial skeleton. They result from either direct anterior force against the midface or inferior impact at the mandibular symphysis transmitted to the midface via the dentoalveolar segments of the mandible. Once again the NM and ZM buttresses are disrupted, this time more superiorly than the Le Forte I level. The fracture line extends from the nasal root via the lacrimal bone and medial orbital wall, then anteriorly along the orbital floor to the infraorbital canal. From this point, the fracture line follows the ZM suture to anterolateral maxillary wall. Posteriorly, the fracture line passes across the infratemporal surface of the maxilla through the lower pterygoid plates (7,8).

Le Fort Level III fractures, which result in complete separation of facial skeleton from the skull base, are less common. They usually result from anterior force directed obliquely to the plane of the vertical buttresses (1). The vertical buttresses are disrupted at their superiormost extent. The fracture line extends through the root of the nose, across the lacrimal bone and medial orbital wall, across the orbital floor to the inferior orbital fissure. From this point, one fracture line traverses the lateral orbital wall as it approaches the frontozygomatic suture; a second line passes over the back of the maxilla to the lower pterygoid plates. An additional fracture line through the zygomatic arch completes the craniofacial dysjunction (8,7).

In clinical practice, the patterns of maxillary fractures encountered are rarely as orderly as the above suggests. Le Fort's original work demonstrates that he was certainly not unaware of this. The level I to III classification scheme is a distillation of some of his most significant experimental observations. In his experiments, and most definitely in real-life trauma, force is delivered unevenly to each side of the face, at varying angles, and at variable locations. The resulting fractures may be asymmetric from one side of the face to the other (i.e., Le Fort II on the left, Le Fort III on the right), may combine with other fractures to create a more complex pattern (e.g., a Le Fort II fracture and a zygomaticomaxillary complex (ZMC) fracture on the same side of the face constituting a "complex" Le Fort III fracture), or may be maxillary fractures not described by the classification at all.

Other Maxillary Fractures

Anterior forces localized between the nose and malar prominence may produce anterior maxillary wall fractures. Significant force delivered to the lower anterior midface, in addition to generating the classic fracture patterns described by Le Fort, may less commonly cause fractures

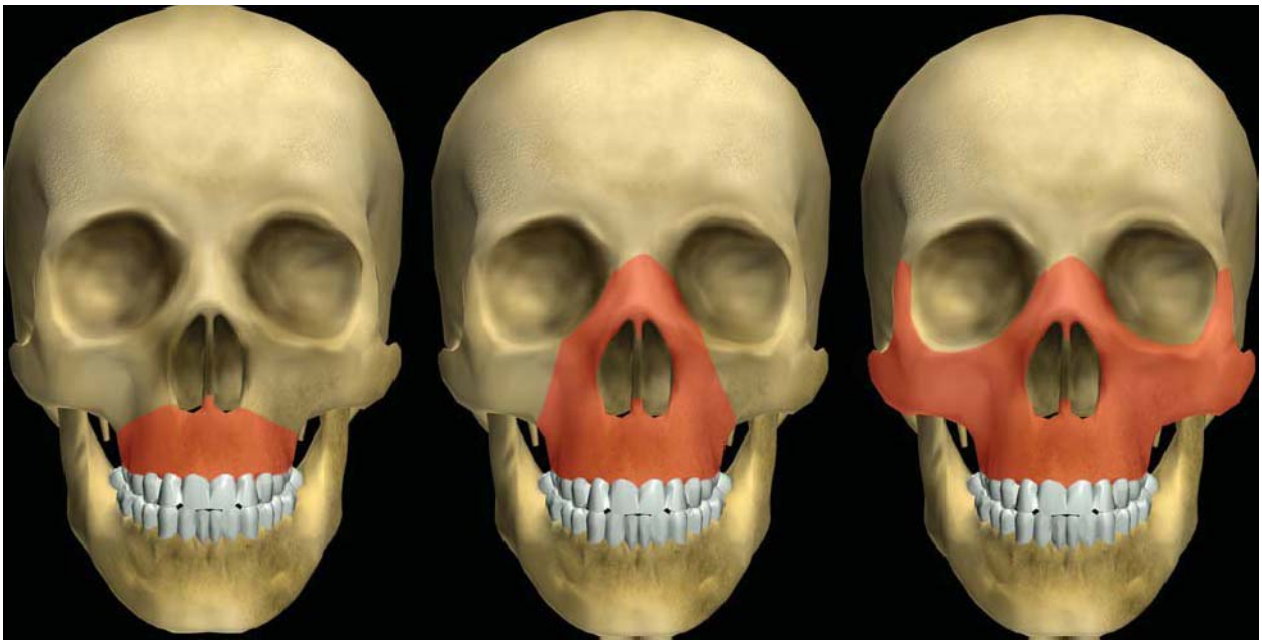


Figure 81.3 Anterior view of facial skeletons. Shaded areas correspond to Le Fort levels I, II, and III fractures. LifeART image copyright (c) (2012) Lippincott Williams & Wilkins. All rights reserved.

of the palate. While they may occur in isolation, *palatal fractures* tend to accompany extensive facial injuries (9). Most often, the palate is fractured in a sagittal fashion, in a paramedian plane (see Fig. 81.11). Fractures in a number of other orientations and locations are also possible (10). Clinical indicators of palatal fractures include palatal lacerations, lip lacerations that extend into the gingivolabial sulcus, maxillary tooth loss, and malocclusion.

Palatal fractures, and in particular those oriented sagittally, alter the width of the maxilla and permit the rotation of the maxillary dentoalveolar segments. One of the fundamentals in management of severe facial fractures is the intraoperative restoration of normal maxillomandibular occlusion, with anatomic reduction of fractures following from this basis. Palatal fractures, by complicating the restoration of occlusion, can confound this strategy if not appropriately addressed first (10,11).

Zygoma

Zygomaticomaxillary Complex Fractures

Various terms are used to describe fractures involving the zygoma and its articulating bones. These include malar fractures (12), zygoma or zygomatic fractures (13), ZMC fractures (14), tripod fractures (15), tetrapod fractures, trimalar fractures, zygomatico-orbital fractures (16), and orbitozygomatic fractures (17). All of these terms emphasize certain salient features of this type of injury. For example, the term "tripod" underscores the observation that blunt force to the zygoma tends to disrupt not the zygoma itself, but rather, its three superficial articulations, to the frontal, maxillary, and temporal bones; the intact body of the zygoma has a tripod-like appearance (Fig. 81.4). The terms "zygomatico-orbital fracture" and "orbitozygomatic fracture" stress that because it forms portions of the lateral and inferior orbit, fractures that involve the zygoma are necessarily also orbital fractures. The most important point for the surgeon-in-training to understand is that all of the terms refer to the same injury. Henceforth within this chapter, the term *ZMC fracture* is used for uniformity.

ZMC fractures generally result from blunt trauma to the malar eminence, the most prominent feature of the lateral midface. They are the second most common facial fracture, after nasal fractures (18). Routinely, they involve disruption of the projections of the zygoma. The severity of ZMC fractures seems most related to the force and velocity of impact (14). In the most severe injuries, the sturdy zygoma itself may be fractured.

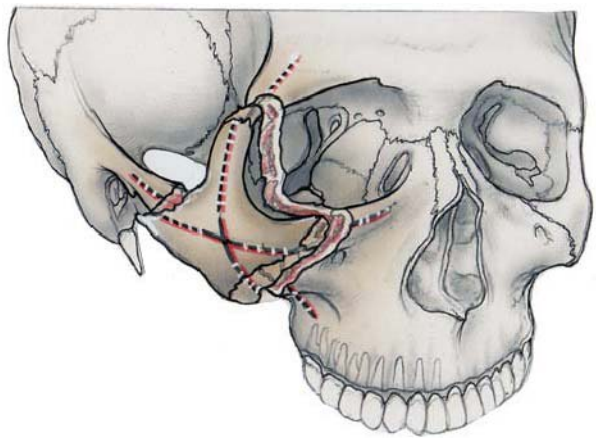


Figure 81.4 ZMC fracture—ZMC fracture, illustrating the tripod-like appearance of the displaced zygoma, as well as the orbital involvement in the injury.

A distinctive clinical feature of ZMC fractures is orbital injuries that differ somewhat from those found in isolated orbital trauma. In a typical orbital floor blowout fracture, orbital volume expands; the extent of expansion predicts the likelihood of enophthalmos and diplopia, and the need for surgical repair. In ZMC fractures, the typical inward and medial displacement of the zygoma often results in a *decrease* in orbital volume (19). Therefore, acute enophthalmos is rarely seen at the time of presentation of a ZMC fracture. The need for floor exploration/repair in ZMC fractures must also take into account the effect that reduction will have on orbital volume.

Another common clinical feature of ZMC fractures is facial numbness and paresthesia. This is caused by damage to the infraorbital nerve (V_2) at its exit from the midportion of the inferior orbital rim, which lies directly within one of the fracture lines. These symptoms are present in as many as 90% of ZMC fracture patients at presentation (20). The symptoms resolve spontaneously in many, but not all, patients after disimpaction of the fragments.

Zygomatic Arch Fractures

The zygomatic arch is most frequently disrupted as a component of a ZMC fracture (21). Less common, and distinct from this type of injury, is the isolated zygomatic arch fracture. Isolated arch fractures result from a direct lateral force to the arch, most frequently the result of a motor vehicle accident or fisticuffs (21).

Several fracture patterns may be seen in isolated arch injuries. The most common pattern is two mobile fragments of arch resulting from a total of three fractures. In this pattern, the fragments are displaced medially, in a v configuration (Fig. 81.5).



Figure 81.5 Axial bone-window CT demonstrates the most common pattern of isolated fractures of the zygomatic arch: a total of three fractures create two fragments, displaced medially in a V-like configuration.



Figure 81.6 Patient who suffered an isolated fracture of the left zygomatic arch after direct blow from a batted softball. Depression of the lateral midface is quite visible in this case.

Patients with isolated arch injuries, particularly those with the characteristic v pattern, will have a palpable, and frequently visible, deformity of the lateral midface (Fig. 81.6). This finding is often accompanied by a degree of trismus, resulting from the impingement of the fracture segments on the underlying coronoid process of the mandible or the temporalis muscle.

PATIENT EVALUATION

Evaluation of the patient is the critical first step to assure complete and accurate fracture repair and optimal aesthetic results. There may be a temptation to truncate the physical exam, in deference to the almost universal use of admission pan computerized tomography (CT) for trauma patients. Although high-resolution CT has been a great advance in the diagnosis, treatment, and postoperative critical evaluation of facial trauma, imaging is not a substitute to the laying on of hands in a focused head and neck trauma evaluation. Poor aesthetic results should not be accepted in facial fracture repair, as the primary motivation for their repair in many cases is cosmesis.

Physical Exam

Regardless of the existence of scans, or the putative diagnosis offered by the consulting physician, each new facial trauma patient should be evaluated in a systematic fashion, beginning with the history and physical exam.

All facial trauma patients are trauma patients, and are best served by the standardized *Advanced Trauma Life Support (ATLS)* approach taught by the *American College of Surgeons*. This evaluation process ensures the orderly evaluation and *prioritization of treatment of the most lethal injuries first*. All residents and those practicing surgeons who manage facial trauma must be familiar with the trauma

evaluation process, and should consider certification in ATLS. We shall highlight portions of the trauma evaluation process that are particularly germane to the care of the maxillofacial trauma patient.

Airway issues can potentially be seen with any head and neck trauma sufficient to result in midface fractures. While isolated midfacial trauma is unlikely to compromise the airway, accompanying mandible fractures are particularly significant in this regard. A loss of continuity of the mandible arch results in retrusion of the tongue and larynx, which may create an obstructed upper airway. When evaluating such a patient, consideration should be given both to immediate need for airway management and its implications for fracture repair. If elective intubation (as opposed to an emergent airway) is possible, alternatives to oral intubation should be entertained if maxillomandibular fixation (MMF) will be required for fracture repair.

Concomitant *C-spine injuries* are also common in patients with facial fractures, with an incidence approaching 10% (22). All facial trauma patients should thus be managed with C-spine precautions as proscribed by ATLS, even though this can significantly complicate the evaluation and management of the facial injuries.

Neurologic deficits should be sought and well documented if they exist. Of particular pertinence in the facial trauma patient are cranial neuropathies. A regimented exam of cranial nerves II–XII should be performed. Findings of significance that may impact the timing and approach to repair include neuropathies affecting the eye (cranial nerves II, III, IV, and VI), the trigeminal nerve, and the facial nerve.

Eye-related cranial neuropathies might make surgery an emergency, especially if associated with an open globe. Conversely, the presence of a compromised optic nerve *(optic neuropathy)* may delay facial fracture management. More details of the ophthalmologic evaluation of facial trauma patients are presented below.

Trigeminal nerve injury is not an emergency *per se* but must be documented preoperatively. If not, the assumption is made that it was a surgical complication and this has been a point of litigation specifically related to facial fracture repair. Facial nerve dysfunction is usually related to a temporal bone fracture or extensive facial soft tissue injury. It is important to know if the nerve was functioning upon presentation or not. This will help with the decision to explore and perhaps repair the nerve immediately or to treat expectantly.

The Facial Assessment

There are key elements of the exam that must be appreciated and documented preoperatively. These elements will help the surgeon appreciate the full extent of the facial trauma as well as avoid problems with litigation that is a potential element in trauma cases.

The appearance of the face is examined. Is it wide or long? Is it asymmetrical? It is helpful but often difficult to obtain current pretrauma photos to assist with this assessment. Appreciation of any lacerations is important for planning surgical access as well as to focus exam for cranial nerve deficits. A full facial movement and sensory examination is also advised regardless of hard or soft tissue injury.

Overlying edema and patient discomfort may limit the utility of palpation. Still, palpation of the facial skeleton is mandatory, and can provide a more thorough understanding of the location of fractures and the extent of their displacement and mobility. A bimanual exam of the face should be performed. Placing gloved fingers in the mouth while stabilizing the head and face at various levels is used to examine for dentoalveolar and palatal stability, as well for the Le Fort fractures. Both visual and subjective (patient's report) occlusal changes are vital to obtaining a successful reduction of facial fractures. Finally, are there exposed fracture elements and what is the status of the soft tissue? Will there be adequate soft tissue for reduction and closure of the fracture?

The Ophthalmologic Evaluation

The ophthalmologic exam of facial trauma patients deserves special emphasis and should never be deleted. Ocular injury is common in the facial trauma patient, at the time of initial injury, during the course of surgical repair, and even postoperatively. These injuries may be particularly devastating for patient and surgeon alike.

Early and complete ophthalmologic evaluation of every patient who has sustained a ZMC fracture (or any fracture involving the orbit) is an ideal yet often unrealized goal. The incidence of major (potentially blinding) ocular injury in ZMC fractures that require repair has been reported as 10% (23). Reconstructive surgeons must be sensitive to the possibility of direct ocular trauma and obtain consultation as indicated. A minimal preoperative examination includes testing of visual acuity (subjective and objective in both eyes), pupillary function, and ocular motility; inspection of the anterior chamber for hyphema; and visualization of the fundus for gross disruption. The presence of an *afferent pupillary defect* should be specifically sought, as this is a sensitive indicator of the presence of *optic neuropathy*. A decrease in visual acuity, alteration in color perception, or any abnormality observed on the other portions of this screening examination warrants detailed examination by an ophthalmologist before reconstruction of the bony injuries is undertaken.

COMPUTED TOMOGRAPHY

Evaluation of a patient with midface trauma has been greatly improved by the use of high-resolution CT. One millimeter slice thickness has become standard in many institutions, allowing for excellent coronal and sagittal

TABLE 81.1 DIAGNOSIS/EVALUATION

- CT scan is the "workhorse" imaging study for the evaluation of midfacial trauma.
- Review of facial CT scan should include the status of the buttress system, zygomatic arches, orbital volume, and herniation of orbital contents.
- Direct coronal imaging for orbital floor and skull base imaging.
- Newer reformatting software of thin axial slice images offers high-quality image and avoids cervical extension.
- Sagittal imaging can facilitate orbital trauma evaluation.
- Postoperative CT imaging can document anatomic reduction.
- Basic evaluation of visual function (and documentation thereof) should precede operative management.

CT, computed tomography.

TABLE 81.2 TREATMENT

- Early repair of midface fractures prevents soft tissue contracture that can be difficult to normalize in a delayed approach.
- Meticulous attention to soft tissue closure and facial soft tissue redraping is essential to achieving a pretraumatic facial appearance.
- Anatomic reduction prior to plate fixation is key. Rigidly fixated, malreduced structures will result in a persistent facial deformity requiring revision surgery.

reconstructions. This modality is the "work horse" for evaluation of midface trauma. Axial and coronal scans identify fracture lines throughout the entire facial skeleton (Table 81.1). The expense of CT evaluation of patients with facial fractures other than simple nasal and mandibular fractures appears justified and can be done in virtually all emergency rooms (24).

Using the CT images, the buttress system, particularly the vertical struts, must be systematically inspected preoperatively to document the degree of malalignment because of fracture fragment displacement. Fracture lines themselves through the buttresses do not mandate open reduction, but comminution, gross malalignment, and instability on physical exam all strongly suggest the need for reduction of the fractures in order to restore facial length and projection. Computed tomographic scans can show fractures of the condylar head, condylar neck, and vertical ramus of the mandible. The status of these structures must be known before fracture dislocations of the maxilla are placed into occlusion with the mandible.

The arcs of contour of the zygoma (see Fig. 81.2) are evaluated for decisions about the need for surgery and the appropriate operative approach. The CT finding of comminution and dislocation of both ends of the horizontal arc of contour indicates that exact reconstruction of the orbitozygomatic complex will be a challenge, and consideration should be given to additional access incisions, including an open approach to the zygomatic arch via a coronal incision.

FRACTURE MANAGEMENT: PRINCIPLES

Immediate Reconstruction

The goal of modern fracture management is acute near-total or total initial reconstruction of the bony architecture of the injured facial skeleton (Table 81.2). Early reconstruction usually is less difficult and more successful than delayed reconstruction, mainly because the latter can be complicated by cicatricial contraction of the facial soft tissues if the underlying skeletal support collapses or is lost. During the acute phase of injury, the soft tissues are pliable enough to allow restoration of the underlying bony configurations with local bone fragments or autogenous bone grafts. If the soft tissues are allowed to contract into a bone defect, restoration of the soft tissue to a normal position by delayed restoration of the supporting bone invariably produces a less desirable result. If revision surgery for minor residual bone defects or lacerations is required, it is greatly facilitated if the overall soft tissue envelope has been maintained in a normal position by a previous anatomic reduction of the facial skeleton.

Maxillomandibular Fixation

MMF maintains an important role in the management of midfacial trauma. In palatal and Le Fort fractures, as well as more complex pan-facial injuries, the relationship between the maxilla and the upper craniofacial structures is frequently altered and always destabilized. Placing the patient into occlusion (MMF) restores the position of the maxilla in the horizontal plane if the mandible is intact and correctly related to the skull base—that is, properly seated in the glenoid fossa. However, it does not automatically reestablish midfacial height if the vertical buttresses have been disrupted by fracture dislocations.

In most midface cases, MMF is used intraoperatively, as a guide to maxillary positioning, and then released at the end of the case. While closed reduction and MMF for 4 to 6 weeks are adequate management of less complex, minimally displaced maxillary fractures, patient discomfort and inconvenience rarely support this approach. Additionally, long-term immobilization of the temporomandibular joint (TMJ) (greater than 4 weeks) places the joint at jeopardy for developing an arthropathy. Early TMJ movement and physiotherapy are ideal. The vast majority of maxillary fractures are best managed by means of open approaches, with direct visualization and anatomic reconstruction of the buttress system with plating. Sometimes in pan-facial injuries, a period of *postoperative MMF* is appropriate as a stabilizing adjunct.

MMF can be accomplished with directly bonded orthodontic brackets applied before open reduction and fracture-line plating. This method reduces the risk of arch bar wiring and can reduce operative time. Other innovations in MMF, which reduce surgeon risk and decrease operative time include four-point screw fixation when tooth-bearing structures are intact and/or rapid plastic zip tie fixation with laced dental chain elastics (25–28).

Approaches

Extended access approaches expose the facial skeleton widely without compromising the facial soft tissue with visible scars. These approaches (coronal, transconjunctival, buccogingival, midfacial degloving, etc.) allow direct visualization and accurate reduction of fracture displacements. The zygoma and all of its projections, including the zygomatic arch, and all walls of the orbit can be safely and almost totally exposed through a combination of incisions, which if properly executed, should be either hidden completely or barely perceptible. The lower ends of the vertical buttresses can be exposed through extended sublabial incisions that essentially deglove the maxilla. Although this frequently removes all residual external periosteal attachments to displaced maxillary fracture fragments, bony union should proceed in a timely manner if the fragments are adequately stabilized and the periosteum is redraped over them. When extended access approaches are used, care should be taken to close them meticulously with attention to periosteal closure, soft tissue resuspension, hemostasis, and wound drainage.

The choice of approaches for a particular patient and a particular injury relies not only on the technical expertise to execute a variety of incisions well, but also wisdom, experience, and judgment. On the one hand, a surgeon may be hesitant to perform extended access approaches in favor of more limited approaches in the hope that any facial asymmetry resulting from incomplete fracture reduction will be imperceptible. However, the range of imperceptible asymmetry is small, and the surgeon cannot rely on it to hide suboptimal results from nonanatomic reductions that might have been improved with more extensive exposure and reconstruction. The classic clinical example is an incompletely reduced zygoma with unilateral facial widening. On the other hand, because these wide access approaches exist it does not mean that they are always indicated. The fact that incisions are hidden does not mean they are completely free of sequelae and the risk of complications. Experienced surgeons obtain excellent results with the judicious use of more "minimalist" approaches to some injuries, such as closed reduction or single incision access to ZMC fractures (29). The increasing use of endoscopes, surgical navigation systems, and intraoperative imaging is likely to facilitate selective use of limited access approaches to facial trauma without compromising accurate reduction.

Stable Internal Fixation

Although the term *rigid* is used to describe the fixation achieved with plating systems, it is somewhat overstated when applied to midface fractures. Rigidity sufficient to allow removal of MMF can be obtained, but it is not always sufficient to allow the patient to return immediately to a normal diet. Fixation devices do maintain the position of the maxillary dentoalveolar complex under the stresses of forces generated by mastication of soft foods, speech, and deglutition. They will preserve the anatomic reduction achieved and allow for bone healing.

FRACTURE MANAGEMENT: SURGICAL TECHNIQUES

Zygomaticomaxillary Complex Fractures

The goals of ZMC fracture repair are (a) restoration of the normal facial width and projection at the malar prominence, (b) restoration of normal orbital volume, and (c) achievement of the first two goals while eliminating, or at least limiting, the sequelae and complications associated with the operative repair itself. These are the considerations the surgeon managing a ZMC fracture must have in mind as he or she considers the options—in terms of incisions used, methods of reduction, and the number, type, and configuration of plates.

The incisions typically employed for ZMC repair are shown in Table 81.3. Each incision offers access to one or more of the articulations of the zygoma, at a variable cost in terms of the residual scar and the other attendant soft tissue changes. Access to articulations serves two purposes: (a) a means to confirm the alignment of reduced fragments visually and (b) the ability to plate the area to stabilize the reduction. Choice of incisions varies significantly based on the severity of displacement and comminution, surgeon preference, and other factors. On some principles, there is considerable agreement—for instance, the subciliary incision has fallen into general disfavor because of the relatively high risk of ectropion and lid shortening with it, in comparison to the other incisions (subtarsal, transconjunctival) that expose the same anatomy (17).

A related issue is the decision regarding how many articulations, and which ones, to expose. Each articulation site has differing value for (a) confirming the alignment of reduction and (b) bearing the hardware required to stabilize reduction. For example, the sphenozygomatic (SZ) articulation within the lateral orbit is generally regarded as best single place to assess the accuracy of reduction (17,30–32). Conversely, the ZM and zygomaticofrontal (ZF) sutures, with their relatively thick bone stock along the load-bearing ZM buttress, are the most favorable sites for plate fixation (33). Table 81.4 describes the relative values for each purpose for each articulation, along with an estimate of the accessibility of the suture, in light of soft tissue cost of approaching it.

TABLE 81.3 INCISIONS USED IN MANAGING ZMC FRACTURES

Incision	Pros	Cons	Exposed for Alignment	Exposed for Plating/Repair
Gingivobuccal sulcus	No visible scar	Oral flora contamination	ZM buttress infraorbital rim	ZM buttress
Lower eyelid subciliary subtarsal transconjunctival	Only access for floor exploration/ repair	Risk of ectropion, scleral show, etc.	Infraorbital rim ZF suture ZS suture	Infraorbital rim ZF suture orbital floor
Upper eyelid lateral brow upper blepharoplasty	No cantholysis needed to access ZF suture	Visible scar	ZF suture ZS suture	ZF suture
Coronal	Excellent exposure of lateral orbit; only practical exposure of arch	Risks of widened scar, facial nerve branch weakness, and temporal hollowing	Arch ZF suture ZS suture	Arch ZF suture

In light of the potential sequelae and complications of surgery, some consideration must be given to *not* repairing non- or minimally displaced ZMC fractures (30). When this plan is chosen, patients should be followed for at least a few weeks to confirm that further displacement doesn't develop as a result of masseter muscle action, and that no unsuspected deformity becomes apparent as edema resolves.

Displaced fractures are generally repaired. Some groups have advocated the use of closed reduction techniques without any plating (34,35) in their efforts to eliminate the soft tissue consequences of repair. However, it has been demonstrated in at least one small study (36) that this approach is significantly inferior to open reduction internal fixation (ORIF) in terms of the accuracy of reduction; use of this should be limited to carefully selected cases.

The use of a single incision and a single point of fixation, either an upper eyelid incision and plating of the ZF suture (37,15) or an upper gingivobuccal sulcus (GBS) incision and plating of the ZM buttress (38), have yielded favorable results for some. More typically, three or more articulations are exposed, and at least two are plated.

One reasonable approach to the displaced ZMC fracture, and that favored by the authors, begins with a GBS incision. Through this, the ZM suture and infraorbital rim suture are both exposed. An initial attempt at reduction is then carried out through the same incision, by inserting an elevator under the body of the zygoma and elevating and rotating it toward a reduced position. In some cases, generally those with no comminution, this results in perfect reduction, and the reduction can then be stabilized with a single, appropriately contoured L-shaped plate along the ZM suture.

More commonly, reduction is incomplete or uncertain at this point, and a second incision is made. The second incision may be a lower lid incision, such as the transconjunctival or subtarsal incision, which allows access to the infraorbital rim, the SZ suture, and with a lateral crease extension and lateral canthotomy/cantholysis, the ZF suture as well. The lower lid incision is facilitated by the partial reduction of the zygoma carried out through the GBS incision; placing the transconjunctival incision properly over a displaced orbital rim is difficult. Another option for the second incision is the lateral portion of an upper blepharoplasty incision, through which the ZF suture and SZ suture (but not the infraorbital rim) may be exposed for inspection and plating.

Through this additional access, the reduction is further fine-tuned and confirmed. Plating on the ZM suture, the infraorbital rim, and/or the ZF suture are then carried out, while the reduction is maintained with the elevator.

TABLE 81.4 ARTICULATIONS WHICH MAY BE EXPOSED FOR MANAGING ZMC FRACTURES

Articulation	Stability	Alignment	Accessibility
Zygomaticofrontal	++	+	++
Arch	++	+	+
Infraorbital rim	+	+	++
Zygomaticosphenoid	*a*	+++	+
ZM	+++	++	+++

[a]Although it has been described as a particularly stable plating position by some authors (Rohner 2002; others), many authorities consider the ZS suture quite difficult to access for plating (AO).

Orbital floor exploration is carried out at this point if indicated (see discussion below). The repair is completed by soft tissue resuspension over the degloved maxilla. The undersurface of the malar soft tissue is sutured with one or more absorbable stitches to a stable superior structure, such as a plate or intact periosteum. If a cantholysis has been performed, canthotomy is performed at this point. Finally, the mucosal and skin incisions are closed.

Other Issues in ZMC Fracture Repair

Methods of Reduction

There are a number of options for the method of reduction of the displaced zygoma. The authors find that in most cases, the introduction of an elevator under the body of the zygoma through the GBS incision provides adequate control of the zygoma to achieve reduction. Other methods, including use of percutaneous hook (34,37), introduction of the elevator through a separate incision such as the Gillies incision (36), and the use of a Carol-Girard screw (33) are usually unnecessary, but should be kept in mind for particularly difficult reductions, or if the GBS incision is not being used.

Hardware

In the past, midface plating systems consisted of progressively thicker plates paired with progressively larger diameter screws, with the screw diameter used as the identifying measurement and a proxy for the thickness and rigidity of the plate. That is, a "2.0" system would comprise a relatively thick and rigid plate and a 2-mm diameter screw, a "1.0" system would consist of a 1-mm diameter screw paired with a thin and more malleable miniplate, and "1.3" and "1.5" systems would occupy intermediate positions. This taxonomy is obsolete now, as most of the hardware manufacturers offer systems in which a single diameter screw is used with all thicknesses of plate, or several plate thicknesses are available for a given screw size. Nevertheless, all manufacturers continue to offer an array of systems with different thicknesses and rigidity within their midface sets. Hardware is chosen for a particular site based primarily on: (a) the load to be borne by that site and (b) the amount of soft tissue coverage available to camouflage the plate. For example, the ZM buttress, which bears a significant load during mastication and is covered by a generous soft tissue envelope, is generally plated with a larger (i.e., the plates formerly known as 1.5 and 2.0), L-shaped, midface plate. Figure 81.7 offers a schematic representation of typical hardware deployment in ZMC fracture repair.

Orbital Floor Management in ZMC Fractures

Prior to the widespread application of CT scans in ZMC fractures, the orbital floor was frequently explored via the same lower lid incision used to repair the ZMC (39). With the routine use of preoperative CT scans in these injuries have come fairly standardized clinical and radiographic

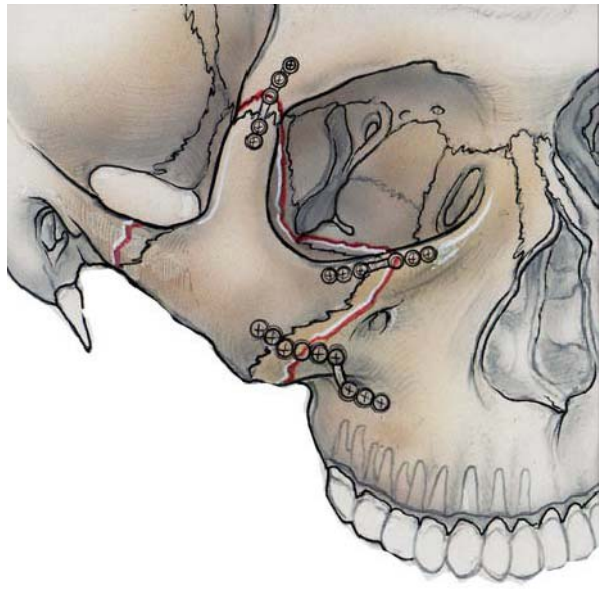


Figure 81.7 The location, shape, and size of some of the plates commonly used in the ORIF of ZMC fractures. (a) ZF suture: a thin (1.3 equivalent), linear midface plate. Alternatively, a box-shaped plate may be used for enhanced stability. (b) Infraorbital rim: a very thin (1.0 equivalent), gently curved, midface plate. (c) ZM suture: an intermediate to thick (1.5–2.0 equivalent), L-shaped plate.

criteria for orbital floor exploration. These include entrapment of orbital soft tissue, herniation of soft tissue into the maxillary sinus, and 2 cm^2 or greater of orbital floor disruption. This has reduced the need for "diagnostic" floor exploration in many ZMC patients, reducing the rate of floor exploration to 30% to 40% (39,40).

The orbital floor injury associated with ZMC fractures is distinct from that seen in isolated orbital injuries, such as "blowout" fractures. In blowout fractures, the orbit volume is almost uniformly increased. In ZMC fractures, the posterior–medial displacement of the zygoma often causes a *decrease in orbital volume*. This has promulgated the theoretic concern that reduction of the zygoma anterolaterally could increase orbital volume, perhaps above the threshold where postoperative enophthalmos might ensue. This issue has been addressed is several excellent recent studies (19,39,40). In each study, the suspicion that reduction of the zygoma might lead to orbital volume expansion beyond that seen of the preoperative imaging was confirmed; however, it was also shown consistently that in nearly every patient, the expansion was not clinically significant—that is, unlikely to expose patients to an increased risk of enophthalmos.

With this in mind, it is clear that the orbital floor in ZMC fractures may be managed selectively, using criteria for exploration similar to those in use for other orbital floor fractures. Many surgeons have taken advantage of this fact by avoiding lower lid incisions entirely in some of their ZMC patients in favor of say, a combined GBS and upper blepharoplasty incision. This spares the patient from the risk of scleral show and ectropion.

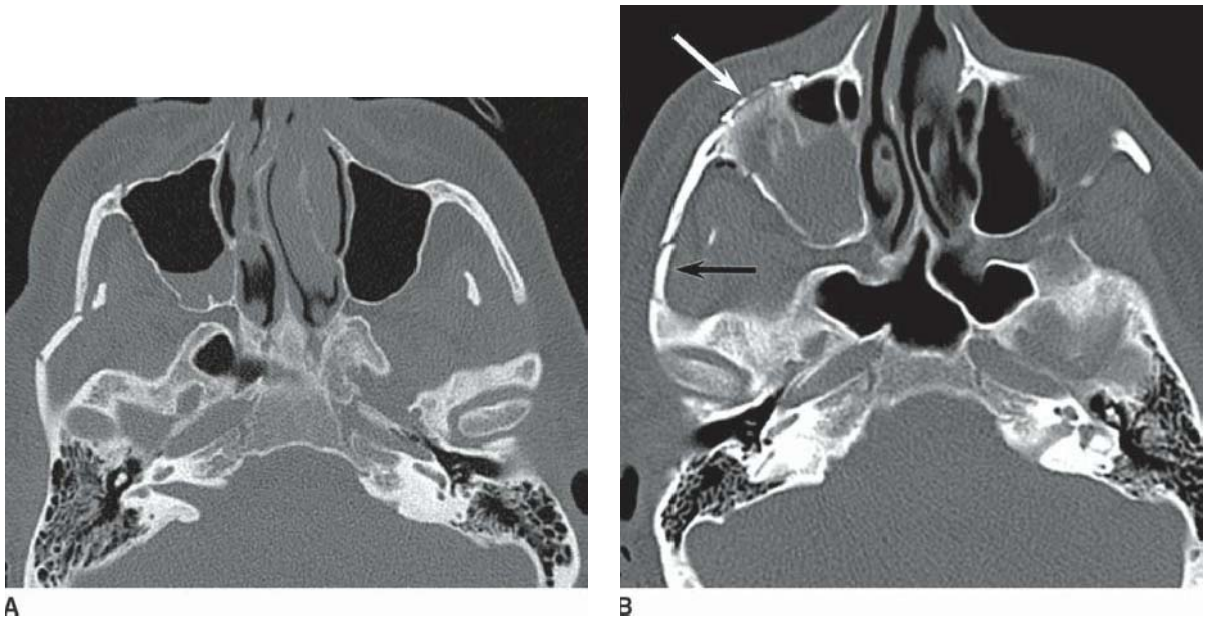


Figure 81.8 **A:** Preoperative axial bone-window CT demonstrates a right ZMC fracture with mild external rotation and medial displacement of the arch. The patient had moderate trismus. **B:** Post-reduction CT of the same patient. Fracture repair was performed through a GBS incision and a trans-conjunctival incision, with plating of the ZM buttress (not shown) and infraorbital rim (*white arrow*). The zygomatic arch alignment has been restored (*black arrow*) without being directly visualized or addressed, simply by reducing the zygoma through the GBS incision.

The technical details of orbital floor repair are similar to those in blowout fractures, which are covered extensively in Chapter 82 of this text. Needless to say, in patients where floor repair is indicated, this is carried out *after* the ZMC reduction and plating.

The above discussion is most applicable to the typical, isolated ZMC fracture that results from low to midenergy trauma. High-energy injuries, those with greater displacement and/or comminution, and those found in the setting of pan-facial injuries require a more aggressive approach. Consideration should be given to the exposure of additional fracture sites, including the zygomatic arch. This allows additional points of reference to confirm anatomic reduction and the placement of other plates to enhance stability. Another factor that favors additional exposure is less experience on the part of the surgeon (33).

In summary, repair of ZMC fractures offers the surgeon many options. An effective approach to management carefully balances the benefits of exposure, for alignment, plating, and orbital floor repair, with the cost in terms of soft tissue sequelae and potential complications incurred by each incision. As long as this balance is respected, excellent results can be achieved in a variety of ways.

Zygomatic Arch Fractures

In arch fractures that are a component of a ZMC fracture, reduction of the zygoma frequently results in satisfactory reduction of the arch (41) (Fig. 81.8).

In some cases, after reduction and plating of the zygoma, a closed reduction of the arch via a Gillies (described below) or intraoral (Keen) approach may be necessary to realign the arch. It is an uncommon event that the arch component of a ZMC fracture needs to be directly visualized and plated (13). These exceptional cases would typically be in the setting of high-energy injuries or pan-facial trauma.

Isolated arch fractures, especially those with the characteristic V configuration, are amenable to closed reduction by the method described by Gillies (42). In this technique, a small incision is made in a hair-bearing portion of the temporal scalp (Fig. 81.9). Dissection is carried down through the fascia of the temporalis muscle. A blunt instrument can be safely passed in this plane, deep to the frontal



Figure 81.9 Placement of the incision Gillies approach to isolated zygomatic arch fractures. The incision may also be oriented transversely or obliquely—the patient's hair provides excellent camouflage.



Figure 81.10 Incisional scar from Gillies approach to the zygomatic arch at 2 weeks. Even at this early stage, in a patient with short hair, the scar is barely perceptible.

branch of the facial nerve, and underneath the arch. While palpating the fracture with one hand, the instrument is elevated with other, effecting reduction. The reduced fragments, particularly those in a v-shaped arch fracture, are usually stable in the reduced position. In instances when they are not, several transcutaneous sutures may be used to suspend the fragments from a plate or finger splint affixed to the area. Other methods of temporarily supporting the reduction have also been described (43).

The advantages of the Gillies technique for zygomatic arch fracture repair include an imperceptible incisional scar (Fig. 81.10); minimal disruption of the sensitive soft tissue structures adjacent to the zygomatic arch, meaning very little risk of frontal branch injury or temporal hollowing; its simplicity; and the possibility of performing the procedure with local anesthetic, with or even without sedation.

Palate

The integrity of a fractured palate must be reestablished in order to establish a stable occlusion. Palatal fractures, most commonly parasagittal splits, can be reduced anteriorly at the inferior rim of the piriform aperture. Occasionally, the need for stability mandates plate placement posteriorly on the oral surface of the palate to allow a solid, structurally accurate dentoalveolar complex to be related to the mandibular teeth (see below). Open reduction and internal fixation of the anterior extent of a palatal fracture can be accomplished through the same extended gingivobuccal sulcus incision used to expose and repair the vertical buttresses of the face.

The bone above the anterior teeth is more than adequate for placement of a miniadaptation plate with multiple monocortical screws. In some instances, a small amount of bone can be removed immediately below the anterior nasal spine to facilitate placement of a plate with a flat contour under the upper lip and base of the columella. Care to prevent tooth root injuries should be exercised. This can be achieved both by placing the plate above the root tips, using monocortical screws, and ensuring screw holes are placed in the tooth root interspaces.

The posterior extent of a palatal fracture usually can be reduced in a closed manner if the overlying palatal mucoperiosteum is intact. Difficulty can result from an inability to align the lower end of the ZM buttress with an accurately reconstructed zygoma above. Also the need to overtighten the MMF wires to pull the lingual cusp tips of the maxillary molars and premolars into the central fossae of the mandibular teeth can be problematic. In these cases, an incision can be made over the posterior extent of the palatal fracture, and a transosseous wire or small plate can be placed across the fracture. This wire does not serve as a point of rigid fixation of the palatal fracture, but it reduces the fracture gap posteriorly after it is tightened. Stable fixation is obtained with superficial triangulation of the palate with plates and screws placed across the anterior extent of the palatal fracture and across both ZM buttress areas (Fig. 81.11).

Transoral palatal plates are often difficult to cover with mucosa. These plates can be placed transmucosally and removed once fractures have healed. Posterior distraction of a parasagittal palatal fracture can be overlooked easily if a parasymphyseal mandibular fracture is present that has been incompletely reduced at the lingual cortex. Both dental arches are widened posteriorly, and the maxillary and mandibular teeth can appear to interdigitate correctly. However, when facial edema resolves, the patient

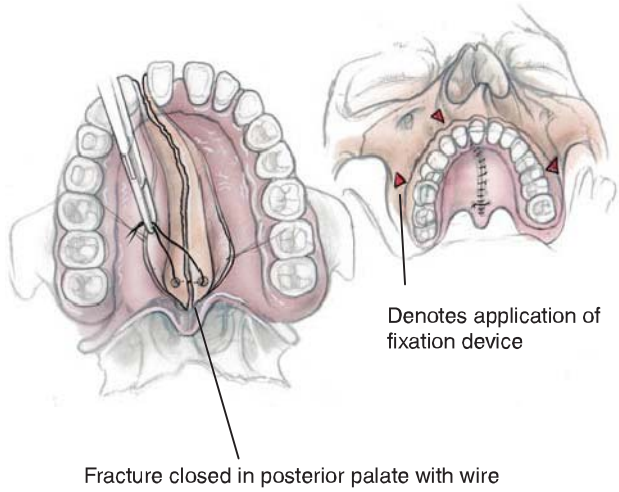


Figure 81.11 Reduction of the posterior gap in a displaced parasagittal fracture of the palate using a transosseous wire. *Arrows* indicate the location of plates that are points of triangular fixation that hold the fracture in reduction.

may notice widening of the intergonial distance and have a "cheeky" appearance.

Palatal fractures exposed by means of laceration of the mucoperiosteum usually are widely separated and impossible to reduce without a transosseous wire to pull the palatal shelves together posteriorly. If this method of reduction is not used, and tightening of the MMF wires only is used to pull the teeth into occlusion, the maxillary teeth probably will be lingually tipped or left in some degree of unilateral or bilateral posterior crossbite deformity. The exposure through the laceration may be adequate to allow placement of a plate across the split palate; however, this procedure can be technically difficult, and these plates frequently become exposed in the mouth and must be removed.

Acrylic palatal splints are essential adjuncts for stabilization of teeth in a segment of maxillary bone separated from the palate by an alveolar fracture. Even if a rigid fixation device cannot be used to attach the isolated alveolar segment to the surrounding maxillary bone, the combination of a sturdy buccal arch bar, a palatal splint, and circumdental wires to cinch the involved teeth between the bar and the splint usually provides enough stability to allow removal of the MMF at the end of the case.

Maxilla

Restoration of the pretrauma relationships of the tooth-bearing segments of the maxilla to the mandible and skull base necessitates reestablishment of the proper occlusal relation of the maxillary and mandibular teeth and stabilization of the midfacial buttress system (Fig. 81.12). If the mandible also is fractured, the lower dental arch must first be stabilized and accurately related to the skull base; proper alignment of the mandibular condyles in the glenoid fossae is an absolute requirement. The anteroposterior position of the maxilla can be established by means of occluding the teeth in stable MMF. The midfacial vertical dimension is established by means of reduction and fixation of all fracture lines between the palatoalveolar complex and the base of the skull. When subcondylar fractures or fractures of the condylar head cannot or should not be managed with open reduction, the midfacial buttress system can be reconstructed first to establish vertical and horizontal positioning of the occlusal plane. This alternative approach may not restore the relation of the maxilla to the base of the skull with the same accuracy that can be achieved if it is first related to an intact or totally reconstructed lower dental arch. This sequence, however, is the preferred sequence if mandibular vertical ramus height cannot be accurately restored because of the presence of posterior mandible fractures or comminution.

Although not a part of the maxilla, each zygoma must be accurately repositioned and stabilized before reattachment of the maxilla to the upper ends of vertical buttresses. Zygomatic fractures associated with Le Fort fractures of the middle third of the facial skeleton often necessitate open reduction and internal fixation of the zygomatic arch to position the

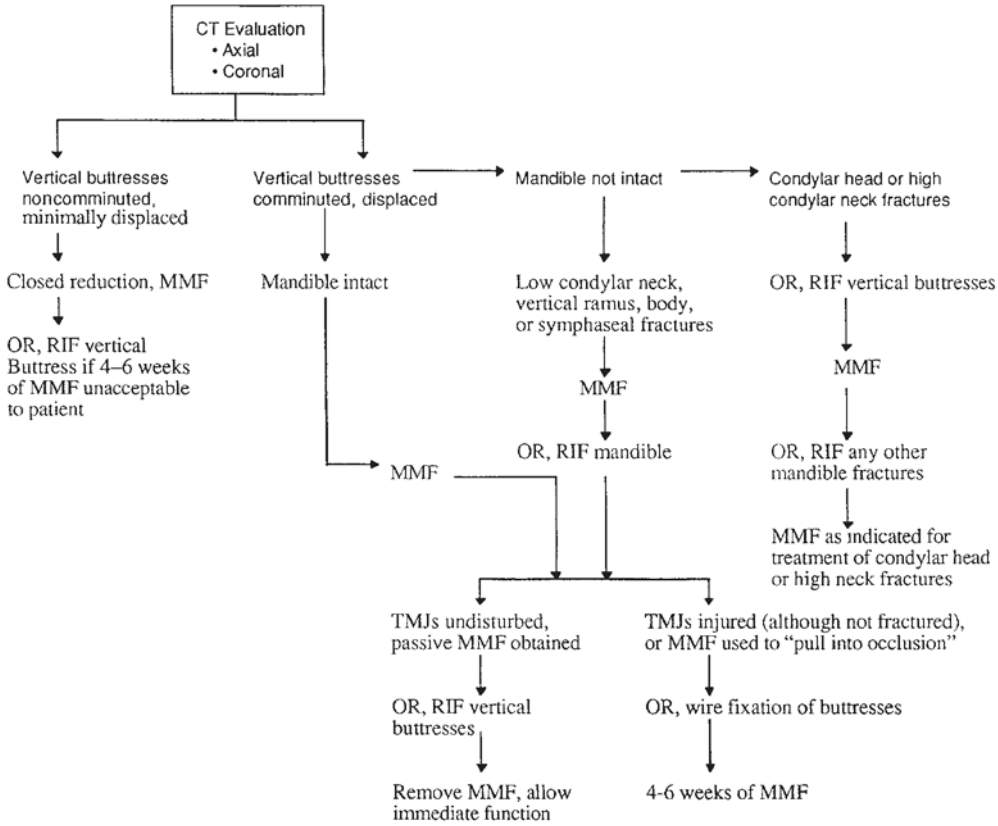


Figure 81.12 Algorithm for the management of fractures of the vertical buttresses.

zygoma correctly before reattachment of the maxilla. This is particularly critical if mandibular condylar fractures necessitate reconstruction of the upper jaw first. Failure to recognize and correct the amount and direction of displacement at the time of reduction leaves a flattened cheek and widened face and can produce a rotation and tilting of the maxilla when it is reattached to a malpositioned zygoma.

Only after the zygomatic and palatal fractures have been repaired can the maxillary complex be reattached superiorly. Reattachment begins with the ZM buttress that has the less severe injury. Unlike the anterior wall of the maxilla, which often is severely comminuted, the ZM buttress often is traversed by a single fracture line that can be easily reduced, or it has a single free-floating fragment that can be accurately related to the zygoma above and the lower maxilla below. At least one ZM buttress usually can be reduced in this way to set the correct vertical dimension of the middle third of the face. After stabilization of this buttress, reduction and fixation of the other ZM buttress and the NM buttresses can proceed. If both ZM buttresses are severely comminuted, reconstruction of the NM buttresses can facilitate reestablishment of the vertical dimension. In most cases of comminution of the ZM struts, however, the NM buttresses are even more fragmented and difficult to realign.

Stability of the reattached maxillary complex is gained mainly through reconstruction of the ZM buttresses. Reconstruction of the NM buttresses can provide some supplementary vertical stability to the overall reconstruction, but only if the upper confluence of these struts (nasoorbitoethmoidal complex) is intact. If plates and screws are used for fixation and the patient is allowed to function early, a delicate nasoorbitoethmoidal repair cannot be relied on to transmit occlusal forces to the base of the skull. Instead, ZM buttress reconstruction must be used to hold the repositioned maxilla in place during healing. Plates must be positioned to overlie the ZM buttresses as closely as possible, and three screws are used to anchor the plate to the zygoma above and the maxilla below. Placement of screws into the lower end of a plate or a bone graft can be difficult if the fracture line closely parallels the apices of the molar and premolar teeth. This problem usually can be overcome with L-shaped plates that allow placement of more screws close to (often in between) but not through the root tips.

Comminution of the lower ends of the vertical buttresses severe enough to mandate bone grafting for adequate stabilization is uncommon, although occasional cases occur in which gaps of 1 to 2 cm of severely comminuted or absent bone exist in one or both lateral antral walls. Onlay split cranial bone grafts are attached across these gaps. The grafts can be contoured and positioned to allow placement of lag screws that do not damage the root tips. Reconstruction of the vertical dimension cannot be done with the same precision for these patients as for those who undergo successful edge-to-edge approximation of *in situ* fracture fragments.

COMPLICATIONS AND SEQUELAE

Perhaps the most common complication of midface fractures is inadequate reduction resulting in facial deformity, and in some cases, functional deformity (see below). This complication represents a technical error at the time of surgery.

Eye/Eyelid/Orbital Complications

Eye-related complications are common in midface trauma (especially in ZMC fractures) and include lower eyelid injury, including ectropion, entropion, and most commonly, scleral show; enophthalmos, with or without diplopia; corneal abrasion; and visual loss (rare). One way that many surgeons are preventing lower lid sequelae of midface trauma is by simply choosing not to make lower lid incisions when possible; for instance, in patients with ZMC fractures who do not require floor exploration, an upper blepharoplasty incision access to the FZ suture is chosen over the lower lid approach to the infraorbital rim. This approach essentially eliminates the risk of scleral show and other lower lid issues, otherwise quite common even with a well-executed transconjunctival incision.

In other respects, the eye, eyelid, and orbital complications of midface trauma mirror those seen in isolated orbital fractures, and are covered in greater detail in Chapter 82.

Lip Distortion

A subtle but disturbing deformity can be caused by use of the sublabial approach to maxillary fractures. This deformity includes hollowing of the soft tissue contours over the canine fossa area and superior deviation of the corner of the mouth and lateral aspect of the upper lip. It is caused by collapse and contraction of the buccal soft tissues into large anterior and anterolateral antral wall defects. Although the exact size of the defect necessary to cause this is unknown, defects of greater than 1.0 cm^2 are considered for overlay bone grafting.

Implant-Related Complications

Miniplates and screws along the lateral orbital rim (ZF suture) and zygomatic arch usually are visually undetectable if low-profile (1.3 mm equivalent) titanium or cobalt–chromium alloy plates with are used. These fixation devices can be left in place permanently. Inferior rim plates are those that most likely produce an irregular contour visible through the thin skin of the lower eyelid. Prevention of this complication is critical because if such a plate is placed and is visible after healing is complete, a second surgical violation of this lower lid to remove the plate exposes the patient to a higher risk for lid complication. Options include the use of very low-profile (1.0 mm equivalent) hardware; wire, rather than plate, fixation of

the infraorbital rim; placement of the plate along the superior surface, rather than the anterior face, of the rim; and avoidance of rim fixation altogether by choosing the ZF suture as a second point of fixation.

Generous soft tissue coverage makes plate visibility along the ZM and NM buttresses extremely uncommon. *Intraoral* plate exposure does occur in these areas however, as well as on the palate; this can be managed expectantly in most cases, or with plate removal after bony union. Finally, plate and screw failure, such as is seen in mandibular fractures, is uncommon in midface trauma.

Malocclusion

While malreduction in ZMC fractures causes *cosmetic* issues such as facial widening and malar flattening, the same errors, when applied to Le Fort and palatal fractures, will have significant *functional* consequences. Rigid fixation is an unforgiving technique that produces serious occlusal disturbances if used inappropriately to manage fractures of tooth-bearing segments. If the plates are not correctly adapted to the bone, tightening of the screws can produce torque in the system, and the fragments can be distracted so that malocclusion is produced when the MMF is removed. This is less likely to occur now that thinner, more malleable titanium or cobalt–chromium alloy plates are being used rather than the stiffer, harder to bend stainless steel plates.

The surgeon must consider the risk of inaccurate condylar seating in the glenoid fossae in all cases involving tooth-bearing segments of bone. Patients with complex maxillary injuries can have a deranged occlusal relation that is difficult to correct and prevents the teeth from interdigitating in a passive manner before application of MMF. One or both mandibular condylar heads invariably are displaced from their normal centric occlusion position in the glenoid fossae if the MMF is used to "pull the patient into occlusion." Even if the plates are subsequently and accurately adapted to the repositioned maxillary fragments, malocclusion develops after MMF is removed and the patient's normal muscle balances return the mandible to its correct position. If gross malocclusion does not result and the patient learns to function in this altered position, chronic TMJ discomfort is likely to develop.

When postoperative occlusion is noted, the only successful form of remediation is revision surgery, *including revision of the reduction and fixation*. Simply reapplying MMF in the hope that the patient's muscles or orthodontic traction bands will pull the patient into occlusion is uniformly unsuccessful because of the rigidity of the fixation devices.

Sensory Disturbances

Numbness and paresthesias in the distribution of the infraorbital nerve (V2) are common in midface fractures, owing to the frequent involvement of the infraorbital canal and foramen within the fracture lines. In many patients, these symptoms resolve with or without treatment. In patients in whom they persist, they can be significant source of annoyance, particularly when eating (44). The impact that fracture management has on these symptoms is uncertain. Clearly, careful dissection around the nerve when exposing the maxilla through the GBS is advisable. Some studies suggest a salutary effect of operative repair on nerve recovery (45), while some authorities specifically advise against operative management to "decompress" the infraorbital nerve in the absence of other surgical indications (18).

Other Complications/Sequelae

Facial nerve injury, particularly to the frontal branch, may result if a coronal approach to the zygomatic arch is performed. Temporal hollowing due to atrophy of the temporal fat pad is a more common sequela of the coronal approach. Despite the transoral placement of implants, infectious complications of midface fractures are unusual (46).

TECHNICAL ADJUVANTS

Surgical Models and Computer-Aided Surgery

Although most information necessary to evaluate midface fractures can be seen on standard axial and coronal CT scans, three-dimensional reconstructions can help surgeons better conceptualize the overall injury. Precise calculation of displacement of superficial bony landmarks is possible with three-dimensional images (47,48). This is particularly valuable for patients who cannot be positioned for true coronal CT for optimal evaluation of the orbital walls. However, coronal reformations generated from fine-cut axial CT scans are less expensive and more readily obtained than three-dimensional reconstructions. Although they do not supply the same detail in equal clarity, the coronal reformations usually supply adequate information.

Additional technologic enhancements to aid the surgeon in repair of complex facial trauma include sagittal CT reconstruction for orbital floor fractures (49), computer-aided surgery navigation for facial fragment reduction (50,51), and preoperative computer-generated models for surgical planning, particularly helpful for reconstruction in the delayed setting and revision cases (52).

Intraoperative CT Scanning

Portable CT scanners allow immediate radiographic evaluation of fracture reduction in the operating room (53,54). The quality of these scans appears sufficient to allow evaluation of relocation of the malar prominence on axial scans and realignment of the orbital walls on

coronal reformations. This technology facilitates the use of closed reduction, single incision, endoscopic approaches, and other "minimalist" approaches to midface fracture repair by confirming the reduction of unexposed fractures. This spares the patient the soft tissue sequelae associated with multiple incisions and periosteal stripping. Furthermore, the expense of the scanner and technologist time can be offset by elimination of the need for extended access approaches to evaluate reduction of each fracture line, thus decreasing operating room time and expense.

HIGHLIGHTS

- Although reduction of the displaced zygoma in ZMC fractures may cause an *increase* in the orbital volume relative to that seen on the preoperative imaging, the amount of the increase is rarely clinically significant. Therefore, the orbital floor components of ZMC fractures can generally be managed according to the same principles applied to isolated orbital floor fractures.
- MMF serves as a very useful guide to the proper relationship between the maxillary dentition and the skull base *in the horizontal plane*. This relationship loses validity, and the patient is at risk of postoperative malocclusion, if the mandibular condyles are not seated properly in the glenoid fossa at the time the patient is placed into occlusion.
- Injuries to the eye and C-spine are common in midface fractures and patients must be carefully evaluated for these injuries. Preoperative visual evaluation is mandatory, and ophthalmologic consultation should be strongly considered, for all patients being brought to the operating room for repair of midface fractures involving the orbit.
- Intraoperative imaging and surgical navigation are two newer technologies that may in the future facilitate less invasive approaches to midface fractures without compromising accuracy of repair.
- Palatal fractures tend to occur in the setting of multiple other facial fractures. Palatal fractures must be addressed early in the sequence of repairing these injuries, in order to allow the use of the patient's occlusion as a guide to the accurate reduction of the other fractures.
- There is a wide array of successful strategies for managing ZMC fractures. Depending on the nature of the particular injury and the experience of the surgeon, options may include close reduction techniques, single incision approaches with plating, and multi-incision, wide access approaches with plating.

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Orbital Fractures

82

Clinton D. Humphrey *J. David Kriet*

OVERVIEW

Orbital fractures occur both as isolated injuries and in conjunction with additional maxillofacial fractures or multisystem trauma. Patients with an orbital injury require initial evaluation by the emergency department (ED) physician and in some cases activation of the trauma team following current Advanced Trauma Life Support (ATLS) protocols (see Chapter 74). The identification of orbital fractures during the initial ED workup should lead to a request for facial trauma surgeon consultation. Computed tomography (CT) scanning is standard for confirming or identifying fractures. Fractures of the zygomaticomaxillary complex (ZMC), orbital rim, medial orbital wall, and orbital floor are most commonly encountered. Fractures of the superior orbit occur less frequently and are often associated with frontal sinus fractures and intracranial involvement. Naso-orbital-ethmoid (NOE) fractures tend to be associated with complex midfacial and maxillary trauma (see Chapter 81). The management of NOE fractures differ from the management of most orbital fractures and is discussed in detail elsewhere. The surgeon's prompt evaluation of orbital fractures is indicated once life-threatening injuries have been addressed and the patient is stabilized. Ophthalmology consultation is appropriate in selected cases (1). Certain indications and ideal timing for orbital fracture repair remain controversial. Surgical intervention should restore preinjury appearance and function.

ANATOMY

The orbital skeleton contains contributions from the frontal, sphenoid, lacrimal, ethmoid, maxillary, zygomatic, and palatine bones. The supraorbital rims are entirely comprised of the frontal bone. Laterally, the frontal bone articulates with the zygoma. More posteriorly, within the orbit, the zygoma also articulates with the greater wing of the sphenoid. Portions of both the zygoma and maxilla make up the infraorbital rim and, along with a small contribution from the palatine bone, the orbital floor. The medial orbit is a complex confluence of the ethmoid lamina papyracea, lacrimal bone, maxilla, and nasal process of the frontal bone. The bony orbit and locations of the optic foramen, ethmoid artery foramina, and orbital fissures are shown in Figure 82.1A. Moving posteriorly, the anterior ethmoid artery, posterior ethmoid artery, and optic nerve are located approximately 24, 36, and 42 mm, respectively from the anterior lacrimal crest Figure 82.2B. Upper and lower eyelid layers are detailed in Figure 82.2 (2).

The lateral canthal tendon consists of two limbs. A thin anterior limb blends with the orbicularis oculi muscle fibers and periosteum of the lateral orbital rim; a thicker posterior limb attaches to Whitnall tubercle of the zygoma. The medial canthal tendon attaches via two limbs as well. A thicker limb extends to the anterior lacrimal crest and a thinner limb containing Horner muscle to the posterior lacrimal crest. Intimately related to the medial canthal tendon is the lacrimal system. Upper and lower puncta begin 5 to 7 mm lateral to the canthus and continue as a common canaliculus into the lacrimal sac located between the anterior and posterior limbs of the medial canthal tendon within the lacrimal fossa. The sac empties into the inferior meatus via the nasolacrimal duct. Figure 82.3 demonstrates the complex relationship between the lacrimal drainage apparatus and the medial canthal tendon. The lacrimal gland is located along the superolateral orbit within the upper lid and divided into a larger orbital portion and a smaller palpebral portion by the lateral horn of the levator aponeurosis. Anteriorly, the gland's orbital portion is in contact with the orbital septum (3,4).

Extraocular muscles include the two oblique and four rectus muscles. The course of the superior oblique muscle brings it into nearly direct contact with the periorbita of the orbital roof and medial wall at the trochlea. The inferior

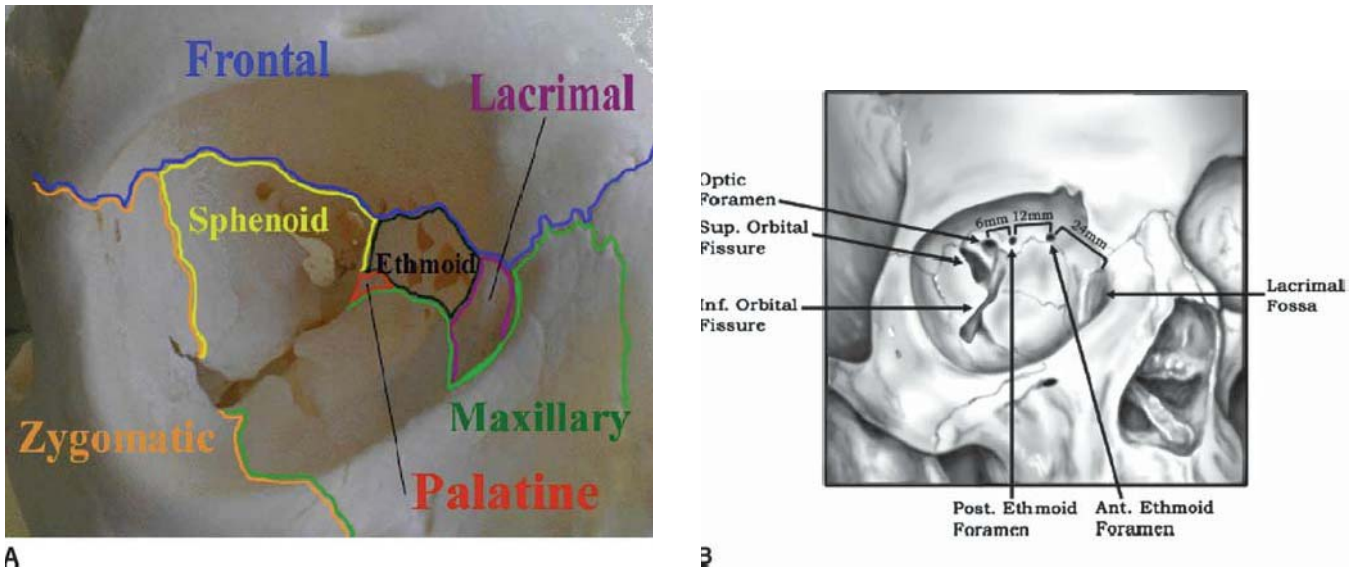


Figure 82.1 **A:** The frontal sphenoid, lacrimal, ethmoid, maxillary, zygomatic, and palatine contributions to the orbit are shown. **B:** As measured from the anterior lacrimal crest, the anterior ethmoid artery, posterior ethmoid artery, and optic foramina are located at 24, 36, and 42 mm, respectively. (**B** from Humphrey C, Kriet JD. Surgical approaches to the orbit. *Operat Tech Otolaryngol Head Neck Surg* 2008;19:132–139, with permission).

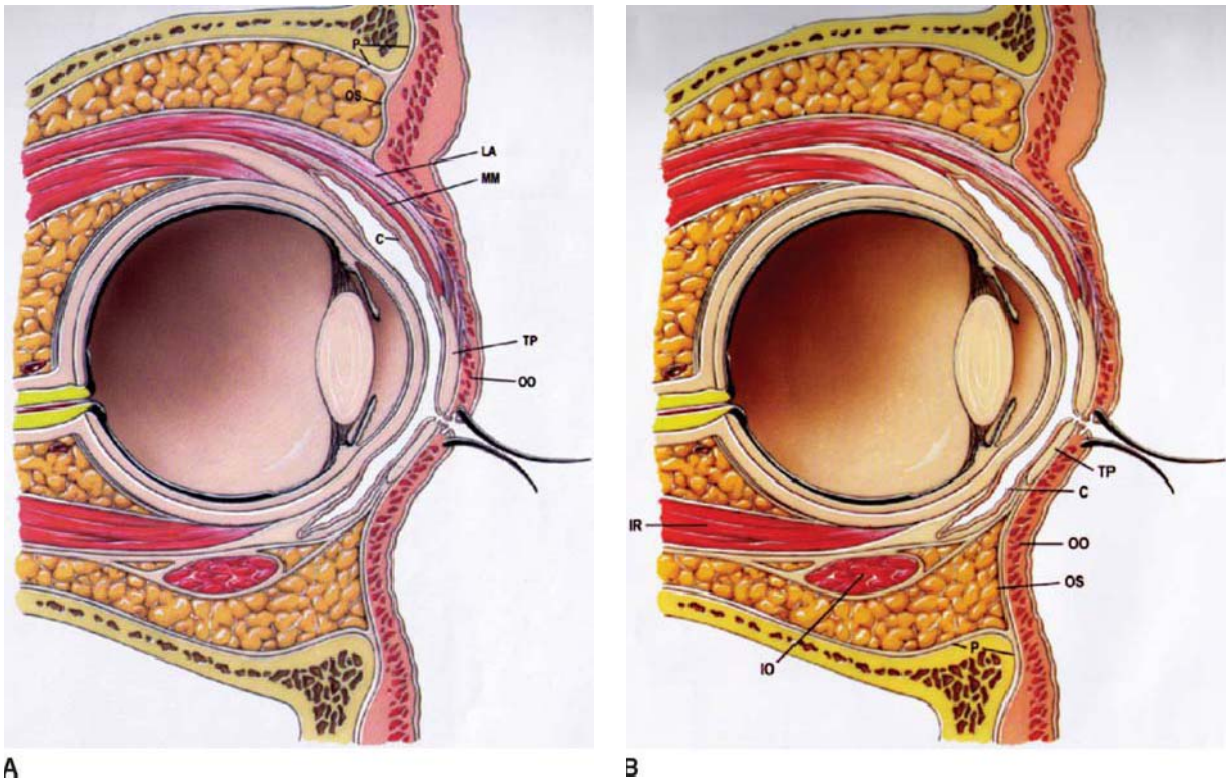


Figure 82.2 Lower eyelid layers include skin, orbicularis, oculi, tarsal plate, conjunctiva, and orbital septum **(A)**. Upper eyelid components include skin, orbicularis oculi, levator palpebrae superioris aponeurosis, Müller muscle, tarsal plate, conjunctiva, and orbital septum **(B)**. C, palpebral conjunctiva; IO, inferior oblique muscle; IR, inferior rectus muscle; LA, levator palpebrae superioris aponeurosis; MM, Müller muscle, OO, orbicularis muscle; OS, orbital septum; P, periosteum/periorbita; TP, tarsal plate. (From Ellis E, Zide MF. Surgical approaches to the facial skeleton 2nd ed., Philadelphia, PA: Lippincott Williams & Wilkins 2006, with permission).

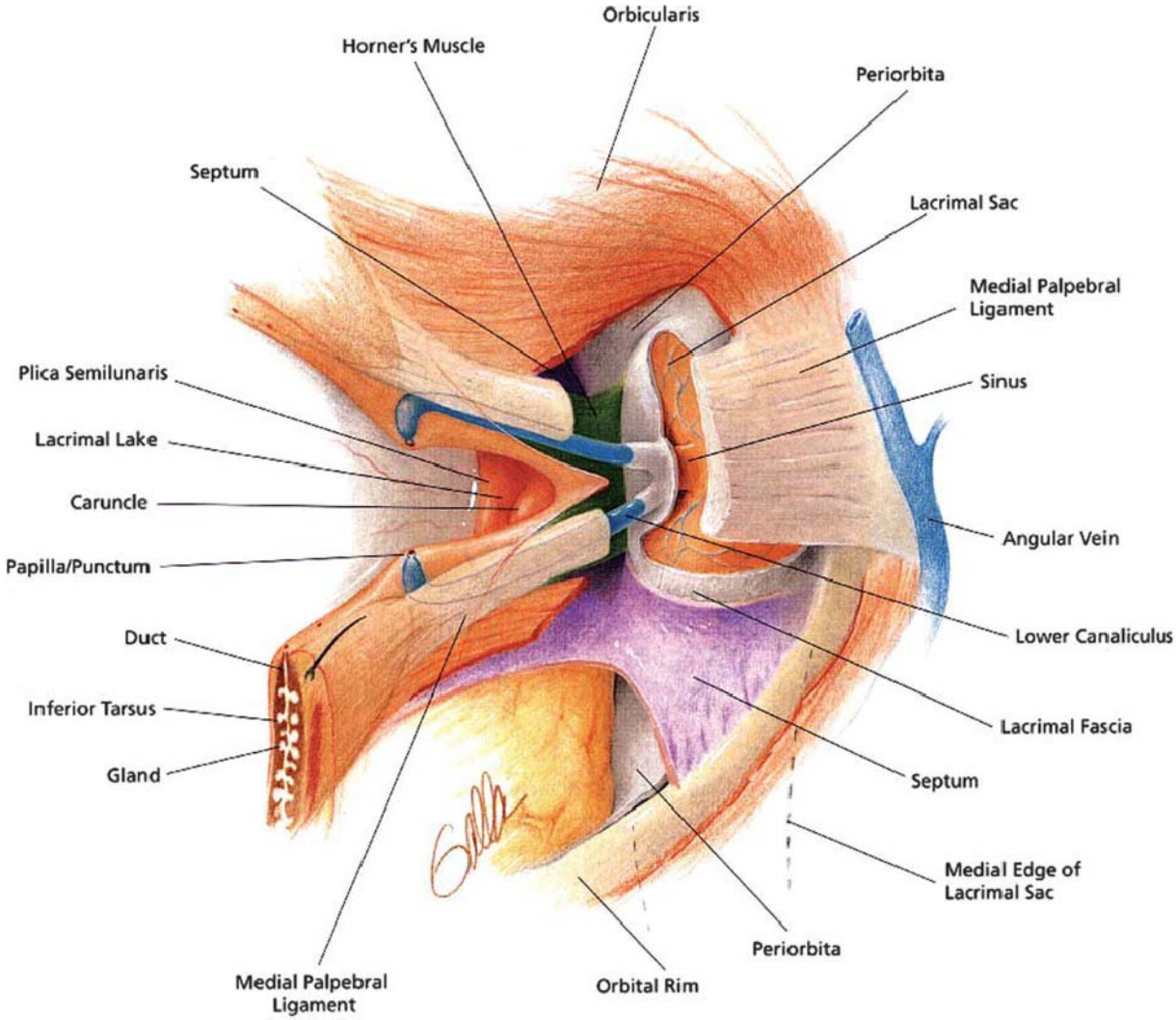


Figure 82.3 Upper and lower puncta begin 5 to 7 mm lateral to the canthus and converge to form the common canaliculus. The common canaliculus enters the lacrimal sac that is located between the anterior and posterior limbs of the medial canthal tendon. The posterior limb of the tendon contains Horner muscle. (From Janfaza P, Nadol JB, Galla, RJ, et al. Surgical anatomy of the head and neck, Philadelphia, PA: Lippincott Williams & Wilkins 2001, with permission).

oblique is in proximity to the orbit at its origin just posterior to the inferomedial orbital rim, lateral to the superior end of the nasolacrimal canal, and occasionally from the fascia over the lacrimal sac. The superior, inferior, lateral, and medial rectus muscles originate from the annulus of Zinn. All of the extraocular muscles insert directly onto the sclera.

DEMOGRAPHICS AND ETIOLOGY

Orbital fractures requiring treatment commonly occur secondary to blunt trauma incurred during violent assaults, accidental injury (falls, sports injuries, work-related), or motor vehicle accidents. While these fractures occur at any age, young males are most often affected. The most typical injury patterns among all patients are isolated blow-out fractures of the orbital floor and fractures of the ZMC. ZMC fractures by definition involve the orbital floor and lateral orbital wall (5). Isolated trapdoor type fractures of the floor are more common in the pediatric age group than in adults (6,7). Orbital roof fractures occur with high-energy injuries that often produce concomitant intracranial sequelae.

Orbital Blow-Out Fractures

The majority of orbital floor blow-out fractures occur medial to the infraorbital nerve and inferior orbital fissure with preservation of a medial strut extending posteriorly off of the nasomaxillary buttress and adjacent to the lacrimal bone (Fig. 82.4). Two wall fractures involving both the orbital floor and the medial wall are less common but must be identified preoperatively as reconstruction is exponentially more challenging, especially if the medial strut is disrupted. In both orbital floor and medial wall fractures, an intact posterior shelf of maxillary or palatine bone will be preserved that must be identified for stable and anatomic implant placement (Fig. 82.5). In medial wall

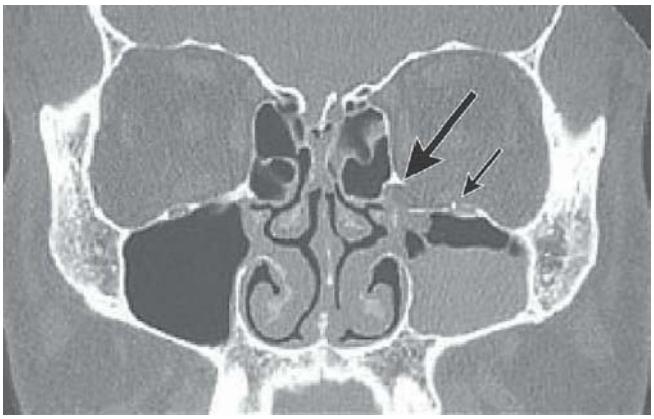


Figure 82.4 A medial strut extending posteriorly from the vertical nasomaxillary buttress is typically preserved following an orbital blow-out fracture. This strut is a useful landmark for orientation and provides a stable anteromedial shelf for implant placement when attempting repair. (From Farwell DG, Sires BS, Kriet JD, et al. Endoscopic repair of orbital fractures: use or misuse of a new approach. *Arch Facial Plast Surg* 2007;9(6):427–433, with permission).

fractures, there is usually a stable superior shelf of frontal bone above the level of the anterior and posterior ethmoid arteries. These arteries indicate to the surgeon the level of the cribriform plate and skull base.

Yano et al. presented a simple classification system for blow-out fractures, separating them into "linear," "punched-out," and "burst" fractures. Linear fractures were minimally dislocated. Punched-out and burst fractures referred to fractures involving respectively less than half or more than half of the wall (orbital floor or medial) (8). Unfortunately, this classification system and alternatives offered by others generally do not correlate well with the likelihood of developing enophthalmos or persistent diplopia (8,9). Further, any classification system based on radiologic findings alone is unlikely to reliably predict these sequelae and the need for surgical intervention.

Zygomaticomaxillary Complex Fractures

Classic "tripod," or tetrapod, fractures of the ZMC involve medial rotation of the zygoma at the arch due to blunt trauma at the lateral aspect of the malar eminence. Significant dislocation results in disruption of the horizontal buttresses at the infraorbital rim and zygomatic arch. The vertical zygomaticomaxillary and zygomaticofrontal buttresses are disrupted as well. Rotation of the body of the zygoma causes displacement along the lateral orbital wall at the zygomaticofrontal and zygomaticosphenoid suture lines (Fig. 82.6). The orbital floor is disrupted by an extension of the orbital rim fracture that runs posteriorly along the zygomaticomaxillary suture line and adjacent to the infraorbital nerve. Infraorbital anesthesia or dysesthesia is present in almost 25% of cases (10).

Zingg proposed a classification system that would stratify ZMC fractures based on concise description of the anatomic sites involved. Type A fractures are isolated to the zygomatic arch, lateral orbital rim, or infraorbital rim alone. Type B fractures are classic monofragment tetrapod fractures as previously described that involve disruption of all four zygomatic articulations. Type C fractures are more complicated tetrapod fractures in which there is comminution of the zygoma. This system does guide treatment somewhat as closed reduction was appropriate for select type A and B ZMC fractures, and open reduction was always indicated for type C fractures in a series of over 1,000 cases (10).

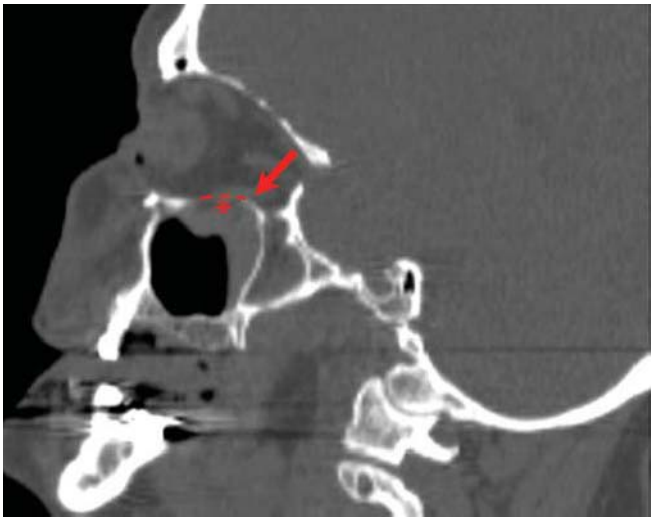


Figure 82.5 A posterior shelf of maxillary and/or palatine bone will be preserved following an orbital blow-out fracture (*large arrow*). During repair, this shelf must be identified and used for stable and anatomic implant placement. Note the convex contour of the posterior orbital floor (*asterisk*). An implant must also replicate this convex contour in order to correctly restore orbital volume. (Figure courtesy of Dr. Barton Branstetter).

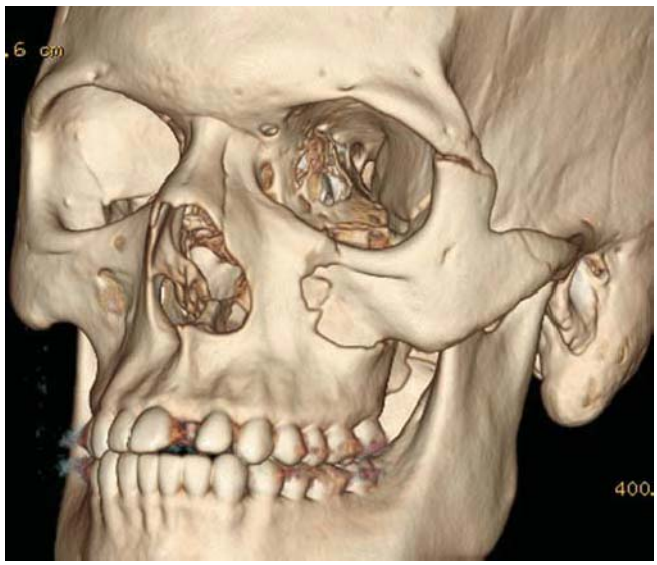


Figure 82.6 This three-dimensional CT reconstruction demonstrates a classic tetrapod fracture of the ZMC resulting from impact at the lateral aspect of the malar eminence. The impact results in counterclockwise rotation and posterior displacement of the zygoma. (Figure courtesy of Dr. Barton Branstetter).

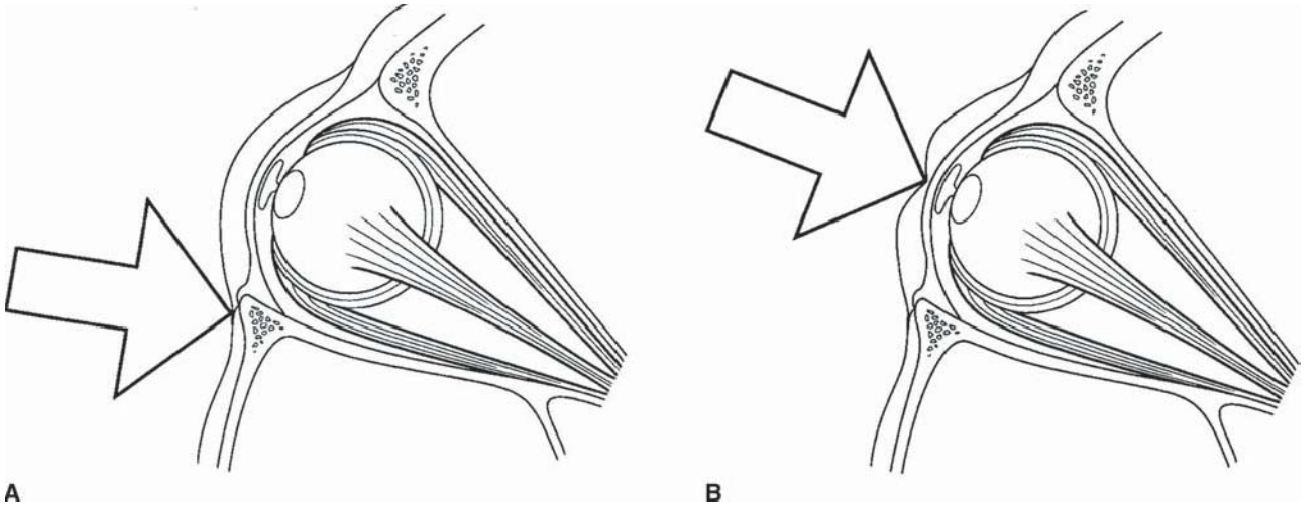


Figure 82.7 Two theories are used to explain the mechanism by which orbital blow-out fractures occur. The bone conduction theory states that force is transmitted through an intact infraorbital rim to the thinner orbital floor **(A)**. The hydrostatic theory suggests that impact to the globe increases intraorbital pressure, causing the orbit to fracture at the weakest point, typically the orbital floor or medial wall **(B)**. (From Waterhouse N, Lyne J, Urdang M, et al. An investigation into the mechanism of orbital blowout fractures. *Br J Plast Surg* 1999;52:607–612, with permission).

Orbital Roof Fractures

Orbital roof fractures are uncommon with an estimated incidence of 1% to 9% of all facial fractures (11). In adults, they are most commonly produced as a result of a high-energy impact such as a motor vehicle accident. In children, fractures may occur as an extension of a linear frontobasal fracture with falls being the most common etiology. One must maintain a high index of suspicion for intracranial injuries manifesting as pneumocephalus, cerebrospinal fluid (CSF) leaks, or encephalocele formation in patients with orbital roof fractures (12).

Biomechanics and Pathophysiology

The pathophysiology for most facial fractures is straightforward in that the fracture occurs at the site of impact. For example, ZMC fractures result from impact sustained at the prominent malar eminence. Orbital blow-out fractures occurring in the absence of an infraorbital rim fracture are unique because the fracture-producing force is transmitted indirectly. Two popular, but not mutually exclusive, theories have traditionally been used to explain the mechanism of these blow-out injuries. The first, bone conduction (or buckling) theory, was originally described by Le Fort (13) and maintains that force is transmitted through the thicker bone of the rim into the thinner bone of the floor, resulting in a fracture of the floor but maintaining an intact rim. The bone conduction theory does not as adequately explain how isolated medial wall blow-out fractures might occur. Alternatively, the hydrostatic theory suggests that impact to the globe results in increased intraorbital pressure that fractures the orbital floor and/or medial wall at the weakest points (14). Figure 82.7 illustrates both theories. A third hypothesis—a modification of the hydrostatic theory—proposes that it is displacement of and direct contact of the globe with the orbital floor or medial wall that results in the fracture. A cadaver study by Rhee et al. in 2002 provides strong support for the hydrostatic theory by demonstrating that increased pressure within the orbit in the absence of rim impact results in blow-out fractures. This study also suggested that direct contact of the deformed globe with the orbital floor or medial wall is not required for fracture (15). Despite this evidence bolstering the pure hydrostatic theory, each of these mechanisms could potentially play at least some role in the clinical setting.

EVALUATION

All trauma patients should initially be stabilized and evaluated according to ATLS protocol by an ED physician or the trauma team. Patients with severe orbitofacial trauma, decreased visual acuity, and/or double vision should be evaluated by the facial trauma surgeon acutely and admitted to the hospital if warranted. Conversely, discharge from the ED and follow-up within 3 to 5 days for outpatient evaluation is appropriate for carefully selected patients. Periorbital edema will decrease in the interval, making the examination less difficult and offering an improved assessment of potential enophthalmos. Comprehensive screening CT scans have become increasingly common in complex trauma cases. Identification of orbital fractures on these screening CT scans is often the impetus for consulting the facial trauma surgeon. In the event that fractures are initially discovered on physical exam or noted on plain films or a head CT, a fine cut (less than 2 mm) maxillofacial scan with axial, coronal, and sagittal reconstructions is indicated. Axial images are useful in evaluating medial

wall fractures. Coronal images provide excellent views of the orbital floor, medial wall, and roof. Sagittal images are helpful in assessing the position of the stable posterior shelf. When available, three-dimensional reconstructions are useful for gaining a broad overview of fracture patterns and fragment orientation.

The availability of a high-quality screening CT scan should not preclude the facial trauma specialist from obtaining a detailed history and performing a thorough physical examination. The historian should inquire about mechanism of impact, previous eye surgery, double vision, numbness, preinjury vision status, and use of anticoagulant medications or other comorbid factors. The physical examination begins with assessing pupillary response and visual acuity. The use of a pocket-sized Snellen chart is helpful for performing an initial vision check. Most smartphones are now able to display such a chart, making the documentation of visual acuity feasible in most circumstances. Color perception is another useful bedside test. Patients with traumatic optic neuropathy may perceive a bright red object (e.g., light shining through the closed eyelid) as a dull brown. While the facial trauma surgeon may not have access to a slit lamp for funduscopic examination, the anterior chamber should be inspected for the presence of hyphema (Fig. 82.8). If available, a Naugle exophthalmometer can easily be used in the clinic to objectively determine the presence and degree of enophthalmos (Fig. 82.9). Extraocular movements (EOMs) are assessed, observing for symmetry and the presence of diplopia during the exam. It is not uncommon to note some diplopia at the extremes of gaze, especially after a fracture causes substantial edema in the affected eye. The status of other cranial nerves, particularly the facial and trigeminal, is determined. Anesthesia or dysesthesia in the distribution of the infraorbital branch of the trigeminal frequently occurs in association with orbital fractures. Likewise, paresis in the buccal branch of the facial nerve can be seen. It is imperative that any neural deficits be documented preoperatively. The combined findings of neurologic injury and an upper eyelid hematoma in a child should raise suspicion for the less common orbital roof fracture (16). The zygomatic arches, zygomaticofrontal sutures, infraorbital rims, and nasal bones are palpated for tenderness or step-offs. The zygomaticomaxillary buttresses are most effectively palpated intraorally. Occlusion and midface stability are also scrutinized.

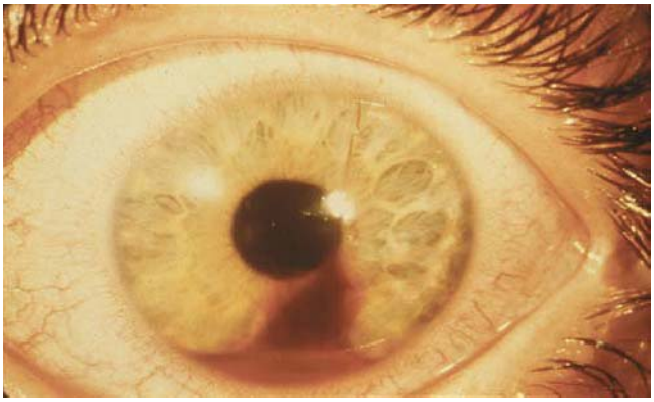


Figure 82.8 Visible hyphema (blood in the anterior chamber of the eye) shown in a patient. Hyphema is most frequently caused by blunt trauma. (Photograph courtesy of Michael P. Grant, MD.)

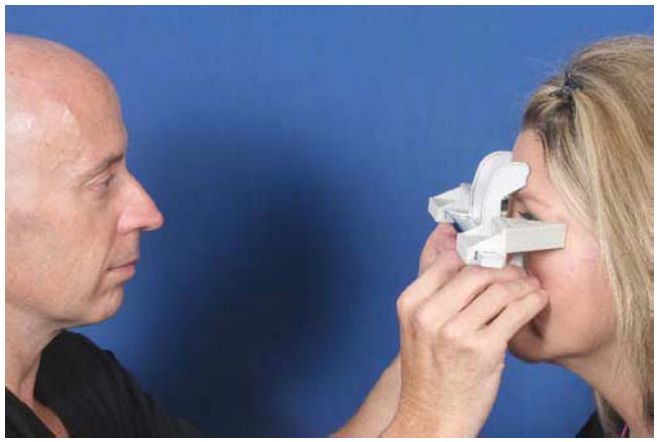


Figure 82.9 A Naugle exophthalmometer can be used to objectively measure enophthalmos. This exophthalmometer is stabilized on the supraorbital and infraorbital rims.

Indications for ophthalmologic evaluation in patients with orbital fractures remain controversial. Some advocate for an immediate and comprehensive ophthalmologic evaluation of every patient with an orbital fracture. In many institutions, this is difficult to achieve and probably unnecessary. At a minimum, it is advisable that the facial trauma surgeon document EOM, pupillary response, and an objective exam of visual acuity prior to any surgical intervention. A prospective study by Grant (17) has demonstrated that up to 30% of patients with orbital fractures have significant ocular injury that could lead to at least partial loss of vision if undiagnosed. Another study by Mellema et al. on the incidence of ocular injuries in patients with orbital fractures demonstrated that severe ocular injuries are extremely uncommon when patients are visually asymptomatic. Surprisingly, changes in visual acuity alone are a poor predictor of ocular injury. Pain, double vision, flashes of light (photopsias), blind spots (scotomata), and floaters are more sensitive indicators. The presence of any of these symptoms including changes in visual acuity is a clear indication for immediate consultation of an ophthalmologist (1).

INDICATIONS FOR SURGICAL MANAGEMENT

Many orbital fractures require intervention to return the patient to preinjury appearance and functional status. Modern approaches are safe and aesthetically acceptable when performed properly. Selecting the most appropriate surgical approach will optimize exposure and increase

the likelihood of successful treatment. Most orbital fractures do not require urgent intervention and can be repaired within 2 weeks. Resolving soft tissue may uncover enophthalmos and allow transient diplopia to resolve (18). Decreased swelling also facilitates improved surgical exposure. If any ocular injury is suspected, we obtain ophthalmology consultation after complex orbital trauma prior to surgical intervention. Evidence of hyphema, ocular rupture, or other globe injury should delay internal orbital approaches until an ophthalmologist can address the injury (19).

Orbital Blow-Out Fractures

Urgent treatment of orbital blow-out fractures is prudent in a select group of fracture patients. Though possible in adults, it is most often children who develop the closed trap door or "white-eyed" fracture that traps periorbital tissues and frequently the inferior rectus muscle (20). Profound entrapment and, rarely, the oculocardiac reflex (OCR) ensue. Even if the OCR is not present, these fractures should be repaired early to prevent irreversible damage to the incarcerated and ischemic inferior rectus muscle.

Indications and ideal timing for repair of more routine isolated orbital floor and medial wall blow-out fractures are unclear in many circumstances. Certainly patients with diplopia secondary to entrapment on the basis of physical examination (positive forced duction testing) or radiologic evidence merit exploration and repair within 2 weeks (18,21). Likewise, enophthalmos that develops immediately after a blow-out fracture will not improve and is likely to worsen without surgical intervention. Surgical candidacy of patients lacking early functional deficits is a greater dilemma. Traditionally, a CT demonstrating a fracture that involves at least 50% or 2 cm^2 of the floor and/or medial wall has been an indication for repair to prevent late enophthalmos. Pronounced rounding of the inferior rectus muscle is also used to identify patients who will benefit from surgery. Rounding of the inferior rectus with a height-to-width ratio greater than or equal to 1.00 on coronal CT scan is predictive of late enophthalmos development (22). Greater than 2 mm of soft tissue prolapse into the maxillary or ethmoid sinus is another proposed indication (5,23). Observing patients with less extensive fractures for 3 weeks or more may help to identify those who do not meet the aforementioned thresholds or criteria but will still develop enophthalmos. Patients in this category can be repaired in a delayed fashion and still have excellent outcomes (24).

Zygomaticomaxillary Complex Fractures

ZMC fracture repair is indicated whenever significant displacement occurs. The least invasive approach to achieve stable anatomic fracture reduction should be utilized. In select cases, a closed reduction alone is adequate. In many cases, multiple open approaches are required for exposure, anatomic reduction, and internal fixation. The most complex cases require a coronal approach to reestablish the contour of a comminuted zygomatic arch. The surgeon should consider intervention for patients with rotation and/or displacement of the body of the zygoma more than a few millimeters. Facial asymmetry will often be perceptible later if a displaced ZMC fracture is left untreated.

Though ZMC fractures involve the orbital floor, orbital floor exploration and repair is not indicated for all patients with ZMC fractures. Ellis reported that patients with preserved orbital contour did not receive orbital exploration at the time of ZMC repair and did not experience long-term sequelae from their orbital injuries. On the other hand, patients with one of the following two criteria were more likely to benefit from surgical exploration of the orbital floor while repairing the ZMC fracture: (a) comminution of the internal orbit sufficient to change orbital shape, increasing the volume of the bony orbit, and (b) significant prolapse of orbital soft tissues into the maxillary and/or ethmoid sinuses through the displaced fracture of the orbital floor even when it is not comminuted (5).

Orbital Roof Fractures

Since the majority of orbital roof fractures are non- or minimally displaced, they are often managed expectantly. Exceptions are blow-in fractures (Fig. 82.10) resulting in exophthalmos, levator dysfunction, or superior rectus entrapment (12). Growing linear fractures requiring repair



Figure 82.10 Orbital roof blow-in fractures are rare but can result in exophthalmos, levator dysfunction, and/or superior rectus entrapment. (Figure courtesy of Dr. Barton Branstetter).

are reported in children (25). Late complications such as encephalocele formation are sometimes cited as indications to uniformly intervene and repair orbital roof fractures. Encephaloceles do not occur routinely, and, if they do develop, delayed surgical management is effective (12,26).

SURGICAL TECHNIQUE

For orbital fractures requiring treatment, adequate exposure facilitates successful repair. A variety of surgical approaches will be described that can be used individually combined gain access to any area of the orbit. Once exposed, ZMC and orbital rim fractures are reduced and if necessary stabilized with low-profile titanium screws and miniplates. Blow-out defects can be successfully repaired with a variety of autogenous and alloplastic materials. While autologous materials, such as cranial bone grafts, were used extensively in the past, the majority of surgeons have switched to alloplastic materials for their ease in use and predictability (i.e., no potential for resorption) (23,27). Popular alloplasts include titanium mesh, porous polyethylene, or composite titanium mesh–porous polyethylene implants (28–30). Titanium mesh plates preformed to simulate the three-dimensional anatomy of the entire orbital floor and medial wall have become available in recent years. These plates are particularly useful for anatomic reconstruction of combined blow-out injuries to these areas. A common error when using any material to replace missing portions of the orbital floor or medial wall is inadequate restoration of the convexity that is present posteromedially (Fig. 82.5). Identifying an intact and stable posterior bony shelf—frequently the orbital process of the palatine bone—during fracture exposure is imperative for proper and anatomical implant positioning. Dissection distances of 40 mm from the infraorbital or medial orbital rim to identify this shelf are often necessary in severe fractures. Dissection to the stable shelf can be accomplished safely with meticulous technique. Still, surgical dissection to this shelf brings the surgeon within millimeters of the optic nerve, especially when dissecting along the medial orbital wall. Medial wall landmarks such as the ethmoid arteries must be utilized to prevent injury to the optic nerve.

New technologies including intraoperative CT scanning, stereotactic guidance, and three-dimensional modeling have bolstered facial trauma surgeons' armamentarium for the treatment of orbital fractures. Confirming anatomic reduction or repair with instant CT images is likely to improve outcomes and can potentially prevent or decrease costly returns to the operating room for revision procedures. The ability to preoperatively and intraoperatively mirror normal contralateral skeletal structure with stereotactic guidance makes restoring normal anatomy a more attainable goal in the most difficult cases where normal landmarks have been obliterated. The production of a three-dimensional model from preoperative CT scans for reconstructive planning can be useful in these circumstances as well. Use of new imaging technologies will increase in coming years as their availability expands and surgeons accumulate more experience with these valuable tools.

Orbital Floor

Transcutaneous approaches to the orbital floor were the mainstay for treatment of blow-out fractures for many years and continue to be in widespread use. Converse originally described the subciliary approach to the orbit in 1944 (31). He and others have also advocated a subtarsal variation of this approach. Both provide access to most of the orbital floor. The orbital rim incision is an alternative that the authors do not use or recommend because of the potential for visible scarring.

For the subciliary and subtarsal approaches, local anesthetic with epinephrine is infiltrated subcutaneously in the lower eyelid and along the inferior orbital rim. A lateral temporary tarsorrhaphy is performed on the operative eye for protection and retraction. The subciliary cutaneous incision is made 2 mm below and parallel to the lash line using a no. 15 blade (Fig. 82.11). The incision should be carried no further medially than the lower lid punctum. Laterally, the incision can be extended up to 15 mm beyond the lateral canthus. If this lateral extension is performed, it should be directed horizontally and not inferiorly to promote an aesthetically acceptable scar. A subcutaneous dissection superficial to the orbicularis oculi is followed inferiorly using either sharp dissection or the Colorado dissector until just inferior to the tarsal plate where the orbicularis is divided parallel to its fibers. It is crucial to preserve this rim of orbicularis over the tarsal plate to maintain lower lid structure and support. A preseptal plane is then followed down to the orbital rim. The

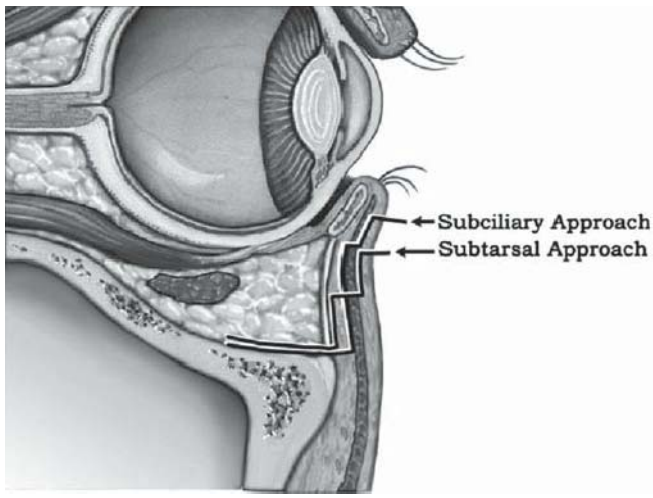


Figure 82.11 Paths traversed by the subciliary and subtarsal approaches through the lower eyelid are shown. It is important to step the incisions as shown to preserve lid integrity and avoid scar inversion. (From Humphrey C, Kriet JD. Surgical approaches to the orbit. *Operat Tech Otolaryngol Head Neck Surg* 2008;19:132–139, with permission).

periosteum is incised on the anterior aspect of the inferior orbital rim, and elevation proceeds posteriorly onto the orbital floor using a periosteal elevator. For the subtarsal variation of this approach, the skin incision is made in the subtarsal fold or 5 to 7 mm below the lash line when the fold is obscured by edema (Fig. 82.11). The orbicularis oculi is divided a few millimeters below the level of the skin incision to discourage scar inversion. Careful layered closure is the rule, taking care to restore orbicularis oculi continuity. A Frost suture is sometimes used to support the lid in the early postoperative period.

Over the past two decades, the transconjunctival approach has supplanted transcutaneous approaches in many surgeons' hands to decrease risks of postoperative lower lid malposition. Bourquett first described the inferior fornix conjunctival or transconjunctival approach for blepharoplasty in 1924 (32). Tenzel and Miller (33) later employed this approach for repair of orbital floor defects in the 1970s. Exposure of most of the orbital floor can be achieved through the transconjunctival approach.

To prepare for the transconjunctival approach, local anesthetic with epinephrine is infiltrated at the lateral canthus, just under the conjunctiva of the lower lid, and transcutaneously down to the orbital rim. Lateral canthotomy and inferior cantholysis is optional and can be performed using curved iris scissors and is optional to increase surgical exposure and minimize retraction of the lower eyelid. If the canthal release is not performed, great care must be taken to avoid excessive retraction that may lead to a higher incidence of lower eyelid malposition. With a Jaeger lid plate protecting the globe, the lower eyelid is everted and an incision is made with a Colorado dissector through the conjunctiva at least 2 mm inferior to the tarsal plate. The incision is continued through the lower lid retractors. Blunt dissection between the orbicularis oculi and orbital septum—a preseptal approach—proceeds using the malleable retractor and cotton-tipped applicators. Alternatively, the orbital septum can be incised to reveal a dissection plane between the orbital septum and periorbital fat—a postseptal approach (Fig. 82.12). A 5-0 silk mattress suture is placed through posterior edge of the conjunctival incision and positioned to passively retract the conjunctiva superiorly such that it covers the globe. Blunt dissection with a malleable retractor over the septum or orbital fat and a Ragnell retractor on the lower lid and orbicularis oculi will reveal the periosteum of the inferior orbital rim. The Colorado dissector is used to incise the periosteum on the anterior surface of the rim. The periosteum is elevated, and the malleable retractor can be used to continually retract the orbital contents and expose the desired portion of the orbital floor. No closure of the conjunctiva is needed so long as it is properly repositioned at the conclusion of the procedure. If canthotomy and cantholysis are performed, the tarsal plate is resuspended to the orbital periosteum near Whitnall tubercle using a single 5-0 polydioxanone suture. The canthus is reapproximated using a single 6-0 fast absorbing gut suture placed through the grey line of the lateral upper and lower lids. Interrupted sutures are used as needed to close any remaining canthotomy defect laterally.

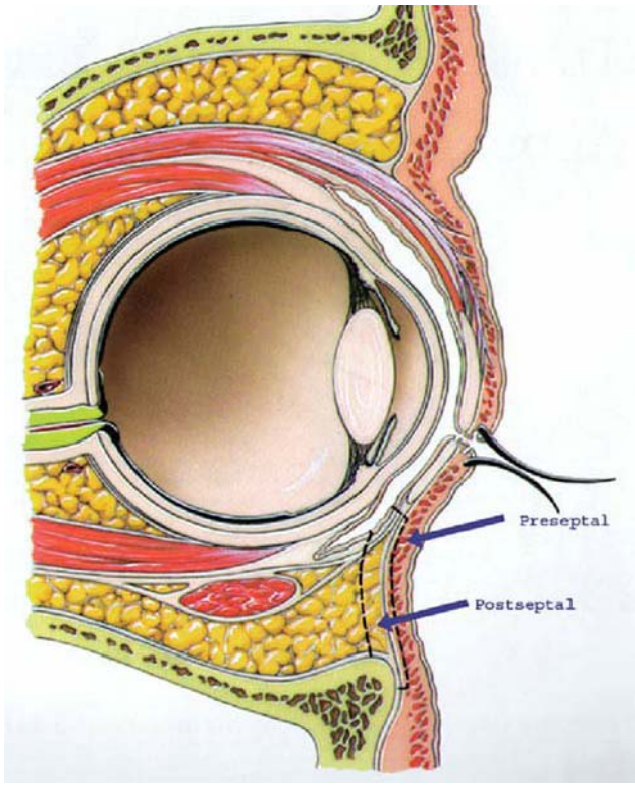


Figure 82.12 Paths traversed by the pre- and postseptal variations of the transconjunctival approach are shown. A hypothetical advantage to the postseptal approach is avoidance of undesirable scar formation between the orbicularis oculi and orbital septum. Such scar formation could contribute to postoperative lower lid malposition. (From Humphrey C, Kriet JD. Surgical approaches to the orbit. *Operat Tech Otolaryngol Head Neck Surg* 2008;19: 132–139, with permission).

Advantages to the subciliary and subtarsal approaches are that they are easy to learn and offer broad access to the orbital floor. Disadvantages are higher rates of postoperative lower lid malposition and visible scarring when compared with the transconjunctival approach (34,35). Technique in a transcutaneous lower lid approach must be flawless to minimize the risk of scleral show and ectropion. Rohrich argues that the subtarsal variation of this approach produces less risk of vertical lid shortening, scleral show, and ectropion but slightly greater risk of visible scarring. Innervation to the pretarsal and much of the preseptal orbicularis is better preserved through the subtarsal variant which may help maintain the preoperative lower lid position (36). Advantages of the transconjunctival approach include no visible scarring and decreased risk of ectropion when compared with the subciliary and other transcutaneous approaches (34,35). While the continually protruding periorbital fat can be an annoyance, a theoretical advantage of the postseptal variant is decreased incidence of postoperative lower lid malposition since the plane between the orbicularis oculi and orbital septum is not violated.

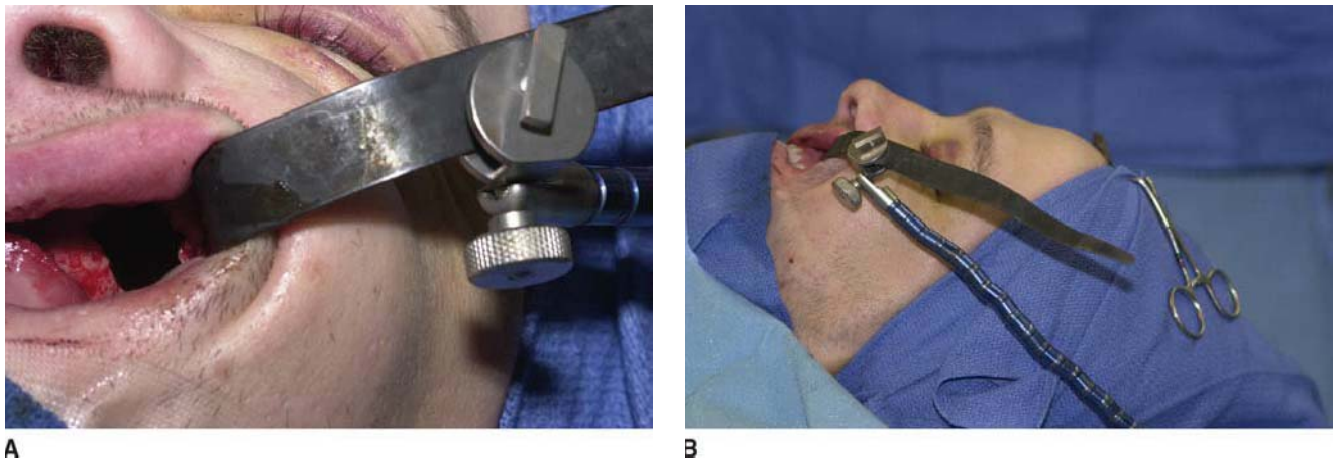


Figure 82.13 A 10- by 20-mm defect is then created in the anterior wall of the maxillary sinus for access to the orbital floor. As shown, the medial buttress, lateral buttress, and inferior orbital rim remain intact **(A)**. A Davida malleable neurosurgical retractor (Flexbar Machine Corporation, Islandia, NY) or similar is positioned to retract the ipsilateral cheek **(B)**. (From Humphrey C, Kriet JD. Surgical approaches to the orbit. *Operat Tech Otolaryngol Head Neck Surg* 2008;19:132–139, with permission).

A transantral endoscopic approach to the orbital floor has been advocated by some surgeons (37). This approach may be used as an isolated technique or combined with a more traditional periorbital approach to assist in fracture visualization and reduction. Endoscopic technique is not indicated for and has lost favor for treatment of routine orbital floor fractures (38).

The transantral endoscopic approach begins with a gingivolabial sulcus incision. The surgeon must preserve a 4- to 5-mm cuff of mucosa on the gingival side for closure. Maxillary periosteum is then incised. The lip is retracted, and a periosteal elevator is used to expose the anterior wall of the maxillary sinus up to the level of the infraorbital nerve. An osteotome and Kerrison rongeur are used to make a 10 by 20 mm defect in the anterior wall of the sinus (Fig. 82.13). Zero- and thirty-degree 4-mm telescopes are then inserted through the antrostomy to visualize the orbital floor (Fig. 82.14). The floor defect is usually obvious and mucosa can be elevated adjacent to the defect for visualization and reduction of the orbital contents.

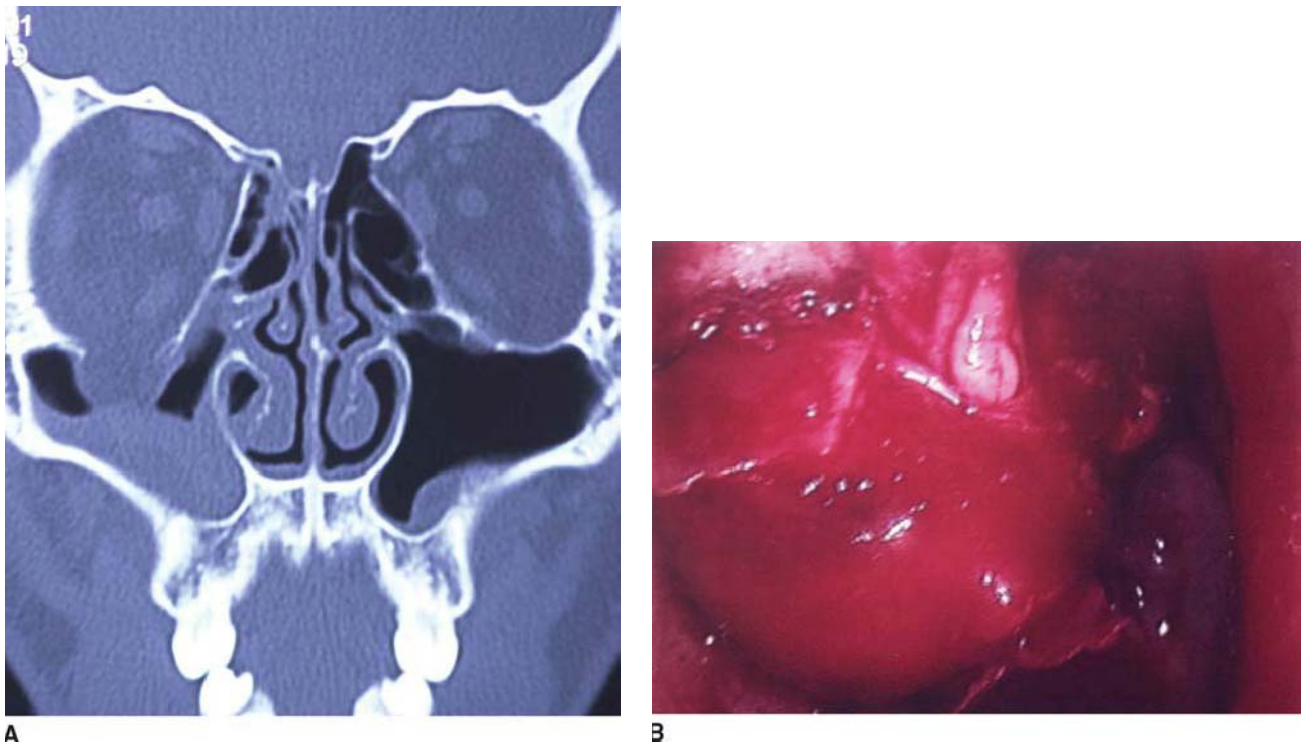


Figure 82.14 A right orbital blow-out fracture as identified with CT **(A)** and as visualized endoscopically via a transantral endoscopic approach with herniation of bone fragments, periorbita, and orbital fat into the maxillary sinus **(B)**. (From Humphrey C, Kriet JD. Surgical approaches to the orbit. *Operat Tech Otolaryngol Head Neck Surg* 2008;19:132–139, with permission).

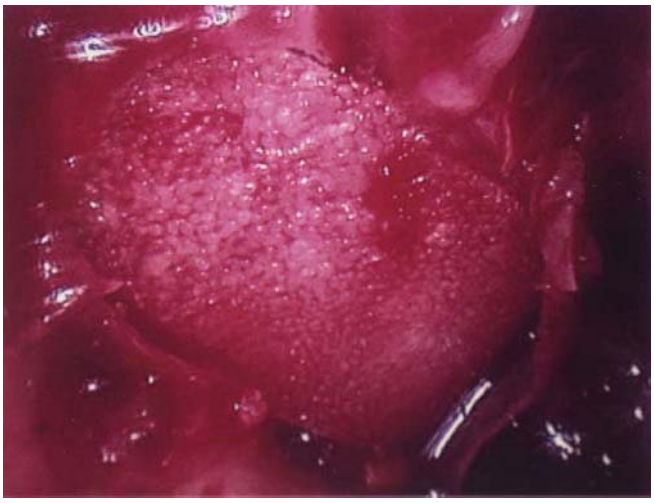


Figure 82.15 Orbital blow-out fracture shown in Figure 82.14 following reduction of herniated orbital fat and placement of a Medpor linear high-density polyethylene implant (Porex Surgical Inc, Newnan, GA) supported by the anterior and posterior shelves of the floor defect. (From Humphrey C, Kriet JD. Surgical approaches to the orbit. *Operat Tech Otolaryngol Head Neck Surg* 2008;19:132–139, with permission).

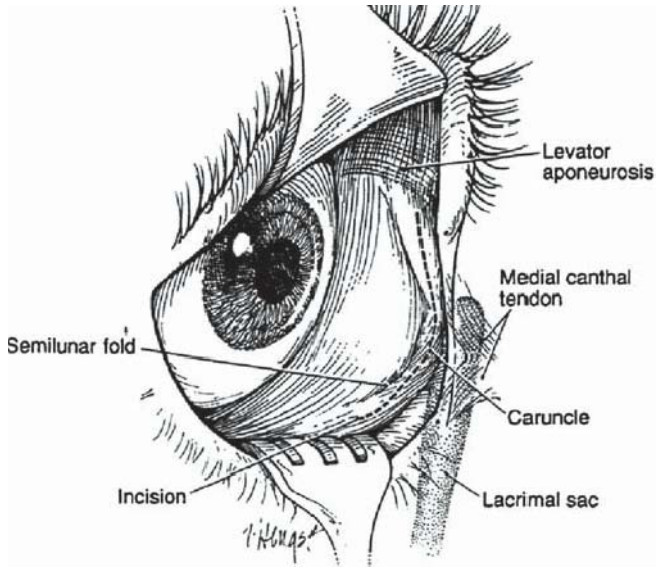


Figure 82.16 The transcaruncular incision is placed either over or just posterior to the caruncle in the sulcus between the caruncle and the semilunar fold. (From Shorr N, Baylis HI, Goldberg RA, et al. Trancaruncular approach to the medial orbit and orbital apex. *Ophthalmology* 2000;107:1459–1463, with permission).

Trap door or greenstick type fractures can occasionally be reduced using this approach alone without need for fixation if the bony floor "locks" into place. An implant can also be inserted if necessary by placing it first onto the posterior shelf and then sliding it up onto the anterior shelf (Fig. 82.15). Closure proceeds by reapproximating the gingivolabial sulcus mucosa using interrupted 3-0 polyglactin suture.

Reported advantages to the transantral approach include improved visibility of the posterior orbit and especially the posterior shelf of a floor defect. Disadvantages include difficulty in reconstructing the orbital floor lateral to the infraorbital nerve, the need to violate the anterior maxillary face in an isolated orbital floor fracture, and the need for specialized endoscopic instrumentation. Though perhaps a useful adjunct for complex cases, the transantral endoscopic approach does not seem to decrease morbidity or improve outcomes for most floor fractures (38).

Medial Orbit

Lynch first described his transcutaneous approach to the medial orbit and frontal sinus for sinusitis in 1921. Though refined somewhat, the approach is relatively unchanged from this original description. Access to most of the medial orbital wall is achievable through this approach (39).

Local anesthetic with epinephrine is injected over the ipsilateral nasal bone and the medial orbital rim. An incision is made with a no. 15 blade over the superomedial orbital rim from a point inferior to the medial brow to the superior aspect of the nasofacial junction. This incision is carried down through periosteum using the Colorado dissector. A periosteal elevator is used to expose the medial orbital wall, staying superior to the medial canthal tendons and lacrimal apparatus until posterior to these structures. If exposing the superomedial orbit, care should be taken to identify and cauterize or ligate the ethmoid arteries. The anterior and posterior ethmoid arteries serve as a useful depth gauge for the surgeon to estimate distance from the optic canal.

An alternative to the Lynch incision is the transcaruncular approach as described by Shorr. It allows access to the entire medial orbital wall posterior to the lacrimal fossa via a conjunctival incision (40). A Colorado dissector is used to make a 12 to 15 mm incision either through or just posterior to the caruncle and anterior to the semilunar fold (Fig. 82.16). The upper and lower lids are retracted with Desmarres retractors, and the globe is protected using small malleable retractors. A plane posterior to Horner muscle is developed with iris scissors until the posterior lacrimal crest is palpated. The Colorado dissector is then used to incise the periosteum posterior to the lacrimal crest, medial canthal attachments, and the lacrimal sac (Fig. 82.17). The periosteum is elevated along the lamina papyracea until the desired exposure is obtained. The anterior and posterior ethmoid arteries are ligated as necessary. If exposure of both the medial wall and floor of the orbit is desired, the transcaruncular approach can be combined with an inferior transconjunctival approach. In most cases, an implant can be placed to reconstruct two-wall defects while working around the inferior oblique muscle. If this is not possible, the inferior oblique can be divided near its insertion and reapproximated at the completion of the case. The surgeon should realize that any manipulation of the inferior oblique may have functional implications.

The transcaruncular approach is replacing Lynch's technique as the standard for access to the medial orbital wall because it eliminates the potential for visible scarring and webbing associated with the transcutaneous incision in this

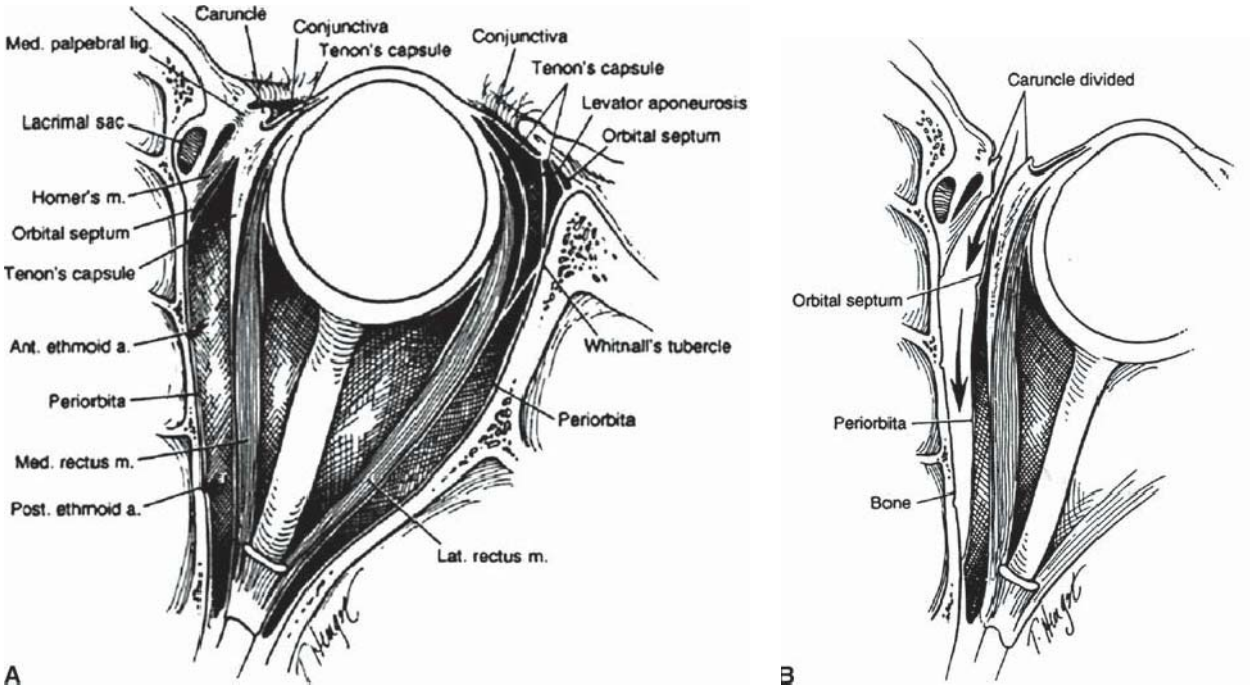


Figure 82.17 The transcaruncular approach follows a plane immediately posterior to Horner muscle down to the periosteum of the medial orbital wall posterior to both the canthal attachments and lacrimal apparatus **(A)**. Periosteal elevation can then proceed without disturbing these structures **(B)**. (From Shorr N, Baylis HI, Goldberg RA, et al. Trancaruncular approach to the medial orbit and orbital apex. *Ophthalmology* 2000;107:1459–1463, with permission).

area. One disadvantage to the transcaruncular approach is that it can be difficult to insert and manipulate an implant through the relatively small incision. Care must be used to avoid injury to the lacrimal apparatus by following the proper dissection plane to the posterior lacrimal crest.

Similar to transantral approaches to the orbital floor, transnasal approaches to the medial orbit have been proposed. Rhee described using a transnasal endoscopic approach either to place stenting material between the middle turbinate and a medial orbital defect or in conjunction with a transcaruncular or transconjunctival approach to facilitate precise placement of an implant for medial orbital wall reconstruction (41).

Prior to inserting endoscopes, the nose is first decongested using oxymetazoline on Cottonoid pledgets. A 4-mm 0 degree endoscope is then advanced into the nasal cavity. The middle turbinate is gently medialized with a Frazier suction or blunt-tipped right angle probe to visualize the uncinate process. Local anesthetic with epinephrine is injected along the uncinate process. A Kerrison rongeur is then used to remove the uncinate, leaving 3 to 4 mm superiorly to prevent formation of nasofrontal recess synechiae. The ethmoid bulla and maxillary os are identified. The majority of medial orbital injuries are associated with nasal trauma, and there may be significant intranasal damage in addition to the prolapsing orbital contents. Care must be taken to bluntly dissect the tissues and definitively identify landmarks as one proceeds to avoid creating or enlarging an orbital or skull base defect. The ethmoid bulla is entered using a small Frazier suction, and the ethmoid cells are opened back to the ground lamella, exposing the lamina papyracea and medial orbital defect. Orbital contents can be carefully reduced using both the transorbital and transnasal approaches at this point. When available, a CT stereotactic guidance system facilitates identification of the orbital defect and skull base.

A combined approach to the medial wall may offer the advantages of superior visualization and improved access during implant manipulation. A disadvantage of the transnasal approach is the potential increased risk for skull base injury and CSF leak. This approach also lacks utility as a single approach because of both limited space for implant introduction and the need to insert an implant blindly toward the eye. No increased morbidity from sinus disease postoperatively has been described (42).

Lateral Orbit and Orbital Roof

The lateral brow and upper blepharoplasty approaches are useful for accessing the zygomaticofrontal and zygomaticosphenoid sutures, most often affected in ZMC fractures. The lateral portion of the superior orbital rim and orbital roof can be exposed as well. Incision placement for each of these approaches is shown in Figure 82.3.

For the lateral brow approach, an incision is made just inferior and parallel to the hair follicles of the lateral 2 to 3 cm of the inferior brow. Some advocate making this incision within the brow, but this may result in undesirable

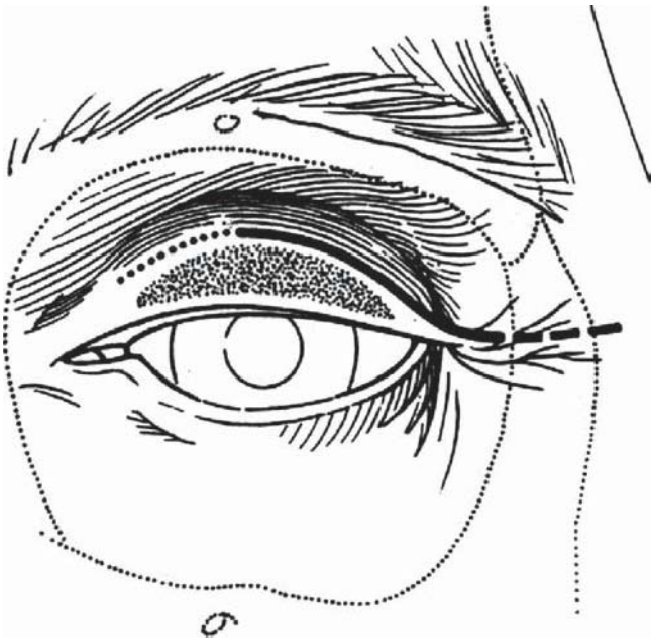


Figure 82.18 The brow incision is placed within or just below the hair follicles of the lateral 2 to 3 cm of the eyebrow. An upper blepharoplasty incision is placed in the lateral one-third to one-half of the supratarsal fold and can be extended as necessary, following a horizontal crease above the lateral canthus. (From Humphrey C, Kriet JD. Surgical approaches to the orbit. *Operat Tech Otolaryngol Head Neck Surg* 2008;19:132–139, with permission).

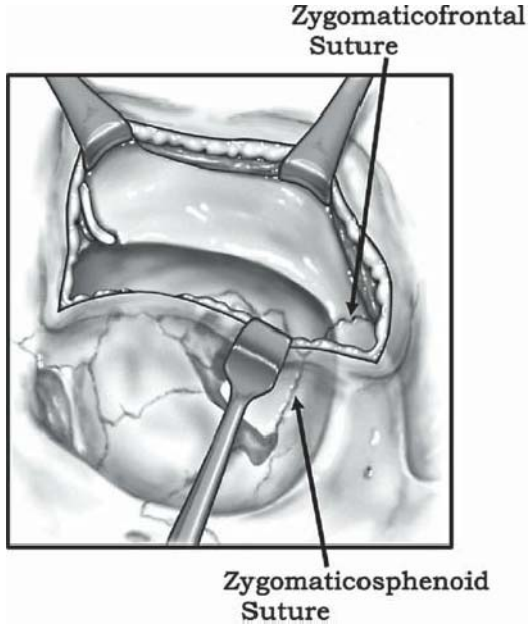


Figure 82.19 Zygomaticofrontal and zygomaticosphenoid sutures are exposed after subperiosteal elevation through an upper blepharoplasty approach. (From Humphrey C, Kriet JD. Surgical approaches to the orbit. *Operat Tech Otolaryngol Head Neck Surg* 2008;19:132–139, with permission).

alopecia. The periosteum over the lateral orbital rim is sharply incised and raised with an elevator to obtain the desired exposure. Meticulous layered closure should reapproximate the periosteum. It is crucial that meticulous layered closure is performed to secure the periosteum over any plates and reestablish orbicularis oculi continuity.

For the upper blepharoplasty approach, the supratarsal fold is marked (typically 7 to 9 mm above the ciliary line). The incision is extended within the fold and horizontally beyond the lateral canthus in a rhytid or skin crease as needed for exposure (Fig. 82.18). Local anesthetic with epinephrine is injected subcutaneously and down to the lateral orbital rim at the zygomaticofrontal suture. The skin is incised, and scissors or a Colorado dissector can then be used to traverse the orbicularis oculi, dividing the muscle parallel to the fibers. Dissection then proceeds to the lateral orbital rim and zygomaticofrontal suture in a plane superficial to the orbital septum and lacrimal gland. The periosteum is elevated over the rim and zygomaticofrontal suture as needed. If necessary, the superiolateral orbital wall can be dissected to assess zygomaticosphenoid suture alignment or gain access to the orbital roof (Fig. 82.19). Closure is performed in layers, again meticulously reapproximating the periosteum, orbicularis oculi muscle, and skin.

The primary advantage of the lateral brow approach is the simplicity of the technique. Disadvantages include the possibility of visible scarring and brow alopecia. It is because of this scarring that this approach has largely been abandoned and replaced by the upper blepharoplasty approach. The advantages of the upper blepharoplasty approach include ample access as well as a cosmetically superior scar (43,44).

For more extensive craniomaxillofacial reconstruction requiring broader access to the superolateral orbit, the coronal approach remains the workhorse. Additionally, it provides access to the medial orbits and zygomatic arches. Access to the lateral aspect of the infraorbital rims is possible by extending the incision along the preauricular creases. The coronal approach has been well described in the literature. For further reading, Frodel provides an excellent discussion of anatomical considerations and surgical technique for this approach (45). The primary advantage of the coronal flap is broad exposure and access to both orbits and the nasal skeleton that is unparalleled by any other approach. Disadvantages include incision length, extensive dissection, and potential morbidity including alopecia, forehead numbness, and potential for injury to the temporal branch of the facial nerve.

POSTOPERATIVE CARE

Forced duction testing should be performed in the operating room following any orbital approach with bony manipulation or implant placement. There should be unrestricted ocular mobility. Following surgery, the authors currently observe most patients undergoing orbital approaches in an inpatient facility overnight. Observation in this setting expedites recognition and treatment of postoperative orbital complications such as expanding hematoma. Vision checks for light perception and acuity are performed every 4 hours.

As previously discussed, color discrimination is a very sensitive indicator of optic nerve injury, and the ability to perceive the color red is a useful bedside test. Pain should also be monitored closely. Corneal abrasion is the most common cause of pain in the early postoperative period. However, an expanding retrobulbar hematoma should be suspected in the presence of progressive pain, visual changes, or increasing proptosis. These findings should prompt physician evaluation. A determination can then be made whether intervention or further observation is warranted.

Ice should be applied to the operative eye for 36 to 48 hours following surgery to decrease swelling and promote vasoconstriction. Tobramycin and dexamethasone ointment is applied to the eye twice daily for 1 week to maintain lubrication and decrease inflammation.

COMPLICATIONS

Diplopia

Diplopia may be the most common complication after surgical treatment of orbital fractures. In many cases, it is documented preoperatively and will persist temporarily because of edema. Forced duction testing showing free ocular mobility at the conclusion of the procedure gives the surgeon confidence that no persistent entrapment is present. Forced duction testing demonstrates clear improvement after release of entrapped rectus or periorbita in early cases but can be much more ambiguous if a delayed repair is performed (8). A postoperative CT scan can also be useful for ruling out entrapped soft tissues. In cases of entrapped rectus muscles that have been released, recovery of function can take many months and may not be complete. If the diplopia is persistent and bothersome to the patient, referral to ophthalmology is indicated for evaluation and treatment.

Vision Loss

Vision loss can occur with direct injury to the optic nerve or its vascular supply. Intraoperative mydriasis is a sign of pressure on the ciliary ganglion (located 1 cm anterior to the annulus of Zinn between the lateral rectus and optic nerve). When mydriasis develops, it should serve as a warning that excessive pressure is being applied to the intraorbital contents; it is not necessarily a direct indication that the optic nerve has been damaged (46). Postoperative hemorrhage can result in blindness if not treated immediately. If the patient develops visual changes such as decreased color discrimination or loss of acuity associated with increased intraocular pressure and proptosis, an expanding retrobulbar hematoma must be suspected. Canthotomy and cantholysis should be performed immediately at the bedside to decrease intraocular pressure. Wound exploration, removal of the implant, and hematoma evacuation in the operating room are also indicated. Immediate ophthalmology consultation should be obtained in any case of decreasing visual acuity but should not delay initial treatment.

Lid Malposition

Lower lid malposition in the form of retraction or ectropion is a complication that develops at least temporarily in 28% to 42% of transcutaneous approaches to the orbital floor (34,35). In transconjunctival approaches, the combined incidence of ectropion, entropion, and scleral show has been reported at less than 0.5% (47,48). Misplaced conjunctival incisions or thermal cautery injury may damage the tarsal plate and increase the risk of entropion and scleral show. There is also potential for symblepharon, or scar formation between the tarsal and bulbar conjunctival surfaces. A theoretical and controversial increased risk of lower lid malposition exists using a preseptal rather than a postseptal approach because of scar which may form between the orbital septum and orbicularis oculi following a preseptal dissection. Some cases of postoperative ectropion and entropion are transient and will resolve with massage and observation over a few weeks. If persistent, surgical repair may be required for correction.

HIGHLIGHTS

- Orbital fractures requiring treatment commonly occur secondary to blunt trauma incurred during violent assaults, accidental injury (falls, sports injuries, work-related), or motor vehicle accidents. These patients must be initially evaluated according to current ATLS protocols. Once stabilized, the facial trauma surgeon performs a focused orbital evaluation.
- Fine-cut CT scanning is the gold standard for radiographic evaluation of orbital injuries. Axial images are useful in evaluating medial wall fractures. Coronal images provide excellent views of the orbital floor, medial wall, and roof. Sagittal images are helpful in assessing the position of the stable posterior shelf.
- Clinical history should document mechanism of injury, previous eye surgery, double vision, numbness, preinjury vision status, and comorbidities. The physical examination should document visual acuity, pupillary response, ocular trauma, globe position, extraocular motility, diplopia, and cranial nerve function.
- Urgent treatment is indicated for closed trap door or "white-eyed" blow-out fractures. These fractures occur most commonly in the pediatric population and may be associated with the OCR.

- Firm indications for repair of orbital blow-out fractures include clinical enophthalmos or diplopia associated with entrapment confirmed by forced duction testing or radiographic imaging. The finding of inferior rectus rounding on CT scanning may identify patients at risk for developing delayed enophthalmos.
- For orbital floor fractures, the transconjunctival approach has largely replaced transcutaneous approaches given a lower incidence of ectropion.
- The transcaruncular approach is a versatile alternative to the Lynch approach for the treatment of medial orbital wall fractures. The former avoids the medial canthal scarring and webbing associated with the Lynch approach.
- The lateral orbital wall can be approached via an upper blepharoplasty incision that avoids brow scarring. Exposure of the zygomaticofrontal and zygomaticosphenoid sutures is readily accomplished with this approach.
- Newer technologies include interoperative CT scanning and navigation, preoperative planning software, and rapid prototype modeling. Increasing availability will assist surgeons in the successful treatment of the most challenging cases.
- While postoperative complications are rare, the clinical finding of progressive pain, increasing proptosis, and visual changes should alert the physician to the possibility of an expanding retrobulbar hematoma. When suspected, emergent bedside canthotomy and inferior cantholysis should be performed.

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Nasal Fractures

83

Grant S. Gillman *Carlos M. Rivera-Serrano*

INTRODUCTION/PERSPECTIVE

The face is the most visibly apparent feature of the body, and even a subtle alteration or asymmetry may be appreciable to the untrained eye. Due to the thin skin overlying the nasal dorsum, it has been said that a displacement of even as little as a few millimeters may be perceptible (1). Furthermore, beyond the aesthetics of the nose, it is equally important to consider the functional impact that trauma may bring to bear on the nasal airway.

Not surprisingly given the prominence of the nose as a facial feature, the nasal bones are the most commonly fractured of all facial bones and the third most common fracture of the adult human skeleton (2–14). It has been estimated that there are approximately 50,000 nasal fractures per year in the United States though the actual number is likely higher due to underreporting, patients not seeking medical attention, and fractures that are overlooked in the multitrauma setting (7,9). Nasal fractures occur two to three times more frequently in males and are most commonly seen between 14 and 50 years of age (7) with a peak incidence between the second and third decades of life (6).

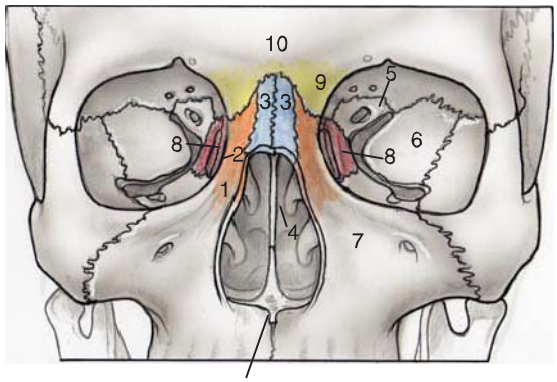
Of all facial fractures, about 40% involve the nose (3,9,15). When one considers all patients with facial skeletal fractures, about 20% will have multiple facial bone injuries and so even in those cases where only an isolated nasal fracture is suspected, it becomes critical to complete a thorough examination (16). Kim and Yoon (17) have reported that 47% of all nasal bone fractures are associated with fractures of the nasal septum, and in a different study where the septum was explored in all patients undergoing fracture reduction, Rhee et al. (11) reported that septal fractures were actually identified in over 90% of nasal fractures (8).

Individuals with a prior history of nasal fractures have a 15% to 20% chance of sustaining another nasal trauma in the future, as the "lifestyle" of some patients may increase their predisposition to repeated nasal trauma (7). In those who have had a prior rhinoplasty, the nasal bones may fracture more easily and the incidence of nasal bone fractures may also be higher than in the general population (18).

There are multiple considerations, treatments, and differing opinions when it comes to the treatment of nasal fractures but surgeons generally agree that an optimal outcome should address both cosmetic and functional issues. Recommended treatments for nasal fractures range from no intervention at all (if undisplaced and asymptomatic) to extensive surgery using rhinoplasty techniques through open approaches (19,20). One of the most challenging aspects of managing nasal fractures remains the high incidence of a posttraumatic nasal deformity, either externally or in terms of the nasal airway. At a minimum, the goal of nasal fracture management should be to reestablish the preexisting nasal airway and cosmesis. Beyond that, if there was already preexisting pathology, one is very unlikely to attain an optimal nasal airway and cosmetic result with closed reduction techniques alone. The difficulty in the management of nasal fractures is that even when they are recognized, the mechanism of injury and pathophysiology are often poorly understood leading to inappropriate treatment and suboptimal outcomes.

STRUCTURAL ANATOMY

The external nose is pyramidal in shape and mainly composed of the thin nasal bones, the thick frontal (ascending) process of the maxilla, the nasal process of the frontal bone, and the upper and lower lateral cartilages. The paired nasal bones articulate with each other at the midline, with the frontal bone superiorly and ascending process of the maxilla superiorly laterally (Fig. 83.1). The nasal bones tend to be thinner and broader at their caudal end and are therefore more vulnerable to fractures inferiorly than superiorly (21).



1, Ascending process of maxilla; *6*, Sphenoid Greater Win;
2, Fossa for lacrimal sac; *7*, Body of maxilla;
3, Nasal bones; *8*, Lacrimal bone;
4, Nasal septum; *9*, Nasal process of frontal bone;
5, Sphenoid lesser wing; *10*, Frontal bone (Glabella).

Figure 83.1 Structural anatomy of the nose.

The cartilages that contribute to nasal structure are the upper lateral, lower lateral or alar, sesamoids, and the quadrangular septal cartilage. The triangular or trapezoidal-shaped upper lateral cartilages, by virtue of their attachments to the undersurface of the nasal bones superiorly and the dorsal septum medially help provide significant support to the midline location of the septum and the stability of the middle nasal vault (5,22). The lower third of the nose is made up of a complex architecture and relationships between the cartilages, nasal septum, and soft tissue. The lower lateral cartilages are one of the major nasal tip support mechanisms and the strength, resiliency, and orientation of these structures will affect both tip projection, tip symmetry/alignment, and stability of the lower third of the nasal sidewall and the external nasal valve (23).

The nasal septum is made up of the quadrangular cartilage anteroinferiorly, the perpendicular plate of the ethmoid bone superiorly, and the vomer posteroinferiorly. The quadrangular cartilage articulates along its dorsal edge with the upper lateral cartilages and inferiorly along the floor of the nose with the maxillary crest. The septal cartilage acts as a central strut or "tent pole," supporting the middle and lower thirds of the nasal dorsum (20,21). The perpendicular plate of the ethmoid and the vomer articulate with the posterior end of the septal cartilage caudally and the nasal bones anteriorly, but provide less support to the upper third of the nasal dorsum than the quadrangular cartilage does to the lower two-thirds of the nose (20,21).

The nose has a very rich blood supply. The blood supply of the external nose is provided through branches of the internal and external carotid systems—the facial artery anteriorly (which becomes the angular artery superomedially) and the infraorbital and ophthalmic arteries dorsally. Internally, the blood supply to the lateral nasal wall comes from the sphenopalatine artery posteroinferiorly, and the anterior and posterior ethmoidal arteries superiorly (24).

The skin and soft tissue of the nose varies in thickness, being loose and thinner in the dorsum and upper third, and thicker and more adherent at the tip (22). Sensory innervation of the nose is provided by branches of the ophthalmic (V1) and maxillary (V2) divisions of the trigeminal nerve.

PATHOPHYSIOLOGY—MECHANISM OF INJURY

Less force is required to fracture the nasal bones than any other fracture of the facial skeleton (14,25,26). Blunt nasal trauma is a more commonly seen mechanism of injury than penetrating nasal trauma, and lateral forces occur more frequently than frontal or inferior forces. Inherent variations in anatomy as well as the amount and direction of applied forces will influence the fracture pattern and resulting deformity (14,25,26).

With respect to individual anatomic variation, comminuted fractures are more likely to occur in elderly patients because their nasal bones tend to be thinner. In children, dislocations are more common than fractures owing to the fact that the nose has a higher proportion of cartilage to bone in the pediatric population.

In general, the greater the force of impact the more significant the expected nasal deformity. Furthermore, because the caudal end of the nasal bones is thinnest, a fracture of the thicker more cephalic aspect of the nasal bones requires greater force and is therefore more likely to be associated with other facial fractures.

While variability is inevitable with respect to both susceptibility to nasal fractures and nasal fracture patterns, cadaveric studies have enabled some general observations to be made (25,27,28). Although fractures are more commonly caused by a lateral force, a blow from any vector can fracture the nose. A greater force is required to fracture the nose from a frontal impact than lateral impact, because the nasal bones are to some extent buttressed to a frontal blow by the perpendicular plate of the ethmoid bone, the elasticity of the septal cartilage, the anterior nasal spine, and the frontal process of the maxilla.

A less forceful lateral impact may result in undisplaced sidewall fractures, without symptomatic nasal obstruction and should not require any manipulation or treatment. With increasing lateral force an ipsilateral displaced nasal bone infracture first occurs, without affecting either the septum or contralateral nasal bone (Fig. 83.2). This will be apparent externally and can affect the nasal airway as well and as such reduction is recommended. The ipsilateral depression may create the illusion of curvature to the nose (Fig. 83.3), but typically the contralateral bone is not particularly tender, thereby suggesting the diagnosis of a unilateral fracture. As force increases, a lateral impact will break both nasal bones (often an ipsilateral infracture and contralateral outfracture) (Fig. 83.4) as well as the bony and/or cartilaginous septum secondarily with lateral displacement of the entire nasal pyramid and obstruction of the nasal airway (Fig. 83.5).

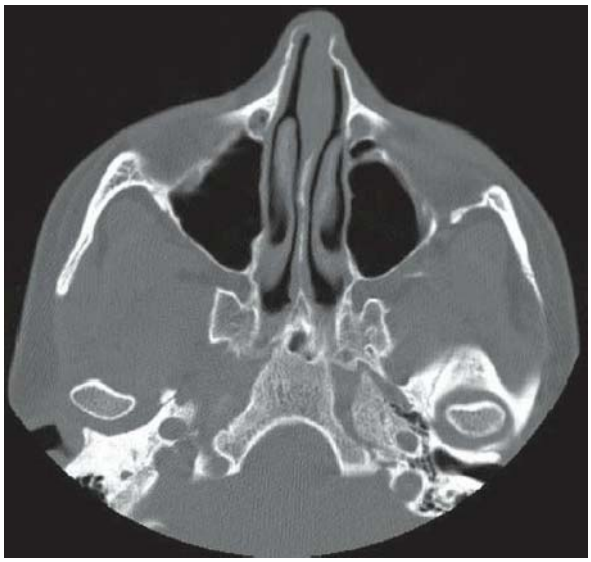


Figure 83.2 Axial CT scan showing unilateral depressed fracture of left nasal bone.

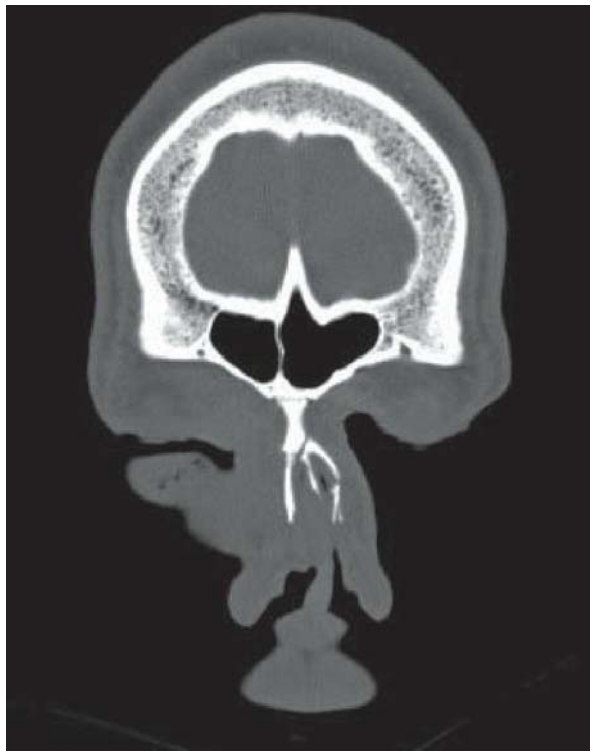


Figure 83.4 Coronal CT scan showing bilateral displaced nasal bone fractures with concomitant nasal septal fracture.

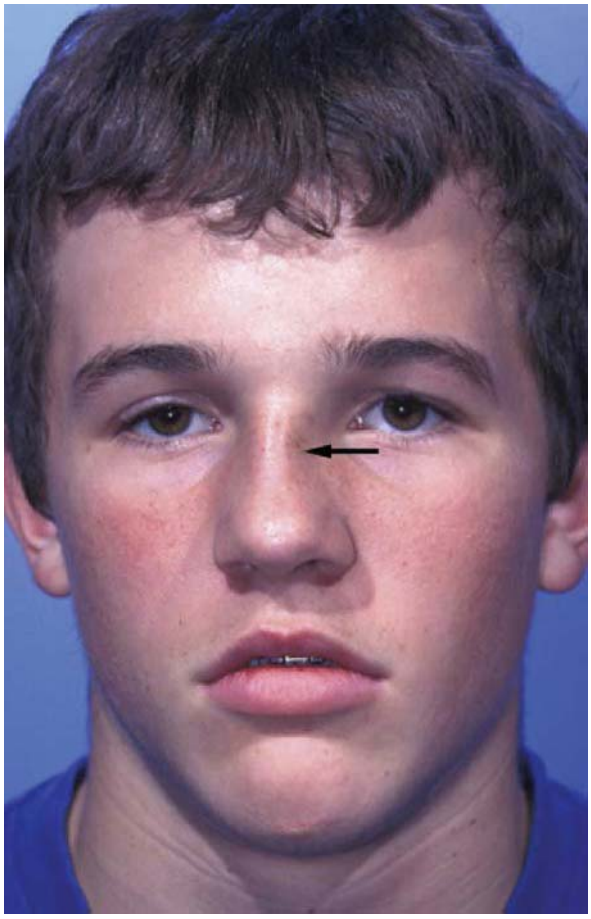


Figure 83.3 Unilateral impacted left nasal bone fracture (*arrow*) generating the illusion of an apparent curvature of the nose to the patient's right.

Similar to the situation with lateral forces, a lesser amount of frontal force may fracture the thinner distal end of the nasal bones without visible displacement or external deviation. If there is sufficient force for displacement of the nasal bones, the upper lateral cartilages, which are attached to the undersurface of the nasal bones may get impacted with the nasal bones or avulsed from the nasal bones with both an external deformity and a reduction in nasal airflow. As the force from a frontal impact increases, the septum may buckle, dislocate, or fracture and the bony nasal cap can be impacted (Fig. 83.6), comminuted, and splayed with widening of the nasal bridge and lateral displacement of the nasal bones. Fracture or dislocation of the septum will inevitably lead to nasal airway obstruction.

A very forceful frontal or central impact to the osseous and cartilaginous nasal structures can be transmitted posteriorly to the nasoorbitoethmoid (NOE) complex leading to nasoethmoidal fractures (8). A NOE fracture is a complex fracture that can involve the nasal, ethmoid, frontal, lacrimal, maxillary, and orbital bones as well as the cribriform plate. A complete review of NOE fractures is beyond the scope of this chapter, but they should be recognized as the treatment is far more complicated and the sequelae, if untreated, much more disabling. These patients will present with additional signs and symptoms that can include marked periorbital edema and ecchymosis, telecanthus, enophthalmos, epiphora, telescoping of the nasal dorsum with a flattened nasofrontal root and midfacial retrusion, and possibly a cerebrospinal

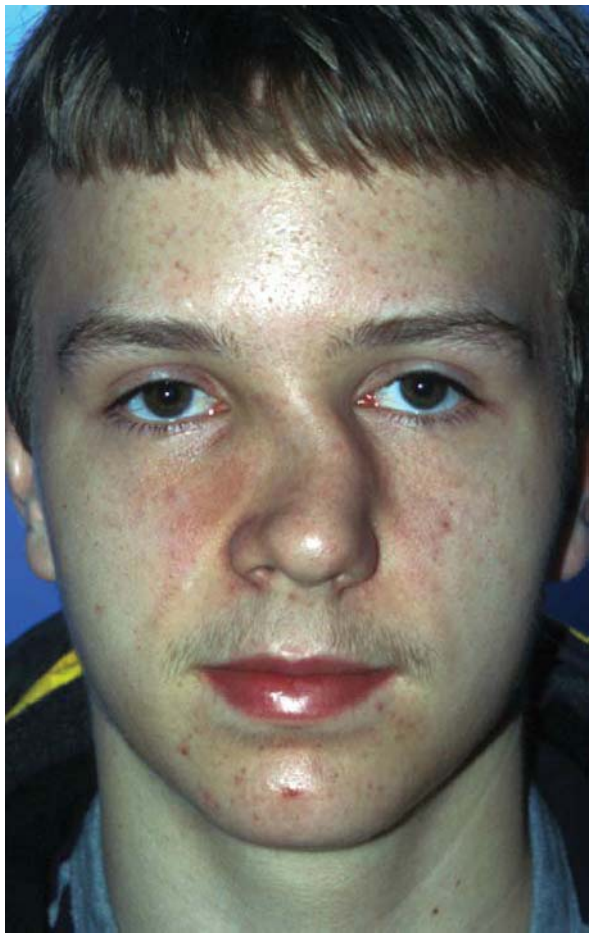


Figure 83.5 Patient with acute, bilateral displaced nasal bone fractures.

fluid (CSF) leak. Further discussion and management is reviewed elsewhere in this text.

Injury to the nose from an inferior vector is more likely to traumatize the cartilaginous septum with or without a fracture of the nasal bones themselves. Sufficient impact from below can dislocate the caudal septum off of the anterior nasal spine or maxillary crest with displacement to one side or the other. This can result in asymmetry of the nostrils and nasal base, inferior septal spurs, and even twisting of the nasal tip because of the proximity of the caudal septum to the lower lateral cartilages. Fractures of the septal cartilage can also occur with telescoping of segments leading to columellar retraction and/or nasal obstruction.

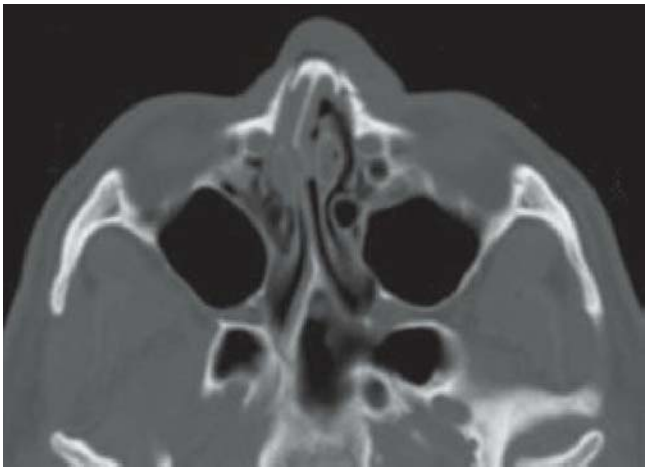


Figure 83.6 Axial CT scan showing impacted fracture of bony nasal cap.

The severity of airway obstruction accompanying nasal fractures depends on the location of the septal fracture and the presence of septal displacement with the latter being the most important variable in nasal obstruction (10). The nasal septum functions somewhat as an energy-absorbing structure (8), with the ability to dissipate a certain amount of force and rebound without significant deformity. Beyond that point, the septum will either dislocate or fracture.

Dislocations, as opposed to fractures, are more commonly seen where the cartilage tends to be thicker and stronger—namely right at the bony–cartilaginous interfaces (28), either posterosuperiorly at the perpendicular plate of the ethmoid bone or inferiorly at the maxillary crest. On physical examination, this would correspond, respectively, to either angulation of the quadrangular cartilage at the junction with the perpendicular plate of the ethmoid or the appearance of a long septal spur inferiorly.

Fractures of the septum on the other hand tend to occur in the thinner central portion of the quadrangular cartilage above the bony cartilaginous interface or through the bony septum (ethmoid and/or vomer) (28). In separate cadaveric studies, Murray et al. (25) and Harrison (28) noted remarkably similar septal fracture patterns with application of sufficient impact force. The fracture line in the cartilaginous septum was typically several millimeters above the maxillary crest, extending posteriorly into the bony septum and curving upward through the vomer into the vertical plate of the ethmoid to yield a C-shaped fracture pattern (Fig. 83.7). Fracture fragments can then either overlap, telescope, or pivot to obstruct the nasal airway. Rohrich and Adams (29) likewise noted that low-velocity injuries tended to occur inferiorly as either dislocations or fractures, while high-velocity injuries or frontal impacts resulted in more extensive fractures in the thin central portion of the septal cartilage extending posteriorly into the ethmoid or vomer.

Another observation of Murray et al. (25) in their cadaveric study of fracture patterns was that if the nasal bones were displaced by more than half the width of the nasal bridge there was inevitably a concomitant C-shaped fracture of the bony and cartilaginous septum as described. Under such circumstances, they concluded that open treatment of the septum with resection of the interlocked or overlapped segments incorporating the fracture inferiorly and posteriorly was required in order to achieve optimal alignment of nasal injuries of this severity. The implication of septal fractures as they relate to success or failure in the management of nasal fractures is discussed at greater length later in this chapter.

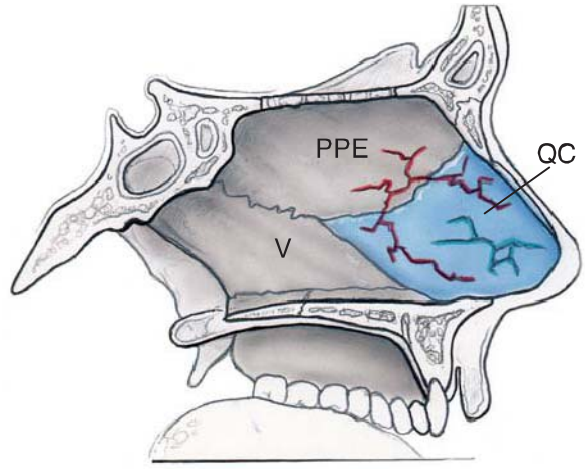


Figure 83.7 Typical nasal septal fracture pattern seen in cadaveric studies. (V = vomer, PPE = perpendicular plate of ethmoid bone, QC = quadrangular cartilage)

DIAGNOSTIC ASSESSMENT

The diagnosis of a nasal fracture is generally made based on the history and clinical exam. Patients who present with nasal trauma may well have additional injuries and should be routinely examined in a comprehensive and orderly fashion as with any other trauma patient to minimize the likelihood of overlooking concomitant injuries.

History

A thorough history is the cornerstone of the diagnosis and will frequently guide the management of nasal fractures as well. It is helpful to know when the incident occurred, the mechanism of the trauma, the direction of the force, patient symptomatology (in particular, whether or not there has been any alteration in alignment or change in the nasal airway), whether or not there is a prior history of nasal trauma or nasal surgery, the patient's medical history and comorbidities, age, and patient expectations. Epistaxis is considered to be a sine qua non for nasal fractures (30) and suggests a disruption of or tear in the nasal mucosa.

Understanding the mechanism of injury is helpful for the workup and management of the patient with nasal trauma, but is not as critical as the physical exam for planning the reduction or surgical technique. As discussed earlier, the velocity and force of impact will influence the pattern and extent of the underlying injury. In general, a greater impact should heighten one's suspicion for additional injuries, for a more complex nasal fracture pattern, and for an associated septal fracture or dislocation.

The timing of the injury is another important variable to know in the scenario of a nasal fracture. Management decisions regarding nasal and septal fractures depend on reliable visual and tactile information that the surgeon interprets when first examining and later manipulating or reducing the nasal complex. Excessive soft tissue edema can mask minor or modest irregularities and preclude an accurate understanding of the fracture pattern and degree of displacement. The classical two windows of opportunity for nasal fracture management described in the literature are therefore based on the rationale of manipulating the nasal complex in the absence of significant edema. Nasal edema is generally limited within the first 2 to 3 hours after the trauma, and has settled to a certain degree 5 to 10 days after the injury. On the other hand, after 2 to 3 weeks of healing a fibrous union is developing across the fracture line making the reduction more challenging and often mandating the use of osteotomies that might have otherwise been unnecessary to enable repositioning of the nasal framework.

As with any surgical patient, the past medical history is relevant. A prior history of nasal and septal trauma or nasal surgery is an important consideration, as it may influence the surgical approach as well as what outcome is potentially achievable. One should also review comorbidities and medications that may contraindicate surgery or influence choice of anesthesia.

It is essential, as much as is possible, to determine the pretraumatic appearance of the nose with respect to alignment and likewise to inquire whether any nasal airway obstruction existed previously. An acute nasal fracture in the setting of an old fracture with secondary deformity is a challenging predicament, as simple closed reduction then becomes unlikely to completely achieve a perfect cosmetic or functional outcome. Patients may not always accurately describe and differentiate between newer and older deformities; therefore, a review of photographs dating from before the injury can be very helpful. On the other hand, most patients are more reliable when it comes to telling the surgeon about the presence or absence of some degree of premorbid nasal airway obstruction. Ultimately, it is perceived changes in alignment and the nasal airway that are the two most important indications for which surgical intervention is warranted.

Questions about rhinorrhea, and new snoring or sleep apnea are also relevant. Persistent clear rhinorrhea after nasal trauma should raise the suspicion of a skull base or frontal sinus fracture and a CSF leak. In these cases, a beta-2 transferrin test is helpful in assisting in diagnosis and more detailed imaging (computed tomography [CT] scan) is warranted. New snoring or apnea may be consistent with new-onset nasal airway obstruction and elevated airflow resistance.

Patient expectations are also very relevant to management decisions. Expectations may vary by age, gender, personality, religion, profession, and education among other variables. In general, there are three types of patients with displaced nasal fractures that are encountered in clinical practice. There are those that are not concerned about minimal or modest change in their nasal appearance or nasal function, those that just want their pretraumatic appearance and/or function restored, and those that see the situation as an opportunity to improve their pretraumatic cosmetic appearance

and/or nasal function. Not uncommonly, older individuals and males tend to be less concerned about changes in nasal appearance or minimal degrees of nasal obstruction.

Those not interested in a reduction when indicated should be advised of the potential for persistent deformity or nasal obstruction, and the possibility of more involved surgery if undertaken once all is healed. As regards cosmetic adjustments (over and above alignment) on the other hand, caution should be exercised before agreeing to undertake any effort to simultaneously implement aesthetic rhinoplasty as swelling and structural instability are likely to thwart such efforts resulting in suboptimal outcomes or a higher risk of needing revision surgery. The fundamental objective of managing nasoseptal fractures is that at a minimum, the surgeon should strive to reduce the fractures to the pretraumatic baseline. In some cases, however, the surgeon may elect to improve the nasal airway at the same time in the patient who had preexisting nasal airway pathology even if not altered by the most recent trauma.

The patient's age is another important determinant in the management of nasal and septal fractures. Nasal fractures in children are discussed later in the chapter. Fractures in elderly people are managed similarly to the rest of adult population. However, owing to different expectations and comorbidities, this patient population will often opt for a less aggressive approach.

Physical Exam

The goal of the physical examination should be to establish a diagnosis, determine whether or not associated injuries may exist, and determine what if any intervention is required. A complete external and endonasal evaluation should be performed. Visual inspection and palpation are equally important.

Physical findings consistent with the diagnosis of a nasal fracture include edema, infraorbital/paranasal ecchymosis, tenderness to touch, bony crepitus, and possibly a palpable step-deformity if new. Any shift or displacement of the nasal pyramid should be noted as well as depressions, ridges, and whether the fracture is unilateral or bilateral. Widening of the midface, telecanthus, restricted extraocular movements, or dental malocclusion are not seen with isolated nasal fractures and should alert one to investigate for additional maxillofacial injuries.

Endonasal examination is performed with a nasal speculum and a headlight (anterior rhinoscopy) and, if available the use of a rigid nasal endoscope enables a more complete evaluation. The endonasal exam is facilitated by the use of a topical decongestant and local anesthetic. Unfavorable functional and aesthetic outcomes are most commonly related to unrecognized septal fractures with significant displacement and accordingly an adequate and complete exam of the nasal septum is critical (5,19,20,29).

Endonasal examination should include an assessment of the septal position and nasal airway, in addition to inspecting for a septal hematoma, abscess, mucosal tears, septal fractures, or dislocation off the maxillary crest. Mucosal tears have been found to be highly suggestive of septal fractures (11). As noted earlier, dislocations or displaced and angulated fractures can be seen anywhere along the septum but occur most commonly at or close to bony–cartilaginous interfaces.

A septal hematoma is characterized by a reddish purple or bluish bulge or fullness along the nasal septum. Septal hematomas can be unilateral or bilateral and typically involve the cartilaginous portions of the septum. If suspected, on palpation of the suspicious swollen area with an instrument or a cotton swab it will feel puffy and compressible. Needle aspiration is frequently diagnostic. If untreated, a septal hematoma can lead to infection, abscess, and secondary septal cartilage necrosis with loss of dorsal support and a supratip saddle deformity (Fig. 83.8). In addition, fibrosis between the perichondrium and septal cartilage can also lead to septal deformities, a thickened septum, and retraction of the columella (31). Small hematomas may be aspirated and observed, but larger hematomas may require incision and drainage, followed by nasal packing to prevent reaccumulation. Systemic antibiotics are recommended while packing is in place.

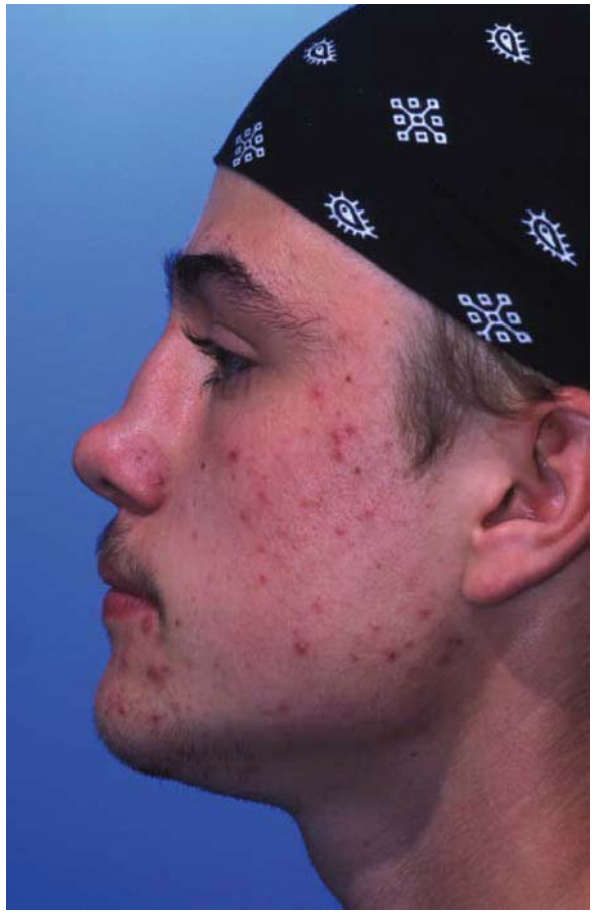


Figure 83.8 Supratip saddle deformity, which developed despite drainage of a septal abscess.

Imaging

Imaging is not routinely required for the diagnosis or clinical management of isolated nasal trauma (32,33). Both false positives and false negatives are commonly seen with plain radiographs and numerous reports have documented their lack of utility in decision making as it pertains to the management of nasal fractures (7,33,34). Old fracture lines, vascular markings, suture lines, and overlapping bone shadows can all be mistaken for fractures on plain x-rays. Furthermore, as most nasal bone fractures heal by a fibrous union, an older fracture line may remain visible and therefore prior or preexisting fractures cannot be reliably distinguished from new ones with imaging. Facial photographs are likely to be of greater benefit both clinically, and if necessary, medicolegally.

If, however, more extensive injury to the facial skeleton is suspected, then a CT scan of the facial bones is warranted. Not infrequently, patients will present to the surgeon with a CT scan ordered for the workup of other injuries, and while this might be helpful to classify or evaluate the characteristics of the fractures, the images are not ultimately necessary for directing the management of isolated nasal injuries.

There are some advocates of ultrasonography as an emerging technology for the assessment and management of nasal fractures. Different authors have suggested that high-resolution ultrasound might be more accurate than a CT scan (35) or plain x-ray (34), and that it may be useful in the evaluation of intraoperative repositioning of the fractures (36). High-resolution ultrasonography has also been reported to be helpful in establishing a diagnosis of nasal fractures in children (37), but ultrasonography is operator dependent and additional studies are required to validate its efficacy.

Ultimately, whereas imaging may confirm a diagnosis or facilitate classification, management decisions for isolated nasal fractures are based primarily on a clinical evaluation. The decision as to whether or not a nasal fracture requires some kind of manipulation or surgical intervention should be based on emergency findings (abscess, hematoma), an alteration of form (alignment), or symptomatic nasal airway obstruction.

MANAGEMENT

Descriptions pertaining to the management of nasal fractures go back over 5,000 years. In the Surgical Papyrus, Edwin Smith outlined treatment methods in ancient Egypt whereby a linen wrap saturated with honey and grease was introduced into each nasal cavity in order to then manipulate the nasal bones for fracture reduction (38). In the fifth century BC, Hippocrates advocated early intervention to reposition the nasal bones, but even at that time, he noted that he was not able to realign the nasal bones appropriately if the septum was deviated (39). Twenty-five hundred years later, debate still exists over the optimal management of the fractured nose and what operation to apply in which circumstances.

Ideally, nasal fractures should be addressed within the first 5 to 10 days of the injury. Beyond about 14 days, the fracture may be less easily mobilized and reduced, and the need for completion osteotomies becomes more likely. Associated lacerations or soft tissue injuries should be repaired within the first 24 hours and routine wound care recommended. Application of ice packs or cold compresses over the first several days is helpful to reduce soft tissue edema and facilitate better evaluation and intraoperative judgment.

If intervention is required, decisions then focus on location (emergency room [ER] vs. office setting vs. operating room [OR]) and anesthesia (local vs. intravenous sedation vs. general anesthetic). Consider that maximal patient comfort will enable the surgeon to apply as much force as is necessary to disimpact and reduce fractures as well as to provide the unhindered ability to progress to more complex intervention (septoplasty, osteotomies etc.) if needed. Treatment in the OR provides the most favorable conditions (patient comfort, instrumentation, lighting, anesthesia options) and as such affords some advantage to the surgeon and possibly therefore patient outcomes as well.

Nasal fracture reduction may be performed under local anesthesia (infiltrative and/or topical), intravenous sedation, or general anesthesia. Both patient factors and intrinsic nasal fracture factors will influence the choice of anesthesia. Patient factors include the age, expectations, tolerance, and comorbidities of the individual. Intrinsic nasal fracture factors include the type and characteristics of the nasal fracture and the status of the septum. Proponents of local anesthesia for closed reduction of nasal fractures, particularly from the United Kingdom and Europe (20,40–48), report that it is faster, uses less hospital resources, is safer in elderly patients, produces minimal discomfort, and has no effect on the result of the reduction (40–49).

The evidence suggests, however, that the debate between local versus intravenous sedation versus general anesthesia is somewhat aimless. It is not that one anesthesia technique is better than the other. In the hands of an experienced surgeon, both techniques are effective if the patient is appropriately selected. In other words, a simple unilateral fracture may be a reasonable candidate for reduction under local anesthesia, whereas a comminuted bilateral displaced fracture with associated displaced septal fractures is likely better managed under general anesthesia. Ultimately, the choice of anesthesia is a matter of surgeon preference but undeniably a general anesthetic (this author's preference) offers safety, a controlled and protected airway, maximum patient comfort, and the uncompromised ability to examine, manipulate, and extend treatment if necessary.

The goal of treating nasal fractures has always been the same—optimize cosmetic and functional outcomes, and minimize revision rates. The traditional technique for

managing acute nasal fractures has been a closed reduction of the fractured nasal bones, and it remains the most widely used today. As far as outcomes are concerned, however, Staffel (50) reviewed 13 reported series of nasal fractures treated with closed reduction alone and found that while patient satisfaction rates in those publications ranged anywhere from 62% to 91%, surgeon satisfaction ranged from only 21% to 65%.

Accordingly, surgeons have sought to improve upon outcomes. Treatment methods have expanded to now include closed reduction, closed reduction with concomitant septoplasty, open reduction, open reduction with concomitant septoplasty, and even early, primary functional septorhinoplasty in select cases. "Closed" reduction implies manipulation of the nasal pyramid with the use of broad instruments and blunt (nonincisional) endonasal techniques. "Open" reduction on the other hand generally implies maneuvers requiring added access through intranasal incisions such as completion osteotomies or bone rasping, for example, but is generally less involved than a formal septorhinoplasty.

If the surgical procedure is well matched to the individual fracture, there is reason to believe that all approaches can have equally good outcomes (19). The challenge then becomes identifying *which* nasal fractures are well managed with a closed reduction and which would merit a more extensive procedure so as to maximize success rates. Clearly, not all patients will do well with a closed reduction alone, and conversely not all patients need an open reduction or primary septoplasty either.

The advantage of a closed reduction lies in the presumed simplicity, shorter operative times, and limited morbidity of the procedure, while the disadvantage may be a suboptimal outcome in more complicated fractures for which an open procedure or septoplasty might have been warranted. On the other hand, an open procedure—surely of outcome benefit to some—involves longer operative times, a greater burden of healing, and arguably the potential for surgical cartilage depletion could make for more challenging revision procedures should they be necessary.

Interpreting published reports within the literature can be difficult. There are many variations from one study to the next in terms of timing of treatment, location of treatment (ER vs. office setting vs. OR), type of anesthetic administered (local vs. sedation vs. general anesthesia), detailed description of technique or lack thereof, inconsistent reporting of assorted variables, unreliable patient follow-up, ill-defined "revisions" (airway vs. alignment vs. both; minor vs. major), and lack of clear fracture classification or treatment stratification among other things.

What has become apparent through various cadaveric and clinical studies is that the greater the force or impact, the greater the disruption and displacement of the nasal bones and that in turn increases the likelihood of associated septal fractures and dislocations. As noted earlier, both Murray et al. (25) and Harrison (28) demonstrated somewhat predictable septal fracture patterns in cadaveric models with application of increasing impact. Murray et al. also noted that if the fractured nasal bones were displaced by more than half the width of the nasal bridge then a fracture of the septum was inevitable and in fact many surgeons have used this as an indication for primary concomitant septal surgery.

Rhee et al. (11), in a prospective study, actually explored the septum through a hemitransfixion incision in all 52 patients with isolated nasal fractures undergoing a closed reduction in their study. They found that only two patients had no septal fracture whatsoever, almost 80% had an identifiable septal fracture with at least mild displacement or more, and 60% were classified as severely displaced or worse (multiple fractures, crushed, comminuted). The presence of a mucosal tear was found to be a statistically significant sign on physical examination for septal fracture. They also found that while a CT scan proved to be helpful in diagnosing septal fractures, it correlated poorly with the severity of the fracture. Their findings would suggest that even with relatively unremarkable nasal fractures, septal fractures are a frequent occurrence. This does not imply that all septal fractures are irreducible or that all fractures require a septoplasty, but rather that the frequency of septal fractures may be underappreciated.

The general consensus within the literature is that unrecognized overlapped, telescoped, or interlocked septal fracture fragments will lead to higher rates of post reduction nasal deformities if unaddressed or if treated with closed reduction alone (9,14,19,29,50). It has been said that "the dorsum follows the septum," meaning that the nasal bones will tend to migrate and heal in the direction of the septal deviation and so if significant septal fractures are not addressed, optimal alignment of the nasal bones is unlikely. With respect to management decisions regarding nasal fractures, it is felt therefore that the single most important determinant would be an accurate evaluation of the septum. Furthermore, a graduated approach beginning with closed reduction and progressing to septoplasty/open reduction if unsuccessful is a reasonable strategy if the patient doesn't have clear indications for one approach or the other.

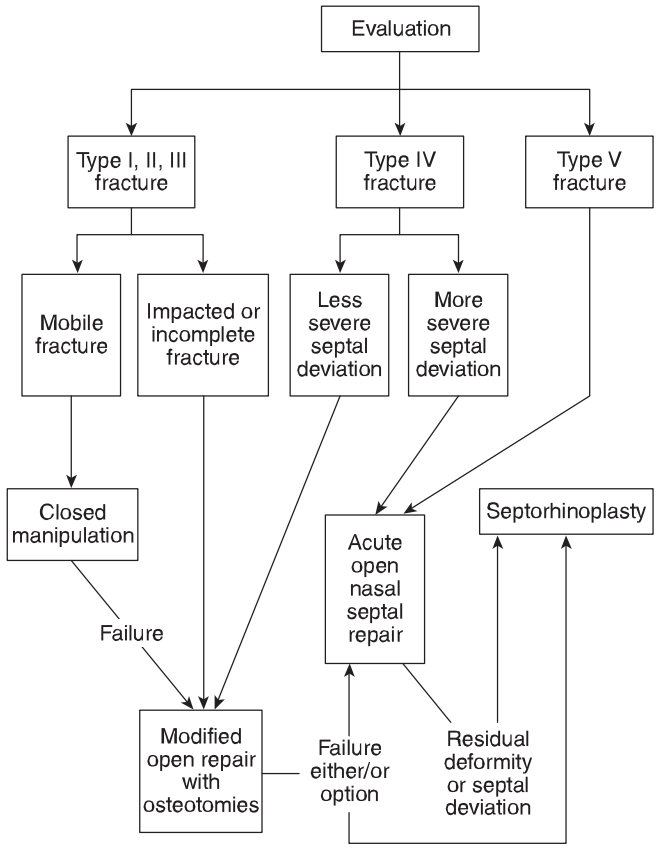
An "ideal" fracture classification scheme would guide appropriate treatment. A variety of classification systems have been proposed in the literature—based on factors such as impact direction, injury plane, or anatomy (i.e., simple vs. comminuted; closed vs. compound), for example. Unfortunately, these tend to be of academic interest but provide little in the way of clear treatment guidance.

Rohrich and Adams (29) proposed a classification scheme and management algorithm, which enabled them to achieve a revision rate of only 9%. In the case of apparent septal fractures, they recommend either reduction of septal dislocations (using an Asch forceps or Boies elevator) or if the former is unsuccessful, proceeding with acute septal reconstruction for which they generally advocate a limited inferior and posterior resection.

Classification of Nasal and Septal Fractures

Type	Description	Characteristics
I	Simple straight	Unilateral or bilateral displaced fracture without resulting midline deviation.
II	Simple deviated	Unilateral or bilateral displaced fracture with resulting midline deviation.
III	Comminution of nasal bones	Bilateral nasal bone comminution and crooked septum with preservation of midline septal support; septum does not interfere with bony reduction.
IV	Severely deviated nasal and septal fractures	Unilateral or bilateral nasal fractures with severe deviation or disruption of nasal midline, secondary to either severe septal fracture or septal dislocation. May be associated with comminution of the nasal bones and septum, which interfere with reduction of fractures.
V	Complex nasal and septal fractures	Severe injuries including lacerations and soft tissue trauma, acute saddling of nose, open compound injuries, and avulsion of tissue.

A



B

Figure 83.9 Nasal fracture classification scheme (**A**) and treatment algorithm (**B**) based on the fracture classification. Reprinted from Ondik, MP et al. The treatment of nasal fractures: a changing paradigm. *Arch Facial Plast Surg* 2009;11(5):296—302, with permission. Copyright © 2009 American Medical Association.

Ondik et al. (19) used a modification of the classification system proposed by Rohrich and then developed a treatment algorithm based on their fracture classification. Their classification and algorithm are seen in Figure 83.9A and B. In their publication, if the septum did not interfere with the bony reduction, then a closed reduction alone was used. On the other hand, if the septum was sufficiently dislocated or fractured so as to compromise midline support with severe deviation or disruption of the nasal midline, then an acute septal repair was performed together with completion osteotomies (if indicated). By classifying patients and stratifying treatment accordingly, they reported an overall revision rate of 6% (2% for closed reduction patients and 9% for those requiring open treatment, which is indicative of a more substantial fracture). They concluded that if the choice of procedure is based upon the type of fracture, both closed reduction and open procedures can have high measures of success.

Staffel (50) also developed and proposed a graduated protocol for the treatment of nasal fractures, which begins with closed reduction and progresses as needed to include a septoplasty (for persistent drift and/or preoperative nasal airway obstruction), completion osteotomies (for persistent drift or memory), release of the upper lateral cartilages (if the nose was crooked before the fracture or remains so despite completion osteotomies), fracturing of the perpendicular plate of the ethmoid bone and lastly, camouflaging onlay grafts for any residual defects. The challenge with this approach might be making some of the finer decisions regarding drift or residual defects when confronted with post-traumatic and intraoperative edema.

Over an 8-year period, Defatta et al. (14) studied only those patients undergoing closed reduction for a nasal bone fracture in whom there was a persistent significant (not defined) septal deformity identified intraoperatively after closed reduction. Under such circumstances, those undergoing concomitant primary septoplasty had lower rates of residual septal deformity at follow-up (12.5%) than those who did not (60% residual deformity). The number of patients over that same time period who underwent closed reduction alone, in whom there was not a persistent septal deformity identified intraoperatively, and their success/failure rates with those patients was not mentioned however so a broader sense of perspective (i.e., what percentage of patients are likely to fall into their treatment group) is not possible.

The treatment dilemma or the difficulty of choosing the correct operation for a given patient is well expressed by Fernandes (15) who commented that "although it is

possible to predict the closed reductions that will definitely fail, I am unable to predict those closed reductions that will definitely succeed despite the patient having a straight nose on the operating table."

Reasonable general recommendations therefore begin with a full evaluation of the injury with particular attention paid to the possibility of septal fractures warranting open treatment. A septal injury more likely to warrant primary repair should be suspected with overlying mucosal tears on physical examination, a collapsed or buckled septum (often associated with acute loss of dorsal height—Fig. 83.10), severe septal angulation posteriorly or inferiorly with symptomatic new-onset nasal airway obstruction, displacement of the external nasal framework by an amount greater than half the width of the nasal bridge, and nasal bones that prove to be irreducible with closed reduction or continue to drift. Primary septal repair, when indicated, should be as conservative as is possible, with particular attention focused toward inferior displacement over the maxillary crest and posterosuperior fractures and angulation or telescoping at the junction of the quadrangular cartilage with the perpendicular plate of the ethmoid bone. Completion osteotomies are indicated for nasal bones, which are displaced and impacted, thereby limiting closed reduction or in situations where early treatment has been delayed (beyond about 2 weeks) and the nasal bones are somewhat immobile.

To summarize, because the untreated post-traumatic nasal deformity—the crooked nose—can be one of the most difficult of all septorhinoplasty procedures, effort should be directed toward minimizing the need for revision procedures when treating an acute, displaced nasal bone fracture in need of reduction. There is a place for both closed and open procedures and properly applied, both can be successful. At the very least, the treating physician should consider the need for extending treatment beyond a closed reduction alone, obtain proper consent to proceed as necessary, and apply a graduated approach as dictated by the circumstances. In all cases, patients should be made aware preoperatively of the possible need for a secondary surgery in the future.



Figure 83.10 Acutely buckled septal fracture leading to septal collapse, nasal airway obstruction, and supratip depression seen before open reduction with acute septal repair.

NASAL FRACTURES IN CHILDREN

The facial bones are much less commonly fractured in children than in adults, with children accounting for only 5% to 10% of all facial fractures (51–53). Falls, blunt trauma, and sports-related injuries are among the more frequent causes, and facial fractures are more common among older teens. Nasal septal deviations and nasal deformities can also be seen in newborns in 1.25% to 23% of cases in association with intrauterine trauma, forceps-assisted deliveries, and breech deliveries (54).

The low incidence of facial fractures in children is a by-product of the elasticity of the bones, craniofacial disproportion, and underdevelopment of the facial skeleton in preadolescent children (51,53,55). With respect to nasal fractures in particular, the child's nose is more cartilaginous than bony and thus more resilient than that of an adult. Fractures of the nasal bones are thus less common, while the cartilage, rather than fracture is more likely to buckle, twist, or dislocate. In such cases, septal mucoperichondrium may separate from the underlying cartilage, even in the absence of mucosal tears or nasal bone fractures. This creates a potential space in which rupture of smaller vessels supplying the mucoperichondrium may lead to a septal hematoma, which is thus more commonly seen in pediatric nasal trauma than in adults (56). Should a hematoma evolve into a septal abscess, the likelihood of septal cartilage destruction and long-term sequelae increases dramatically (57). For that reason, any child with a history of acute nasal trauma complaining of nasal obstruction must be carefully examined with that in mind.

Nasal fractures in children are often overlooked or untreated, leading to adult nasal pathology (7,58). The septum serves as one of the growth centers of the face until about 12 to 13 years of age and as a result, nasal trauma at a younger age may significantly affect subsequent growth, form, and function (5,59). This underscores the importance of establishing a diagnosis and administering treatment when warranted, despite the inherent challenges in both.

Physical findings are often less striking, particularly in the very young child, and radiographs are of even less value than in an adult due to the primarily cartilaginous nature of the nasal structures in children. Substantial septal and mucosal trauma can occur even in the absence of grossly apparent external nasal deformity (58).

In the setting of nasal trauma in children, a history of associated epistaxis, nasal obstruction, and/or subtle physical findings such as nasal dorsal edema, dorsal tenderness, periorbital ecchymosis, and bony crepitus should elevate the examiner's index of suspicion as well the more obvious finding of a visible external deformity or grossly abnormal radiographs. A suspicious or inconsistent history, associated

unexplained injuries, or a history of repeated trauma should prompt consideration of possible child abuse. Given the sequelae that can develop as a result of undiagnosed nasal or septal fractures/dislocations in children, a proper and thorough intranasal examination is required for a complete evaluation and to rule out septal pathology. This can be challenging in the noncompliant child, and in some cases a general anesthetic may be necessary to do so.

Pediatric fractures begin to heal and unite much quicker than those of adults so when intervention is necessary. It should be undertaken within the first week if at all possible. The general approach to the surgical treatment of nasal fractures in children is one that emphasizes conservatism.

A septal hematoma or abscess should be drained in all cases. For fractures, a closed reduction is the preferred approach for all pediatric nasal fractures to decrease the possibility of interference with the bone growth centers—only highly displaced fractures should undergo open reduction and/or primary septal surgery (53). If closed reduction is unsuccessful and open reduction is indicated, the objective at that point should be maximal tissue preservation while optimizing nasal airway function and external alignment. Dissection and excision of tissue should be minimized to whatever extent possible.

TECHNIQUE

Closed Reduction

As mentioned earlier, closed reduction implies manipulation of the nasal pyramid with the use of broad instruments and blunt (nonincisional) endonasal techniques.

Once the patient is anesthetized or the field is blocked, the nose is decongested with pledgets soaked with a topical vasoconstrictor (e.g., oxymetazoline) to open the nasal airway, improve visualization, and decrease bleeding with manipulation. Injection of lidocaine and epinephrine can also be used if desired, but is not absolutely necessary.

The typical instrumentation needed for a basic closed reduction is seen in Figure 83.11. Simple, unilateral depressed nasal bone fractures can be easily reduced using a broad, flat elevator such as a Boies elevator. In such cases, measuring the distance from the nostril rim to the medial canthus externally will give the surgeon a sense of how far into the nasal cavity the elevator must be passed to rest beneath the nasal bone in question. With the elevator thus positioned endonasally, the thumb (for a right nasal bone fracture) or the index and long fingers (for a left nasal bone fracture) of the opposite hand is placed over the ipsilateral nasal bone, in order to maximize fine control and provide tactile feedback to the surgeon as the nasal bone is repositioned (Fig. 83.12).

The nasal bone is then elevated along a vector opposite the direction of impact or bone displacement. A palpable if not audible repositioning of the bone should be evident. Typically, unless severely comminuted, the edges of fracture fragments will interdigitate sufficiently to hold the reduced bone in position. The Boies elevator can also



Figure 83.11 Typical instrumentation needed for a closed reduction—(left to right)—Walsham forcep, Boies elevator, Asch forcep, nasal speculum, nasal suction, bayonet forceps.

be used to reduce a septum, which is dislocated inferiorly back onto the maxillary crest or into the vomerine groove. A Walsham forcep is another instrument that can be used for unilateral nasal bone fracture reduction in lieu of the Boies elevator—it too is designed for manipulation of the nasal bone of one side. With the Walsham forcep, one blade rests in the nasal cavity while the other rests externally on the skin overlying the nasal bone for complete control of the nasal bone during reduction.

While the Boies elevator is well suited for reduction of a simple unilateral nasal bone fracture, it is less well applied to bilateral displaced nasal bone fractures. The Asch forcep offers ideal control of the entire nasal pyramid, in contrast to the Boies elevator or Walsham forceps, which limit the manipulation to one side. The Asch forceps is inserted

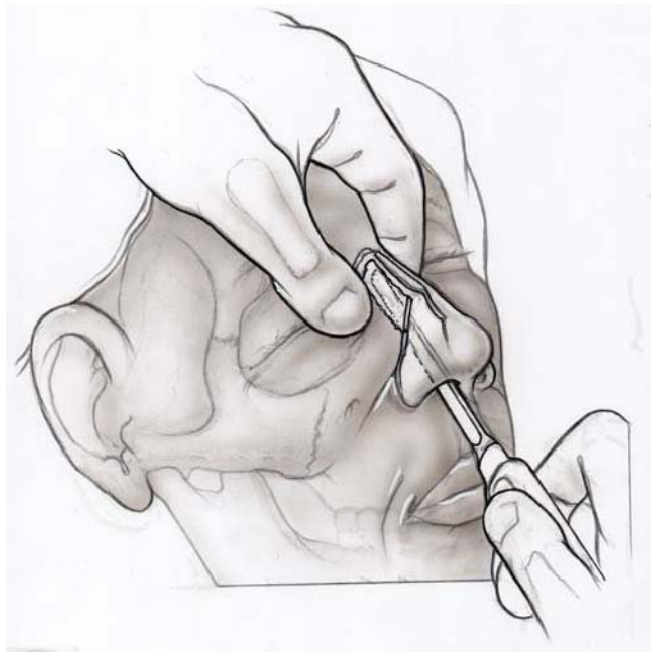


Figure 83.12 Bimanual closed reduction technique using Boies elevator to reduce unilateral depressed nasal fracture.

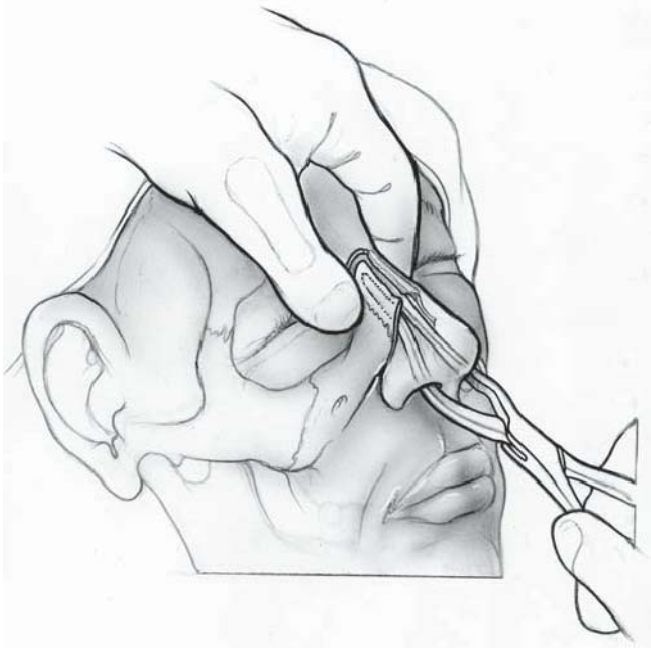


Figure 83.13 The Asch forceps is positioned astride the nasal septum to enable disimpaction and manipulation of the entire nasal pyramid.

straddling the septum, with one blade in each nostril in order to "hug" the nasal septum (Fig. 83.13). Thin pledgets can be left in place on each side, between the tine of the reduction forcep and the septal mucosa to protect the mucosa from further trauma during reduction.

The septum and the nasal pyramid are carefully disimpacted, elevated, and repositioned by manipulating the forcep in the direction opposite that of the fracture impact. The Asch forcep has the distinct advantage of giving the surgeon control over both nasal bones simultaneously and as a single unit. As an added advantage, the Asch forcep serves as a septal reduction forcep as well and some septal fractures may be reduced concurrent with the movement of the nasal bones. In the case of bilateral nasal bone fractures, if the bone on the side opposite the direction of displacement has been noticeably impacted, once the entire nasal framework is repositioned to the midline with the Asch forcep, the impacted nasal bone can be gently elevated into position with the Boies elevator.

Both nasal bone and septal reposition maneuvers are repeated as necessary to obtain the best results; however, excessive manipulation and trauma should be avoided. Once properly positioned, a standard external nasal splint can be applied. Packing the nose is not generally needed although it may help to provide early intranasal support to a badly comminuted or unstable fracture. If a concomitant septoplasty is performed, Doyle splints are used postoperatively to stabilize the septal alignment. External and any internal splints are removed the week following surgery. Prophylactic antibiotics are used in cases where internal splinting or packing is used.

Open Reduction

Open reduction involves the repositioning of the nasal structures via different mucosal and skin incisions, with techniques fundamentally similar to the ones used in functional and cosmetic rhinoplasty techniques. Open reduction techniques, from septoplasty to osteotomies to functional primary septorhinoplasty can be of such range that they are beyond the purview of this chapter but are referenced in part or whole elsewhere in this text. It is worth, however, emphasizing once again the importance of septal reduction to enable satisfactory repositioning of the nasal bones—an inadequate reduction of the nasal septum impedes appropriate repositioning of the external nasal framework.

COMPLICATIONS

Complications of nasal fractures may present in an early or a delayed fashion. A list of more commonly encountered early and late complications is provided in Table 83.1.

Early

Edema and ecchymosis are typically seen early and are more expected than indicative of a complication. Both should resolve spontaneously within 1 to 2 weeks.

Epistaxis is not at all uncommon, and most cases will resolve spontaneously. Less commonly, cauterization or/and intranasal packing may be required, and surgery (electrocautery or vessel ligation) and/or embolization is reserved for the very rare refractory cases. When packing a nose in the setting of a nasal fracture, care should be taken to not to overpack for fear of interfering with blood supply to the already damaged septum. In the setting of suspected skull base fractures, packing is relatively contraindicated and should be performed only under direct visualization and with total control in order to avoid inadvertent intracranial complications.

Wound infections are uncommon, although they can develop with contaminated nasal lacerations (compound fractures). A higher incidence of wound infection can be seen in smokers, diabetics, immunocompromised patients, and those with autoimmune diseases and with poorer nutritional status (60).

TABLE 83.1 COMPLICATIONS NASAL FRACTURES

Early	Late/Delayed
• Epistaxis	• Nasal airway obstruction
• Wound infection	• Synechiae
• Septal hematoma	• Septal perforation
• Septal abscess	• Crooked nose/external deformity
• CSF leak	• Saddle deformity
	• CSF leak

As discussed earlier, a septal hematoma should be suspected with abnormal bluish–purplish compressible swelling over the septum and complaints of nasal pain or congestion that seem beyond the norm for a nasal fracture. Clinical examination establishes the diagnosis, and treatment, whether by aspiration or formal drainage, is essential. Failure to recognize a septal hematoma can result in progression to a septal abscess with secondary cartilage necrosis and saddling of the nasal dorsum.

A CSF leak may be associated with fractures of the cribriform plate or posterior wall of the frontal sinus, and usually present with clear fluid rhinorrhea. This may be evident early but in some circumstances may not manifest for months or even years after the initial traumatic event. As noted earlier, if suspected a beta-2 transferrin test is helpful in assisting in diagnosis, and more detailed imaging (CT scan) is warranted. Smaller leaks often go undetected and may in fact resolve spontaneously. Otherwise, management will depend on etiology and may require neurosurgical consultation.

Late

Late complications are often preventable with proper early evaluation, diagnosis, and appropriate management. Delayed complications may be either functional or cosmetic, and are generally secondary to anatomic displacement and deformity of nasal structures, or tissue loss. Delayed presentation of a CSF leak is noted above.

Delayed complications can include external nasal deformities (a crooked nose or saddle deformity), or endonasal deformities such as nasal airway obstruction (deviated septum, valve collapse), intranasal synechiae, and septal perforations. Disruption of facial growth centers in children can also lead to delayed functional or cosmetic problems. Treatment of delayed complications ranges from primary septoplasty to functional and/or cosmetic rhinoplasty, which are discussed elsewhere in this text.

HIGHLIGHTS

- The nasal bones are the most commonly fractured facial bone and the third most commonly fractured bone in the body
- A complete evaluation should take into account the possibility of other facial skeletal fractures
- The greater the impact resulting in a nasal bone fracture the higher the likelihood of associated nasal septal fractures
- Closed reduction and open reduction are both reasonable treatment options—successful management is predicated upon carefully considering which approach is necessary for a given patient's fracture
- Physical findings may be more subtle in children and the incidence of septal hematoma is higher—both of which mandate greater vigilance

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Frontal Sinus Fractures

84

E. Bradley Strong

BACKGROUND

While frontal sinus injuries are relatively uncommon, the potential for long-term sequelae is significant. It is therefore critical to have a comprehensive treatment strategy. Unfortunately, optimal management of frontal sinus fractures remains controversial (1–8). Most authors would agree that a hierarchical treatment strategy would include: treatment of any intracranial injury, avoidance of short- and long-term complications such as mucoceles, reestablishment of an aesthetic facial contour, and return of normal sinus function if possible. This chapter provides an anatomically based treatment algorithm for the management of frontal sinus fractures, highlighting the key steps to surgical repair.

ANATOMY

The frontal sinus is not present at birth. The anterior ethmoid air cells invade the frontal bone at age 2; developing into a full size frontal sinus by age 15 (Fig. 84.1). The floor of the sinus forms the medial portion of the orbital roof. The posterior table forms a portion of the anterior cranial fossa. The anterior table forms part of the forehead, brow, and glabella (Fig. 84.2). The size and shape of the adult frontal sinus is highly variable. It is commonly asymmetric and may be divided by one or more septations. Less frequently, patients will have a unilateral (10%), rudimentary (5%), or no frontal sinus (4%). Average frontal sinus dimensions are: height 30 mm, width 25 mm, depth 19 mm, and volume 10 mL. The anterior table is much thicker (average 4 mm, but up to 12 mm) than the posterior table (0.1 to 5 mm) (9,10). The nasofrontal recess is the sole outflow tract for the frontal sinus. The ostia are approximately 1 to 3 mm in diameter and located posteriorly, inferiorly, and medially on the floor of the sinus (9,10). They are the narrowest point of an hourglass configuration, with the frontal sinus infundibulum above, and the nasofrontal recess below (Fig. 84.3).

PATHOPHYSIOLOGY

The frontal sinus is protected by thick cortical bone and is more resistant to fracture than any other facial bone (11) (Fig. 84.4). Consequently, frontal sinus fractures account for only 5% to 15% of maxillofacial injuries (1,11). The use of seat belts and airbags has significantly decreased the incidence of frontal sinus fractures (1,12). The majority of these fractures involve young males (average age 30 years) involved in high-velocity injuries such as motor vehicle accidents (52%), assaults (26%), and recreation or industrial accidents (14%) (1,5–6). Greater than 75% of patients will have associated facial fractures (1,7). Isolated anterior table fractures occur approximately 33% of the time. Combined fractures of the anterior table, posterior table, and/or the nasofrontal recess account for approximately 67% of frontal sinus injuries. Isolated posterior table injuries are rare (~2% of injuries) (1,4).

DIAGNOSIS

Physical Examination

Due to the high velocity nature of these injuries, associated intracranial, spinal cord, thoracic, abdominal, and long bone injuries must be ruled out in all patients. A thorough history and complete head and neck examination are critical. Common physical findings include forehead abrasions/lacerations, contour irregularities, tenderness, paraesthesias, epistaxis, and hematoma. Exploration of forehead lacerations should be performed with sterile technique, if there is any question of intracranial violation. Through-and-through injuries of the frontal sinus have a high morbidity and prompt surgical treatment is indicated.

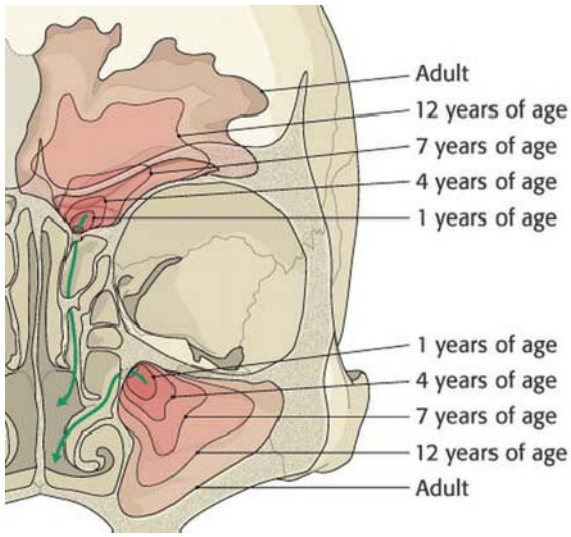


Figure 84.1 Frontal sinus development. The anterior ethmoid air cells invade the frontal bone at age 2. The sinus is fully developed by age 15. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

The presence of associated facial fractures must be ruled out, with special attention to examination of the orbits and nasoorbitoethmoid complex. Conscious patients should be questioned regarding the presence of watery rhinorrhea or salty tasting postnasal drainage suspicious for a cerebrospinal fluid leak. Such fluid should initially be evaluated with a "halo test." The bloody fluid is allowed to drip onto filter paper. If cerebrospinal fluid is present, it will diffuse faster than blood and result in a clear halo around the blood. Beta-2 transferrin is the definitive test to confirm a cerebrospinal fluid leak; however, it is generally a "send out" test and may take 5 to 7 days to receive results.

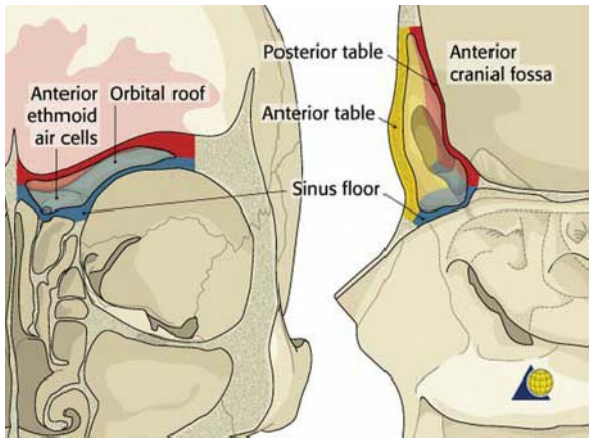


Figure 84.2 Frontal sinus anatomy. The anterior table of the frontal sinus is thick bone and provides forehead contour. The posterior table is thinner and constitutes a portion of the anterior cranial fossa. The floor or the sinus makes up a portion of the orbital roof. The frontal sinus ostia is located in the medial, posterior, and inferior portion of the sinus floor. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

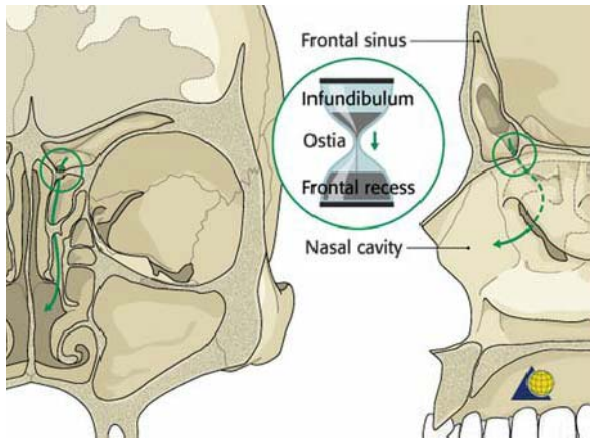


Figure 84.3 Frontal sinus drainage. The frontal sinus drainage pathway has an hourglass configuration with the infundibulum above and the frontal recess below. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

Radiography

Plain radiographs are of little use in the diagnosis of frontal sinus fractures. A thin cut (1.0 to 1.5 mm), axial computed tomography (CT) scan is the gold standard. It is recommended to obtain coronal, sagittal, and three-dimensional (3-D) reconstructions for diagnostic accuracy. The axial images are used to evaluate the anterior and posterior tables (Fig. 84.5); coronal images for the sinus floor and orbital roof (Fig. 84.6). Sagittal images can be useful in assessing the patency of the frontal recess (Fig. 84.7) (13), while 3-D reconstructions help define the shape, location, and orientation of individual bone fragments that are seen less clearly on 2-D views (Fig. 84.8). The 3-D information can reduce the need for surgical dissection, because the surgeon knows the number, location, and orientation of the larger bone fragments. It can also help the patient and/or family to understand the bony anatomy and severity of the injury.

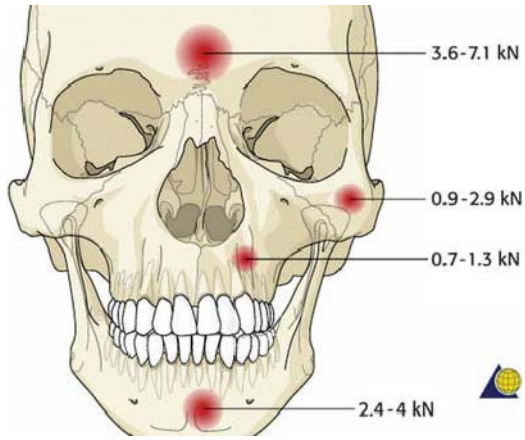


Figure 84.4 The anterior table of the frontal sinus is thick cortical bone. It is more resistant to fracture than any other facial bone. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).



Figure 84.5 Axial CT scan demonstrating a frontal sinus fracture involving both the anterior and posterior tables. **A:** Marked anterior table disruption. The *white arrow* points out a displaced posterior table bone fragment. **B:** Disruption of the nasofrontal recess. (From Strong, EB. Frontal sinus fractures: current concepts. *Craniomaxillofac Trauma Reconstr* 2009;2(3):161–175, figure 2.)

TREATMENT ALGORITHM

The appropriate treatment strategy for the management of frontal sinus fractures can be made by assessing *four* anatomic parameters (Fig. 84.9). These parameters include the presence of: (a) an anterior table fracture, (b) a posterior table fracture, (c) a nasofrontal recess fracture, (d) a dural tear (cerebrospinal fluid leak). These findings can be applied to the algorithm presented to determine appropriate treatment (Table 84.1). The treatment options include: observation, endoscopic repair, open reduction and internal fixation, sinus obliteration, sinus cranialization, and rarely sinus ablation (Reidel procedure). The indications and techniques for each of these procedures are discussed below.

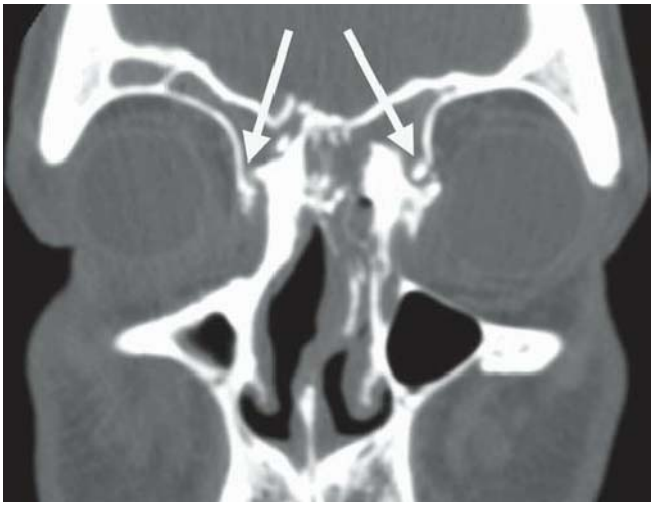


Figure 84.6 Coronal CT scan demonstrating disruption of the medial orbit and frontal recess (*arrows*). (From Strong, EB. Frontal sinus fractures: current concepts. *Craniomaxillofac Trauma Reconstr* 2009;2(3):161–175, figure 3.)

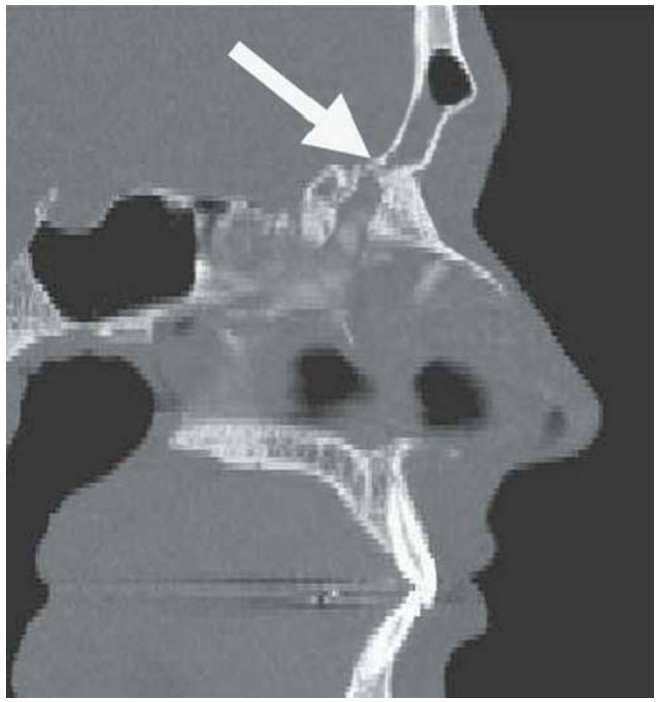


Figure 84.7 Sagittal CT scan demonstrating a frontal sinus fracture. The *arrow* demonstrates narrowing and obstruction of the frontal sinus outflow tract. (From Strong, EB. Frontal sinus fractures: current concepts. *Craniomaxillofac Trauma Reconstr* 2009;2(3):161–175, figure 4.)

Frontal Recess Fractures

Frontal recess fractures result in disruption of the sole frontal sinus outflow tract (Fig. 84.10 and Table 84.1). Frontal recess

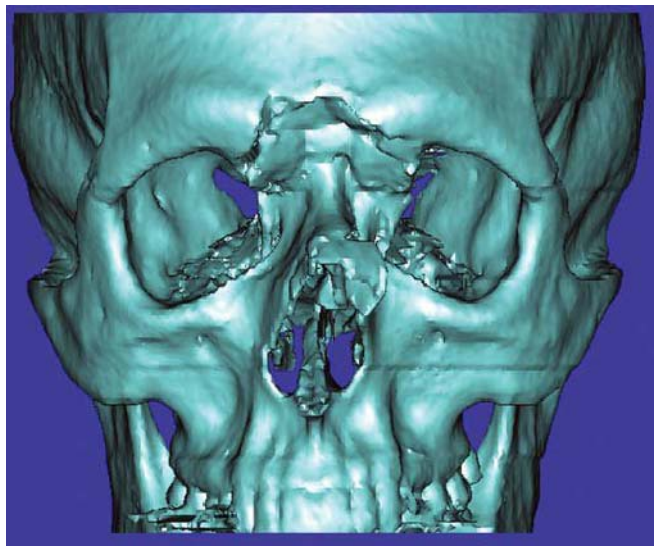


Figure 84.8 3-D CT scan of a frontal sinus fracture. The 3-D reconstruction can be helpful in delineating the position of bone fragments to be located intraoperatively. (From Strong, EB. Frontal sinus fractures: current concepts. *Craniomaxillofac Trauma Reconstr* 2009;2(3):161–175, figure 5.)

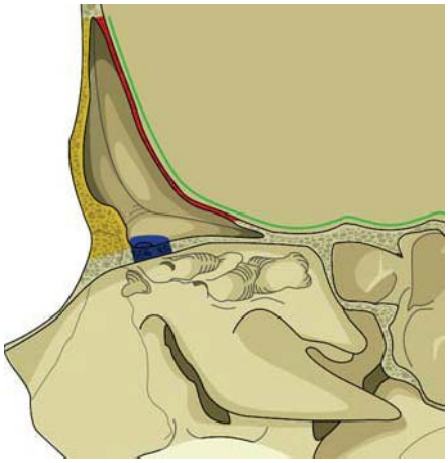
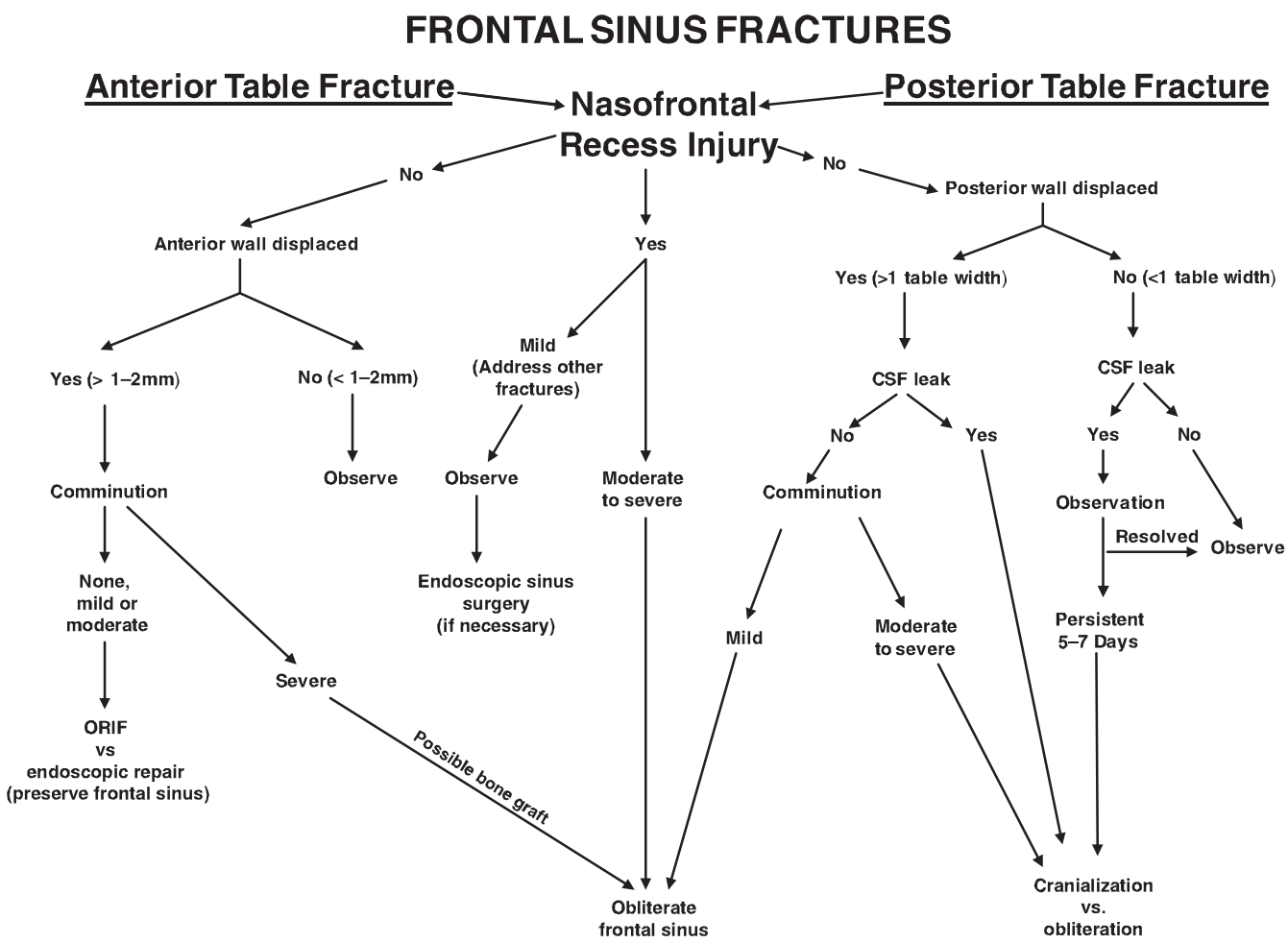


Figure 84.9 Illustration of the anatomic parameters that need to be assessed when developing a treatment plan for frontal sinus fractures. *Yellow*—anterior table; *Red*—posterior table; *Blue*—frontal recess; *Green*—dural integrity. (From Strong, EB. Frontal sinus fractures: current concepts. *Craniomaxillofac Trauma Reconstr* 2009;2(3):161–175, figure 6.)

fractures that result in sinus outflow obstruction will generally require frontal sinus obliteration. Unfortunately, the compact anatomy of the frontal recess makes accurate diagnosis challenging. One option is to perform a frontal sinus trephination to visualize the recess endoscopically. This does, however, require a general anesthetic. Some authors have proposed infusion of dye into the sinus to document frontal recess patency. Unfortunately, the passage of dye into the nose does not confirm or refute the presence of a fracture and has no documented prognostic value for the ultimate patency of the frontal recess. Therefore treatment decisions are generally based on thin cut CT scans. If the frontal recess patency remains in question (and there are no other significant sinus injuries) patients may be followed with sequential CT scans at approximately 1 and 12 months to assure that the frontal recess is patent. If the frontal recess becomes obstructed an obliteration is indicated. A more recently described technique involves observation of limited frontal sinus fractures (with serial CT scans), followed by endoscopic frontal sinusotomy for management of frontal recess stenosis (14). While

TABLE 84.1 FRONTAL SINUS FRACTURES



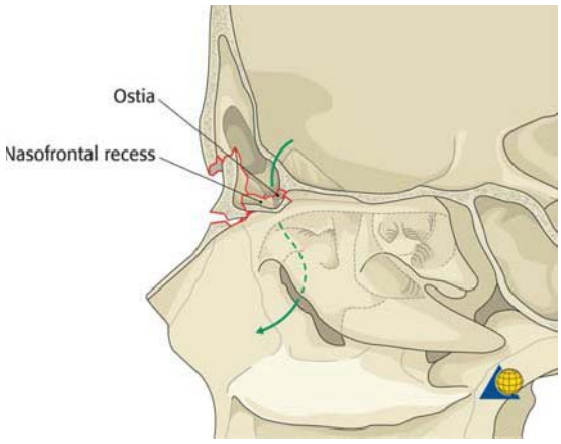


Figure 84.10 Illustration of frontal recess fracture—the sole outflow tract of the frontal sinus. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

this approach shows some promise, it should be reserved for surgeons with extensive experience in both endoscopic sinus surgery as well as open approaches to the frontal sinus.

Anterior Table Fractures

Nondisplaced (0 to 2 mm) anterior table fractures can be observed with little risk of long-term morbidity (Fig. 84.11 and Table 84.1). Fractures with greater displacement (2 to 6 mm) present little risk of mucocele formation; however, the risk of an aesthetic deformity increases with the degree of displacement (Fig. 84.12). In these situations, the decision for an open reduction should *not* be based on the long-term risk of sinusitis/mucocele formation. Most sinuses will heal adequately. The decision for surgery should be carefully weighed against the risks of general anesthesia and the long-term iatrogenic sequelae from a coronal incision (i.e., alopecia, paresthesias, facial nerve injury, etc.). Historically, these sequelae have been downplayed, but they can be more severe than the injury itself. Alternatively, minimally invasive approaches may be indicated with mildly displaced fractures. Transcutaneous upper eyelid approaches have been described, but have not gained significant popularity (15–16). Endoscopic fracture reduction in the acute setting has also been described, but is technically

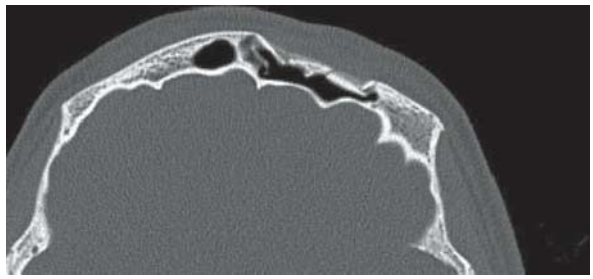


Figure 84.12 Axial CT scan demonstrating a mild to moderately displaced anterior table fracture. These fractures have a more significant risk of long-term aesthetic deformity.

challenging (17–21). The author feels it is not a viable technique for the majority of patients. Therefore, if an endoscopic approach is chosen, the author prefers a camouflage technique (17,18,20). Surgery for camouflage of the external deformities is performed 2 to 3 months after the injury when all facial swelling has resolved. This allows the patient to assess the degree of deformity and make an accurate decision as to whether they desire surgical intervention. Patients with thicker skin are better candidates for this approach because any subtle defects will be more easily camouflaged. If the patient is seen acutely, the rationale and indications for a delayed approach must be clearly explained (i.e., risk of iatrogenic injury may be greater than the traumatic deformity itself); and the patient must understand that a fracture reduction cannot be performed once the fracture has healed. While the risk of mucocele formation is very low, this should also be discussed. In the author's experience, many patients with minimally displaced fractures will desire no surgical intervention due to the lack of significant deformity. More complex anterior table fractures (greater than 6 mm or with comminution) will likely require open reduction using a coronal incision (Fig. 84.13). Uncommonly frontal sinus obliteration may be required when severe mucosal injuries are present.

Posterior Table Fractures

The treatment algorithm for posterior table fractures is complex due to the risk of CSF leak, meningitis, and mucocele formation (Table 84.1) (2,4–7). The primary decision criteria for surgical intervention are the fracture severity (displacement/

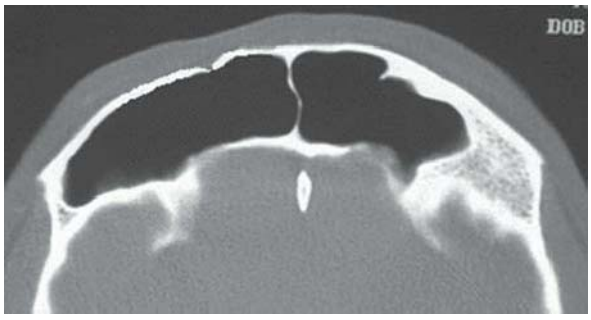


Figure 84.11 Axial CT scan demonstrating a minimally displaced anterior table fracture. These injuries have a low risk of mucocele formation or aesthetic deformity.

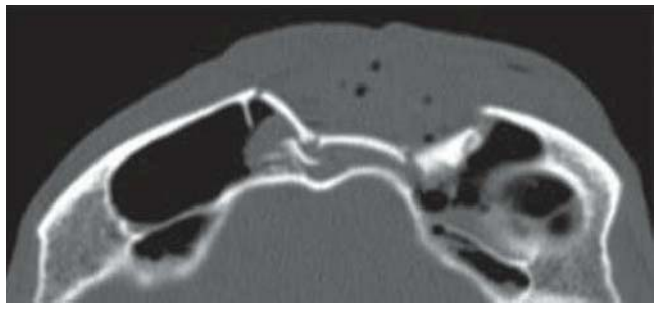


Figure 84.13 Axial CT scan demonstrating a severely displaced anterior table fracture requiring open reduction and internal fixation.

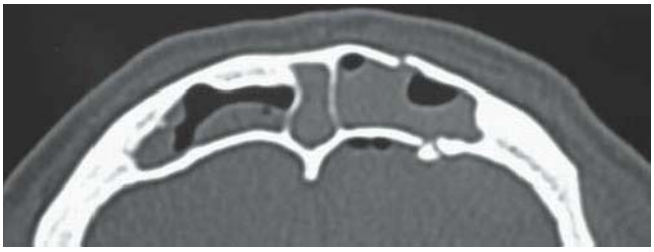


Figure 84.14 Axial CT scan demonstrating a minimally displaced (less than 2 mm) posterior (and anterior) table fracture.

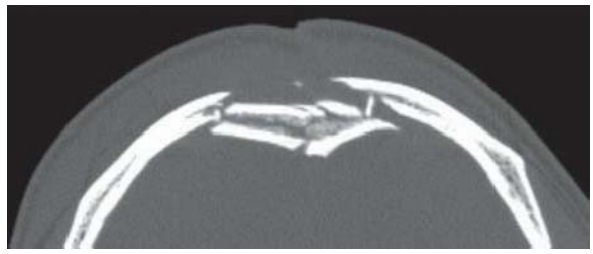


Figure 84.16 Axial CT scan demonstrating a severely displaced and comminuted fracture of the posterior (and anterior) table.

communition) and the presence of a CSF leak. While the degree of displacement that requires surgical intervention is "subjective" and controversial, the author prefers to use 2 mm of displacement as a rule of thumb. Two millimeter is often very close to the thickness of the posterior table, which has been used by some authors as an indication for intervention (5).

Less than 2 mm of Displacement: (Fig. 84.14)

Patients with posterior table displacement less than 2 mm, and no CSF leak, may be observed. Long-term follow-up with repeat CT scans at 1 month and 1 year is appropriate to rule out mucocele formation. If a CSF leak is present at the time of injury, 1 week of observation is indicated; approximately 50% will resolve spontaneously (6). If the leak is persistent, open reduction, dural repair, and sinus obliteration are indicated.

Greater than 2 mm of Displacement: (Fig. 84.15)

Patients with posterior table displacement greater than 2 mm, no CSF leak, and mild comminution should be treated with sinus obliteration. More severe injuries, with a frank CSF leak and moderate to severe comminution, will likely require removal of some posterior table bone to repair the dural tear. If the injury or surgical repair results in disruption of more than 25% to 30% of the posterior table, sinus cranialization should also be considered (Fig. 84.16) (22).

SURGICAL TECHNIQUE

Frontal Sinus Trephination

Trephination and endoscopic visualization of the frontal sinus can be useful to assess the frontal recess as well as the extent of any posterior table injury. After infiltration of local anesthesia, a 1.0 to 1.5 cm skin incision is placed midway between the medial canthus and the glabella, approximately 1 cm inferior to the brow (Fig. 84.17). The incision is best hidden by placing it inferior and deep to the curve of the forehead. A small "V" shaped relaxing incision may be added to reduce the risk of scar contracture and webbing. The incision should NOT be placed within the eyebrow, because it may result in alopecia, and place the supratrochlear neurovascular pedicle at risk. A guarded micro-point, monopolar electrocautery can then be used to dissect through the soft tissues and onto the frontal bone. The location and depth of the sinus should be confirmed on the CT scan or with intraoperative navigation. A depth of at least 7 mm is recommended to avoid injuring the posterior table. A small cutting burr is used to open a 4 to 5 mm frontal sinusotomy (Fig. 84.17 inset). The mucosa is incised and the sinus can be suctioned free of any blood or mucous. A 30 degrees endoscope is used to examine the posterior table and frontal recess for any evidence of injury. A Valsalva maneuver can assist with the diagnosis of a CSF leak (Fig. 84.18). While flexible pediatric bronchoscopes are more cumbersome, they can be used to examine the lateral aspects of the sinus. Once the examination has been completed, the skin and soft tissue are closed meticulously in layers.

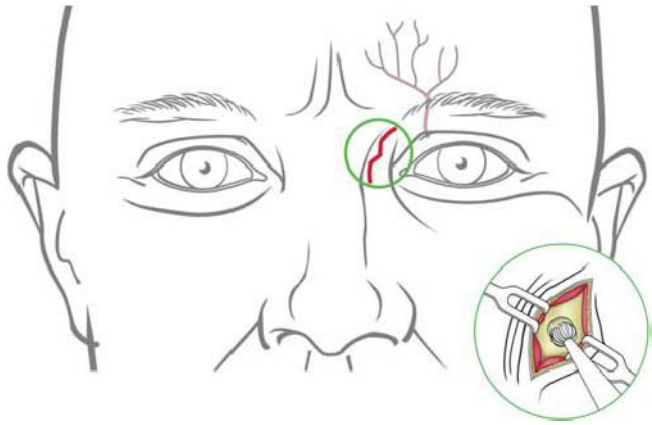


Figure 84.17 Illustration demonstrating the incision for a frontal sinus trephination. The incision should be midway between the medial canthus and the glabella, and approximately 1 cm inferior to the brow. The incision is best hidden when placed inferior to the forehead curvature. Inset: A small cutting burr is used to trephinate the sinus taking care to avoid injury to the posterior table. (From Strong, EB. Frontal sinus fractures: current concepts. *Craniomaxillofac Trauma Reconstr* 2009;2(3):161–175, figure 9.)



Figure 84.15 Axial CT scan demonstrating a moderately displaced (greater than 2 mm) posterior (and anterior) table fracture.

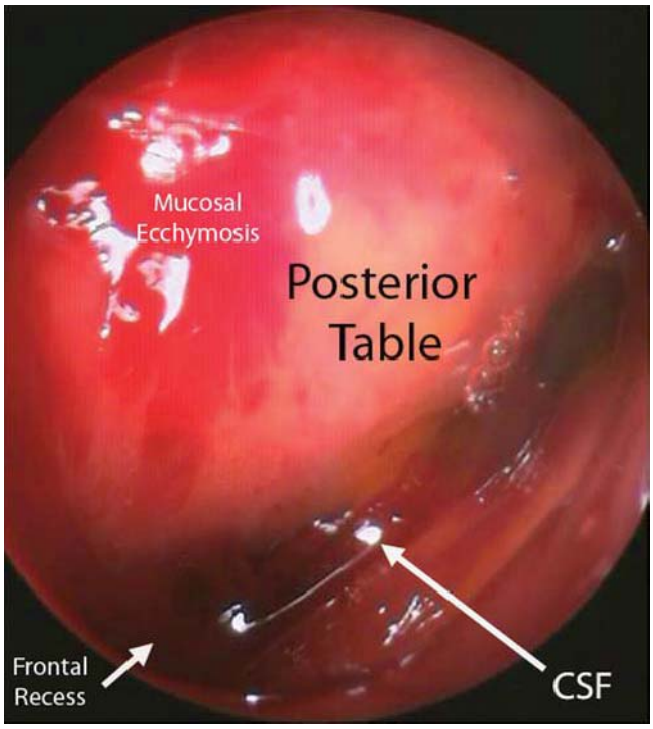


Figure 84.18 Endoscopic view of the frontal sinus using a 30-degree endoscope. A Valsalva maneuver is performed to demonstrate leakage of CSF through a posterior table fracture.

Endoscopic Anterior Table Repair

This technique is appropriate for isolated anterior table fractures above the orbital rim. Several authors have described endoscopic reduction of these fractures; however, the author finds this to be technically challenging (19–21). The repair described below is a camouflage technique. It is performed approximately 2 to 4 months after the injury when all forehead swelling has resolved and an accurate assessment of the deformity can be made. Prior to surgery, appropriate consent is obtained for the procedure including the risks of bleeding, infection, paraesthesias, alopecia, poor aesthetic result, and possible need for open approach if an endoscopic repair cannot be performed. The surgical technique is similar to a brow lift and uses the same instrumentation (23). Local vasoconstriction agents should be used liberally to minimize the need for electrocautery, and reduce the risk of alopecia at the incision site. A 3 to 5 cm parasagittal "working" incision should be placed above the fracture, 3 cm behind the hair line, and carried through the periosteum onto bone (Fig. 84.19). The actual length will vary depending on the size of the fracture and implant to be inserted. A 1 to 2 cm subperiosteal "endoscope" incision is then placed at the same height, 4 cm medial to the working incision. In patients with a prominent forehead or receding hair line, the incisions may need to be moved closer to the hairline, allowing visualization around the forehead curvature.

The initial subperiosteal elevation is carried down to the level of the fracture using an endoscopic brow lift elevator. The dissection is rapid and does not require the use of the endoscope (Fig. 84.20). Caution should be used to maintain the integrity of the periosteal envelope. Tears in the periosteum will "catch" the endoscope when it is inserted and make visualization more difficult. A 4.0 mm, 30-degree endoscope (with a rigid endosheath and camera) is then inserted through the endoscope incision. A large endosheath guard helps to maintain a generous optical cavity (Fig. 84.21). Dissection over the fracture is then carried out under direct visualization. A fibrous scar layer prevents entry into the sinus (Fig. 84.22). The supraorbital and supratrochlear neurovascular pedicles are commonly visualized at the orbital rim. Excessive traction on the pedicles should be avoided as it can result in postoperative paresthesias. Once the limits of the fracture have been visualized, a 0.85 mm thick porous polyethylene sheet is trimmed to approximate the defect (using the depression in the forehead skin as a template) (Fig. 84.23). The superior edge of the implant is marked with a pen to maintain the orientation endoscopically during insertion. The implant is

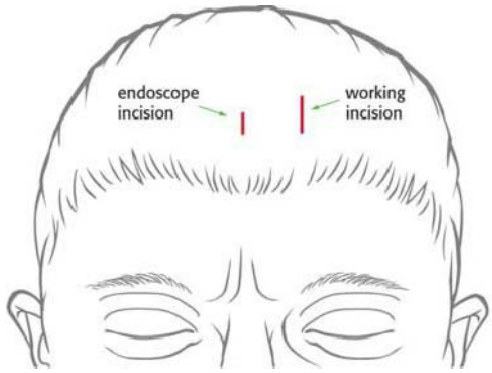


Figure 84.19 Illustration demonstrating the incision used for the endoscopic approach to an anterior table frontal sinus fracture. The "working incision" is placed directly above the fracture, while the "endoscope" incision is placed approximately 4 cm medial. Both incisions are placed 3 cm above the hairline. (From Strong, EB. Frontal sinus fractures: current concepts. *Craniomaxillofac Trauma Reconstr* 2009;2(3):161–175, figure 10.)

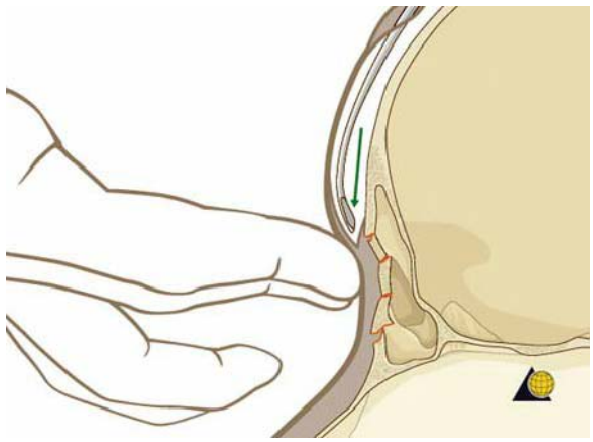


Figure 84.20 Illustration of a subperiosteal dissection used for exposure of an anterior table fracture. The initial dissection is carried down to the level of the fracture using external palpation to define the limits of dissection. An endoscope is not used. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

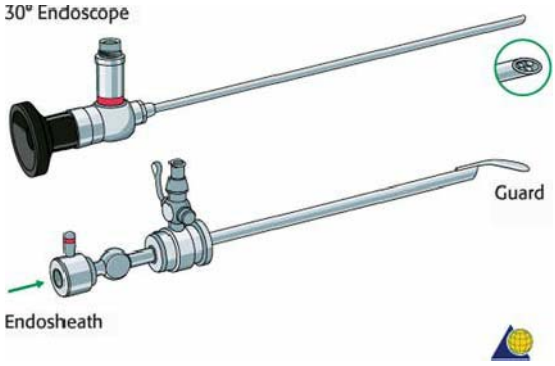


Figure 84.21 Illustration of a 30-degree endoscope and a rigid endosheath with a large tip guard to maintain the integrity of the periosteal envelope and optical cavity. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

inserted through the working incision and manipulated both internally (with instruments) and externally (with fingers) over the defect (Fig. 84.24). Once the implant is in place, the size and shape are evaluated endoscopically and the implant is removed, trimmed, and refined. The process is repeated until the diameter of the implant is approximately 2.0 to 3.0 mm larger than the defect. If necessary for stability, the implant can be sutured together in two to three layers as an inverted pyramid shape to more accurately fill deeper defects (Fig. 84.25). Patients with very thin skin may require a smaller implant that sits flush within the defect. Once the implant is appropriately fashioned, a 25 gauge needle is passed through the skin over the fracture and endoscopically visualized to determine the best site for a percutaneous incision and screw placement. Optimal incision placement will allow screws to be placed on either side of the implant through a single incision (Fig. 84.26). However, some larger implants may require two separate stab incisions. Once the site has been determined, a no. 11 blade is used to make a 2 mm, through-and-through stab incision. A small self-drilling screw (4 to 7 mm

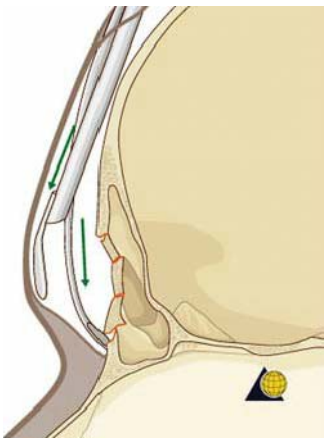


Figure 84.22 Illustration of the endoscopic exposure of an anterior table frontal sinus fracture. A fibrous scar layer prevents entry into the sinus. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

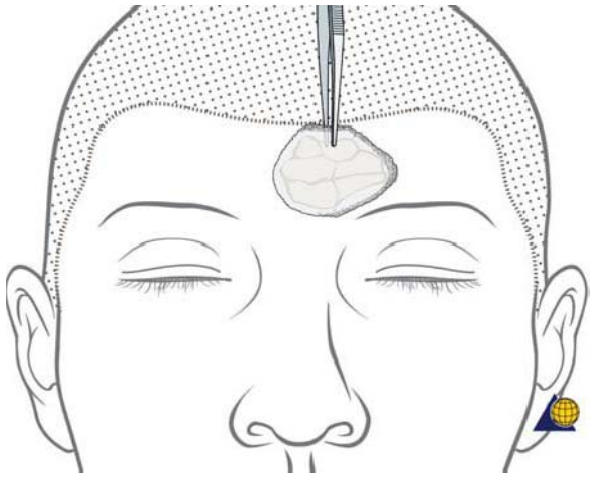


Figure 84.23 A 0.85 mm thick sheet of porous polyethylene sheeting is placed on the skin over the defect and used as a template to approximate the size of the implant to be used. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

in length) is passed through the stab incision, through the edge of the implant (at least 1 mm from the edge to avoid tearing of the implant), and into stable bone at the periphery of the fracture (Fig. 84.27). The screw must be securely attached to avoid dislodging it from the screwdriver as it passes through the soft tissue. If the implant remains unstable after the first screw is placed, a second screw is applied on the contralateral side. The scalp incisions are then closed in layers and a pressure dressing is applied.

Open Reduction and Internal Fixation

Anterior table fractures that cannot be observed or managed endoscopically may require open reduction and internal fixation. The patient consent should include the risks of bleeding, infection, paresthesia, headache, CSF leak, orbital

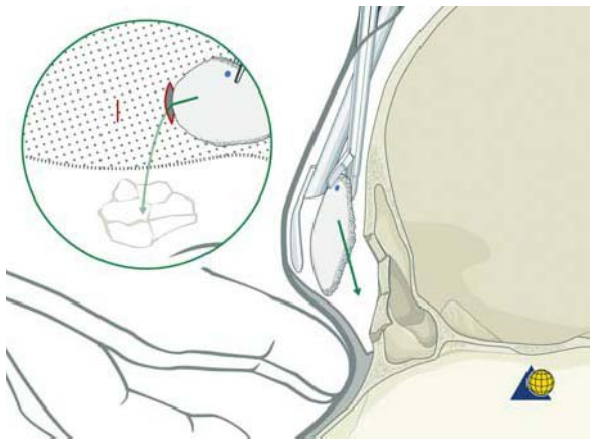


Figure 84.24 Once the implant has been trimmed to size, the superior edge is marked to maintain orientation after insertion. The implant is then inserted through the working incision under direct visualization with the endoscope. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

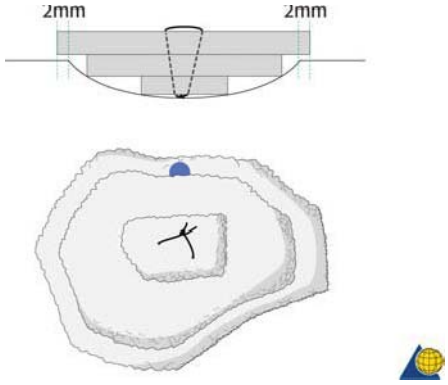


Figure 84.25 The implant may be layered and sutured together for greater stability in deeper defects. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

injury, diplopia, meningitis, external deformity, and late mucocele formation. In the operating room, the bed is turned 180 degrees away from the anesthesiologist and corneal shields or temporary tarsorrhaphies are placed. The hair need not be shaved, but patients with longer hair will require banding to delineate the incision line (Fig. 84.28). Application of a water-based lubricant to the hair facilitates separating the hair and rapid application of the rubber bands. Surgical towels are stapled to the scalp just behind the incision line. An adherent plastic suction pouch is applied at the leading edge of the towel to collect blood and minimize spillage.

The greatest blood loss occurs with the initial incision and wound closure. When possible, generous amounts of a vasoconstrictor agent should be injected in a subgaleal plane prior to surgery. In patients who will wear their hair longer than 3 to 4 cm, the author prefers a "zig-zag" incision, starting *behind the ear* and running 4 to 6 cm behind the hair line (Fig. 84.29). Postoperatively when the patient is upright, the zig-zag pattern allows gravity to pull the hair inferiorly,

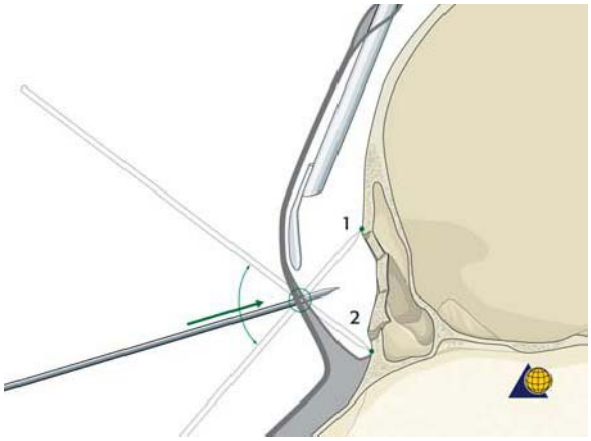


Figure 84.26 Illustration depicting the location of the stab incision used for insertion of a fixation screw to stabilize the implant. A 25 gauge needle is passed through the skin and visualized internally. The ideal location allows for a screw to be placed on either side of the implant through one stab incision. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

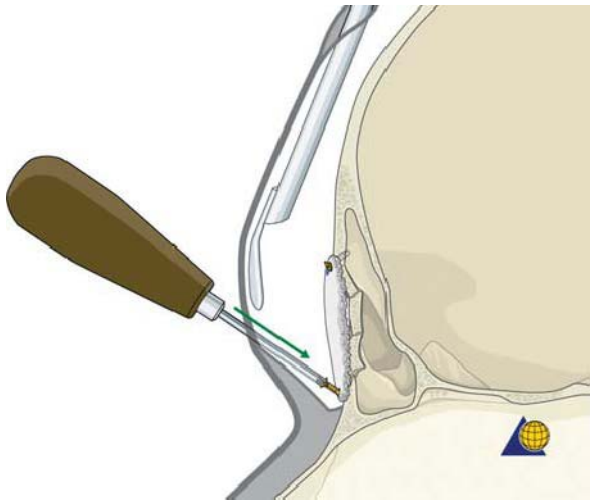


Figure 84.27 A self-drilling screw is passed through the edge of the implant and into stable bone. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

covering the transverse arms of the scar. Excessive trauma to the "tips" of the zig-zag incision should be avoided, as it may increase the risk of alopecia. If the patient wears very short hair, a zig-zag pattern only lengthens and accentuates the incision. In this situation, a traditional straight line incision (with a central "widow's peak" or a methylene blue tattoo for realignment) is more rapid and provides adequate cosmesis (Fig. 84.30). In patients with male pattern baldness, the incision can be moved posteriorly to camouflage it within in the hair. This will necessitate a slightly more extensive lateral dissection to allow forward rotation of the scalp flap. All hair-bearing skin should be handled carefully, to avoid postoperative alopecia. While forehead lacerations can be used to assist with the repair, midforehead, brow, and "gull wing" incisions should be avoided due to the prominent scar and associated forehead paresthesias.



Figure 84.28 Photograph of banding hair to keep it away from the incision. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

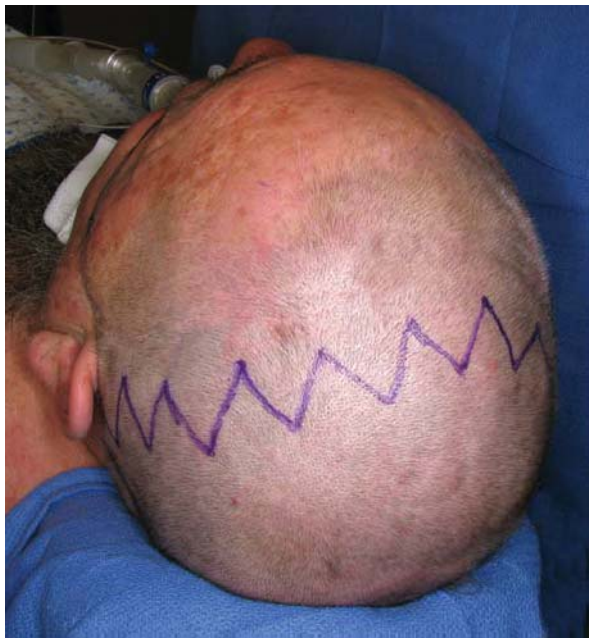


Figure 84.29 Photograph of a "zig-zag" coronal incision. (From Strong, EB. Frontal sinus fractures: current concepts. *Craniomaxillofac Trauma Reconstr* 2009;2(3):161–175, figure 14A.)

The scalp is opened in thirds. This allows time to control of bleeding and minimize blood loss. The central one-third (temporal line to temporal line) is initially incised down to the level of the galea aponeurosis. Electrocautery is avoided to protect the hair follicles. Larger vessels should be tied off individually. If necessary, Raney clips may be applied judiciously, depending on surgeon preference. Double-pronged skin hooks are used to retract the scalp away from the skull and protect the underlying pericranium. Once the galea



Figure 84.30 Photograph of a straight line incision with a "widows peak" at the top for alignment and wound closure. (From Strong, EB. Frontal sinus fractures: current concepts. *Craniomaxillofac Trauma Reconstr* 2009;2(3):161–175, figure 14B.)

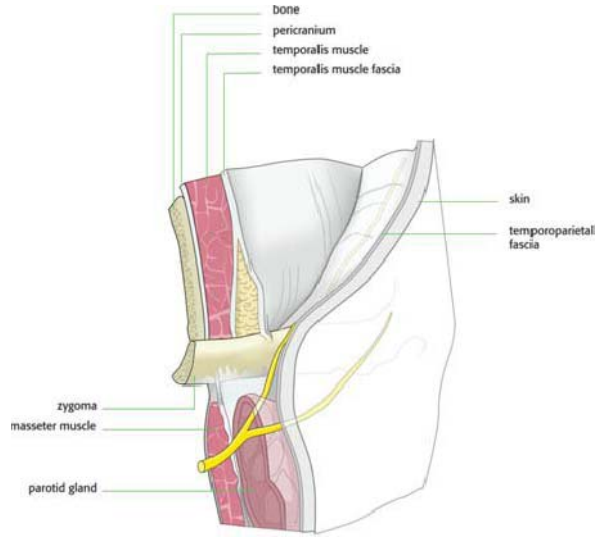


Figure 84.31 Illustration of a coronal incision in the temporal region. (From Strong, EB. Frontal sinus fractures: current concepts. *Craniomaxillofac Trauma Reconstr* 2009;2(3):161–175, figure 15.)

aponeurosis is incised, air will rapidly enter into the subgaleal space, developing an excellent dissection plane just above the pericranium. If there is a need for use of the pericranial flap during the surgical repair, the pericranium is left intact on the calvarium. It is more readily separated from the scalp when it is left attached to the bone. If there is no need for a pericranial flap, it is incised and elevated in one layer with the scalp.

Next, the lateral thirds of the scalp are individually incised. This dissection demands a thorough understanding of temporal anatomy (Fig. 84.31). The incision is extended from the temporal line inferiorly behind the helix (Figs. 84.29 and 84.30). The retroauricular incision is easily extended inferiorly behind the ear as necessary for flap rotation, while remaining completely hidden. A preauricular incision offers no real advantage, and results in a visible scar. The temporal incision should then be carried through the temporoparietal fascia (superficial temporal fascia) and onto the temporalis muscle fascia (deep temporal fascia), traversing the temporal artery and vein, which can be controlled using a suture ligature or bipolar cautery. The appropriate level of dissection can be confirmed by placing a small (1 to 2 mm) nick in the temporalis muscle fascia, exposing dark temporalis muscle beneath. The flap is then elevated anteriorly using blunt finger dissection or gauze, with limited use of the scalpel. The integrity of the temporoparietal fascia must be maintained, as it contains the frontal branch of the facial nerve (Fig. 84.31). As the temporal flap is elevated, it is joined with the central dissection that was performed initially. The fibers along the temporal line are incised sharply.

If the posterior table of the frontal sinus is intact and the surgeon has left the pericranial flap attached to the galea aponeurosis, the central dissection is carried forward in a subperiosteal plane using a wide elevator. The dissection is carried around the fracture taking care to protect the integrity of the bone fragments when possible. As the supraorbital rims are reached, care is taken to avoid injury to the

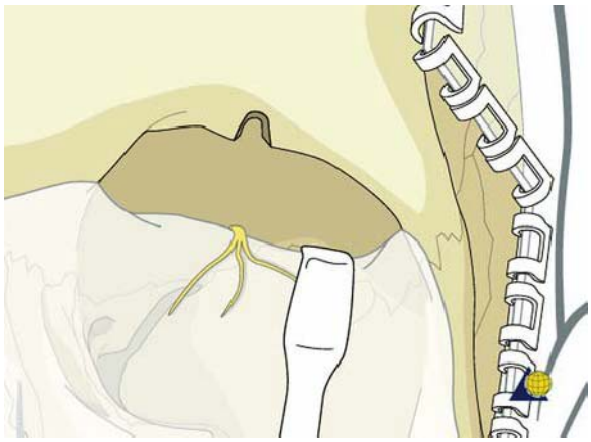


Figure 84.32 Illustration depicting the supratrochlear neurovascular pedicle after being removed from the supraorbital fissure with an osteotome. This provides exposure to the entire orbital roof. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

supraorbital and supratrochlear neurovascular pedicles. If greater exposure is required, the dissection can be carried around the orbital rims into the orbits. The supraorbital neurovascular pedicle can be released, if necessary, using a small osteotome placed at the medial and lateral aspect of the foramina and down-fracturing the bone (Fig. 84.32). Once the pedicle is released, a careful dissection following the internal concavity of the superior orbit will avoid violation of the orbital periosteum and prolapse of orbital fat.

If the periosteum has been maintained on the calvarium, the soft tissue dissection is generally carried to the level of the orbital rims, while attempting to protect the integrity of the pericranium over the fracture site. At this point, the pericranial flap is incised and elevated off the calvarium down to the level of the orbital rims. Lateral incisions are placed 2 cm cephalad to the temporal line (Fig. 84.33). If necessary,

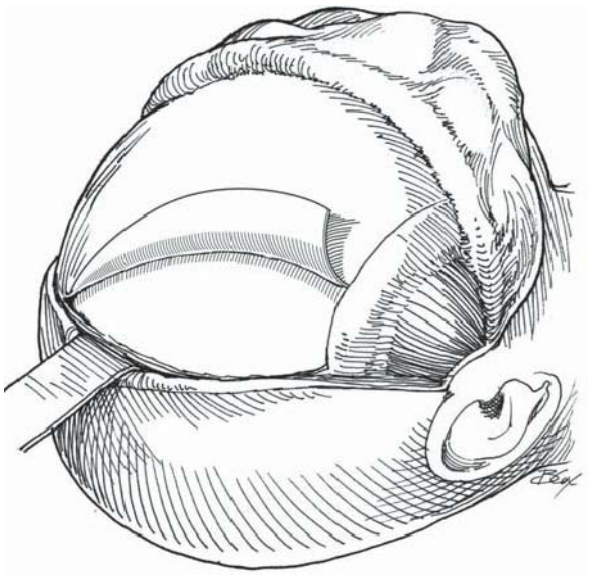


Figure 84.33 Illustration showing elevation of a large pericranial flap. (From Strong, EB. Frontal sinus fractures. *Oper Tech Otolaryngol* 2008;19(2):151–160, figure 9)

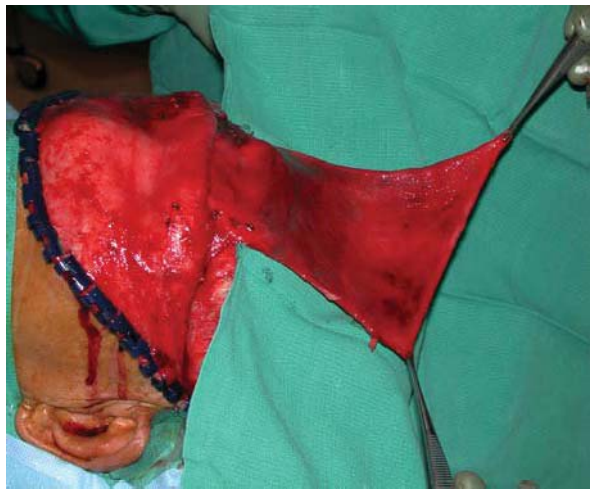


Figure 84.34 Photograph of a large pericranial flap harvested for repair of a dural defect. (From Strong, EB. Frontal sinus fractures. *Oper Tech Otolaryngol* 2008;19(2):151–160, figure 10)

2 to 4 cm of extra length can be obtained by joining the lateral periosteal incisions *behind* the initial skin incision. As the dissection is carried inferiorly, periosteal lacerations may be noted at the fracture site. A careful dissection will usually maintain an intact vascular supply and provide a lengthy flap that can be used for repair of CSF leaks or obliteration of the sinus itself if it is small (Fig. 84.34).

Reduction of noncomminuted fractures can be extremely challenging. When the convex surface of the frontal bone fractures, it goes through a compression phase, before becoming concave (Fig. 84.35). Fracture reduction requires enough force to pull the bone fragments back through the compression phase (Fig. 84.36). It may be necessary to

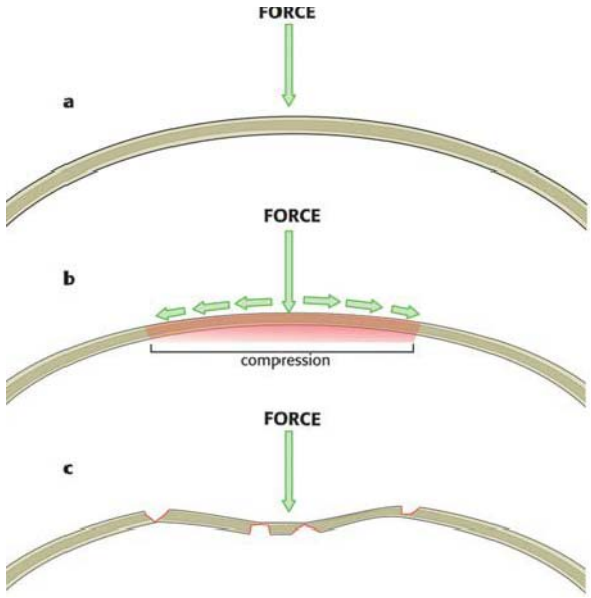


Figure 84.35 Illustration of the forces on the frontal bone when a frontal sinus fracture occurs. Note that as the bone goes from convex to concave that there is a compressive phase the bone must pass through. (From Strong, EB. Frontal sinus fractures: current concepts. *Craniomaxillofac Trauma Reconstr* 2009;2(3):161–175, figure 17A.)

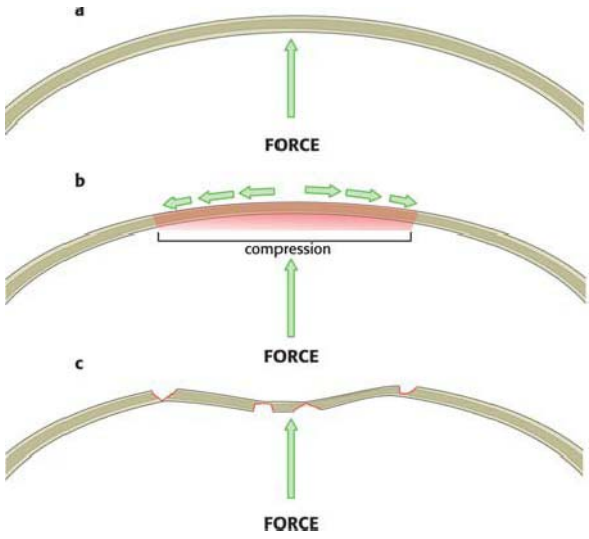


Figure 84.36 Illustration of the forces that must be applied to return the frontal bone in order to reduce a fracture. Note that as the bone goes from concave to convex, it must pass through the same compressive phase seen during fracture. This may require the surgeon to apply significant amount of force or remove a bone segment to release the pressure. (From Strong, EB. Frontal sinus fractures: current concepts. *Craniomaxillofac Trauma Reconstr* 2009;2(3):161–175, figure 17B.)

remove a bone fragment to release the tension and reduce the fracture. If comminution exists or bone segments overlap, a small bone hook may be insinuated between the fragments to assist with elevation. Another technique is to place a 1.5 to 2.0 mm screw in the depressed segment, grasp the screw with a heavy hemostat, and pull upward (with controlled force) to reduce the bone fragments (Fig. 84.37). Once the bone fragments are mobilized, the sinus mucosa should be evaluated. A 30-degree endoscope can be helpful to visualize the sinus and the nasofrontal recess through a limited bone defect. Every attempt should be made to keep the majority of the fragments in place, allowing for a more accurate repair. If bone fragments are removed, arranging them atop a drawing

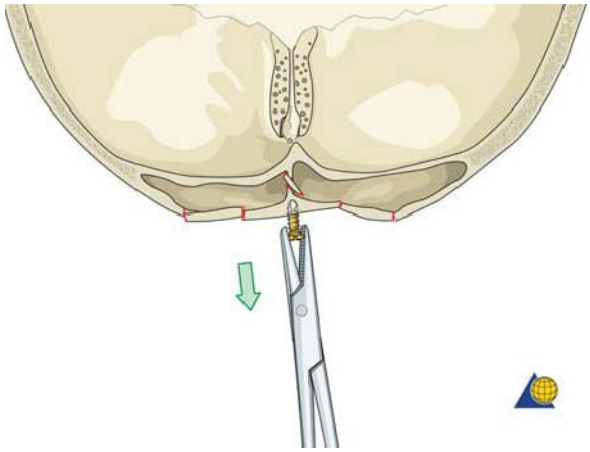


Figure 84.37 Illustration of a bone screw to assist with fracture reduction. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).



Figure 84.38 Any bone fragments that are removed should be kept moist atop a drawing of the fracture. This will help maintain the anatomic orientation for the final reconstruction. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

of the fracture helps to maintain the anatomic orientation for the final reconstruction (Fig. 84.38). The fracture is then reduced and plated with 1.0 to 1.3 microplates. Small gaps (4 to 10 mm) can be reconstructed with titanium mesh. Hydroxyapatite bone cement should *not* be used to fill bone defects. It has an unacceptably high-risk infection and extrusion. During wound closure, it is important to resuspend the temporal soft tissues to avoid long-term ptosis of the forehead and upper midface. Two, 2-0, monofilament sutures are passed through the temporoparietal fascia and suspended up to the temporalis muscle fascia (Fig. 84.39).

Frontal Sinus Obliteration

More severe injuries may require frontal sinus obliteration. A coronal incision is used to expose the fracture as previously described. A pericranial flap should be maintained for any unanticipated injuries that might be found intraoperatively (CSF leak, dural tear, etc.). After complete exposure of

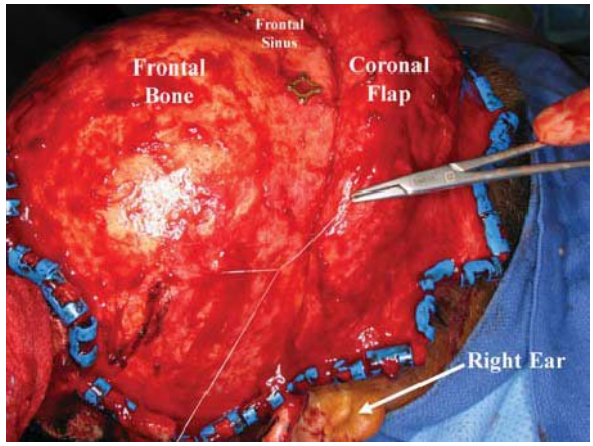


Figure 84.39 Photograph demonstrating resuspension of the coronal flap to the temporalis muscle fascia. (From Strong, EB. Frontal sinus fractures: current concepts. *Craniomaxillofac Trauma Reconstr* 2009;2(3):161–175, figure 18.)

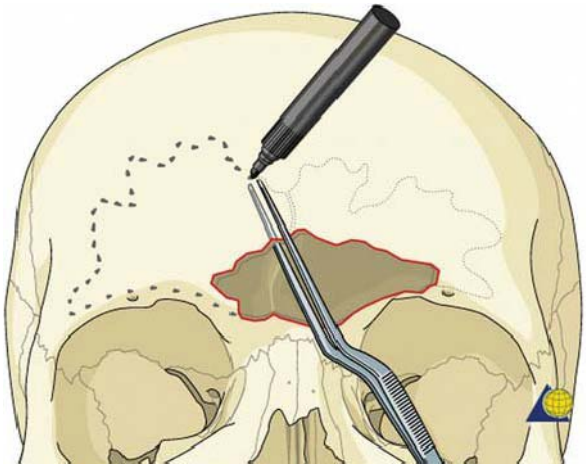


Figure 84.40 Illustration depicting the use of a bipolar forceps to outline the borders of the frontal sinus in preparation for a completion frontal sinusotomy. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

the frontal bone, all anterior table fragments should be carefully removed, kept moist on a side table, and oriented on a drawing to assist with the final repair (Fig. 84.38). In some instances, it may be necessary to perform a frontal sinusotomy to remove the remaining anterior table bone and visualize the entire sinus cavity. Localization of the sinusotomy cuts can be performed in several ways. Historically a "6 foot penny Caldwell" x-ray was used (i.e., anterior–posterior Caldwell x-ray with the patient placed 6 feet from the x-ray tube). However, current digital radiograph technology has made these films very difficult to obtain. Intraoperative navigation is effective but requires a specialized scan and navigational hardware. Alternatively, one tine of a bipolar cautery can be placed through a defect in the frontal bone, while the opposite tine remains visible outside the sinus. The internal tine is then "walked" around the periphery of the sinus, while the outer tine is used to mark an outline the

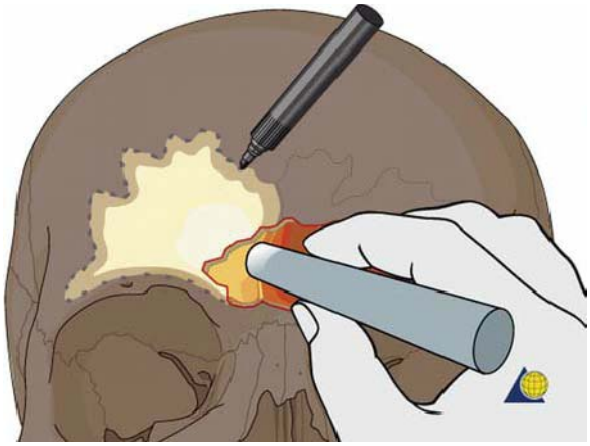


Figure 84.41 Illustration depicting the use of a light source to transilluminate the borders of the frontal sinus in preparation for a completion frontal sinusotomy. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

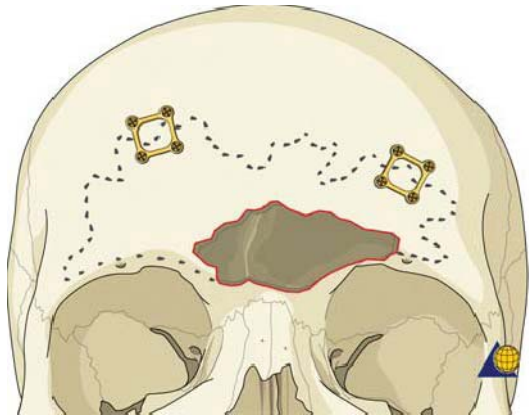


Figure 84.42 Illustration depicting preapplication of microplates spanning the proposed osteotomy line, prior to completion frontal sinusotomy. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

sinus with a drill or ink (Fig. 84.40). Another technique involves insertion of a light source into the sinus through a fracture line; this transilluminates the periphery of the sinus and guides the osteotomy (Fig. 84.41).

After the limits of the sinus have been marked out, two to three microplates (1.0 to 1.3 mm) are "pre-applied" spanning the proposed osteotomy sight (Fig. 84.42). This allows the surgeon to accurately reposition the osteotomized bone even after it is removed. The plates are then rotated superiorly away from the osteotomy, with one screw left in place (Fig. 84.43). A drill is used to "postage stamp" perforations around the periphery of the sinus (Fig. 84.44). It is angled toward the sinus cavity to avoid intracranial penetration (Fig. 84.45). A side-cutting burr is then used to join the perforations and complete the osteotomy (Fig. 84.46). Care should be taken to avoid disruption of the predrilled miniplate holes while performing the osteotomy. Inferiorly, the orbital rims are

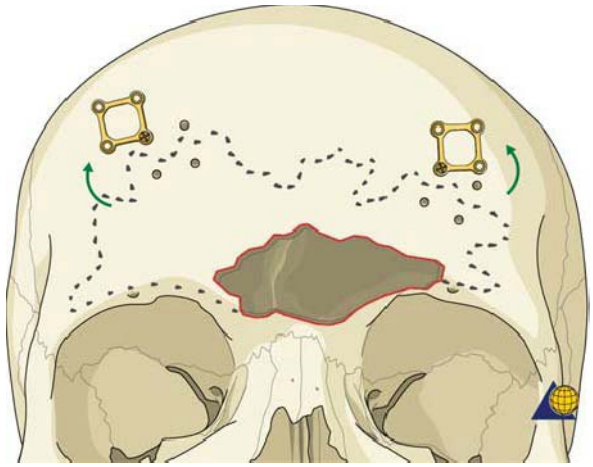


Figure 84.43 Illustration depicting rotation of the miniplates to allow for osteotomy. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

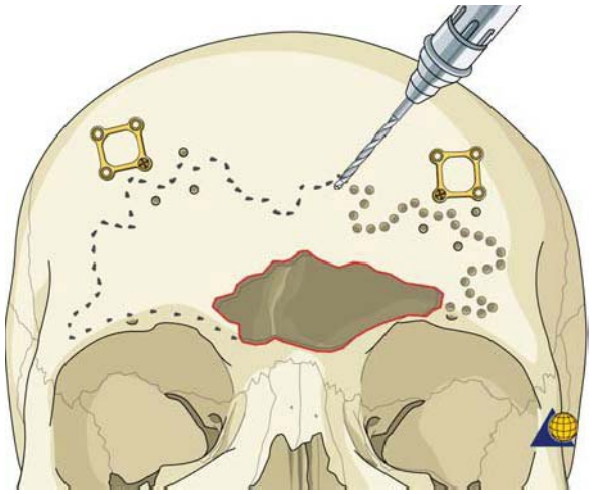


Figure 84.44 Illustration depicting "postage stamp" perforating osteotomies to outline the sinus. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

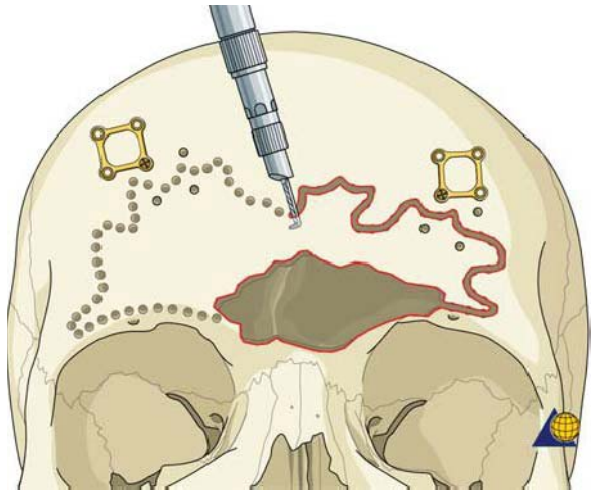


Figure 84.46 Illustration of side-cutting burr used for completion frontal sinusotomy. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

osteotomized at the periphery of the sinus. The glabella is osteotomized approximately 5 mm above the junction with the nasal bones. No osteotomy is placed in the orbital roof. Particular attention must be paid to avoid injury to the supraorbital/supratrochlear neurovascular pedicles. A curved 4-mm osteotome (curved away from the posterior table) is then inserted into the sinus from above, and used to fracture the intersinus septum (Fig. 84.47). Finally, a hand is placed on the anterior table and the osteotome is gently elevated to out fracture the anterior table.

Once the sinus is completely exposed, the posterior table integrity is evaluated. If the bone is stable and free of significant defects, sinus obliteration is acceptable. However, *all* sinus mucosa must be meticulously removed from the entire sinus, including the anterior table bone. Initially a 4 to 6 mm cutting burr is used, followed by a 1 to 4 mm diamond burr for the periphery of the sinus. Access to the deepest portions of the sinus can be challenging, and particular attention must be paid to the scalloped areas above the orbits and at the periphery of the sinus (Fig. 84.48). After complete removal of the sinus mucosa, attention is turned to the frontal recess. The mucosa of the frontal sinus infundibulum is elevated and inverted inferiorly occluding the ostia. A small plug of temporalis muscle is then placed above the inverted mucosa. A *sharp* 5 mm osteotome is then used to obtain two 5 × 5 mm bone chips from the calvarium (Fig. 84.49). These are inserted to block the frontal sinus infundibulum (Fig. 84.50).

Many different autologous materials have been successfully used for sinus obliteration. These include abdominal fat, cancellous bone, muscle, pericranium, and spontaneous osteoneogenesis with "auto-obliteration" (2,6,7). While different authors may advocate a specific material having the "best" success rate in their hands (or at their institution), the success rate is more likely related to the complete removal of all sinus mucosa and meticulous attention to surgical technique

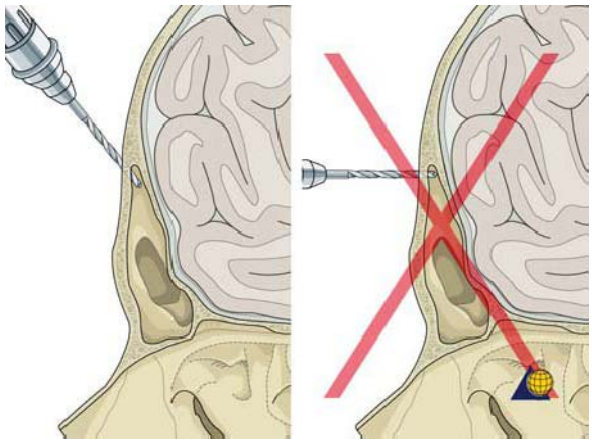


Figure 84.45 Illustration depicting the appropriate angle of approach to safely enter the frontal sinus and avoid violation of the posterior table. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

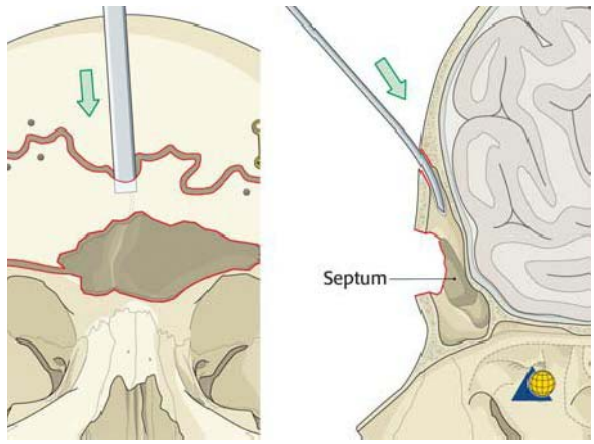


Figure 84.47 Illustration of curved osteotome used to fracture the intersinus septum and release the osteotomized frontal bone. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

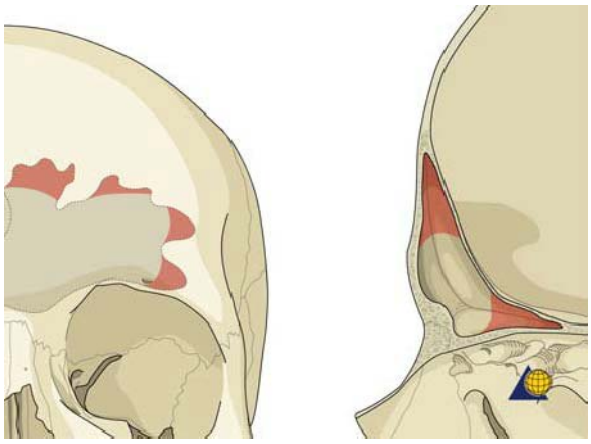


Figure 84.48 Complete removal of the frontal sinus mucosa is imperative to successful sinus obliteration. The areas above the orbits and at the periphery of the sinus (i.e., darkened areas) require special attention as they are more difficult to visualize. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

rather than the type of autologous material used for obliteration. Overall, the success rates are quite high, but there is always small risk of late mucocele formation. The author prefers abdominal fat. Alloplastic materials, such as hydroxyapatite bone cement, should be avoided due to the risk of infection and extrusion. A fat graft is obtained through a left lower quadrant (or periumbilical) incision using a separate, sterile instrument set. The fat graft should be harvested in a single piece if possible, without the use of electrocautery. The fat graft is then inserted into the sinus cavity and trimmed to size. The anterior table fragments are replaced. Anterior table stabilization and wound closure are completed as described above under "closed reduction."

Frontal Sinus Cranialization

The most severe injuries result in disruption of the posterior table. Consultation with a neurosurgical colleague

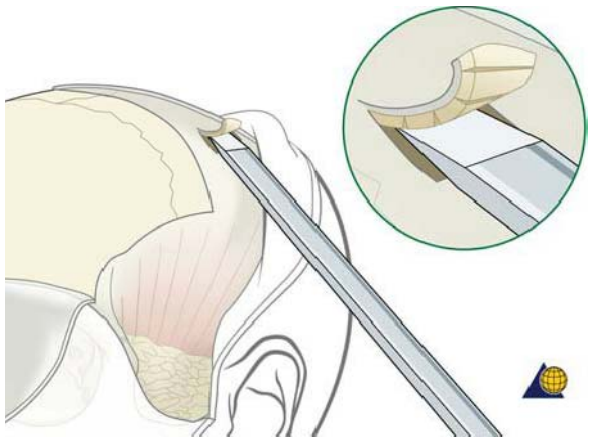


Figure 84.49 Illustration of outer table bone graft harvested from the parietal region. Note the bone graft is taken at a location where the periosteum remains intact. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

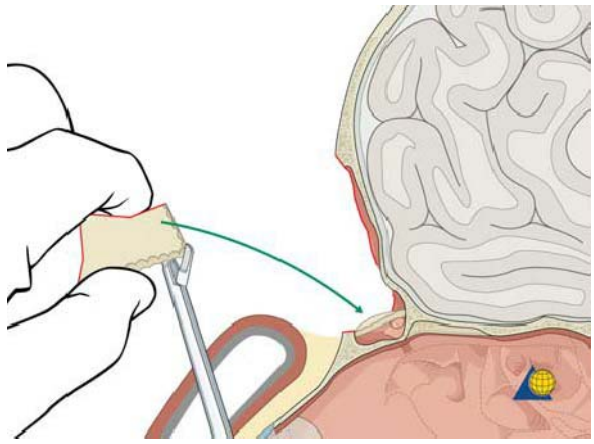


Figure 84.50 Illustration of an out table calvarial bone graft placed into the frontal recess to isolate the sinus from the nasal cavity. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

is recommended. While the exact indications for cranialization of the sinus can be controversial, injuries that: (a) disrupt greater than 25% to 30% of the posterior table wall, (b) result in significant comminution and instability of the posterior table, and/or (c) require repair of a large dural laceration should be considered for cranialization. The surgical approach is described above (see "Frontal Sinus Obliteration"). It does not require a craniotomy and can be performed through the sinus itself. However, maintaining the integrity of the pericranial flap becomes more critical for dural repair and control of CSF leaks. All free bone fragments from the anterior *and* posterior table are removed. Fragments that are adherent to the dura should be freed with Penfield elevators (Fig. 84.51). The dura is then elevated from behind any stable bone at the periphery of the sinus and retracted with malleable brain retractors. Kerrison rongeurs are used to remove any remaining posterior table

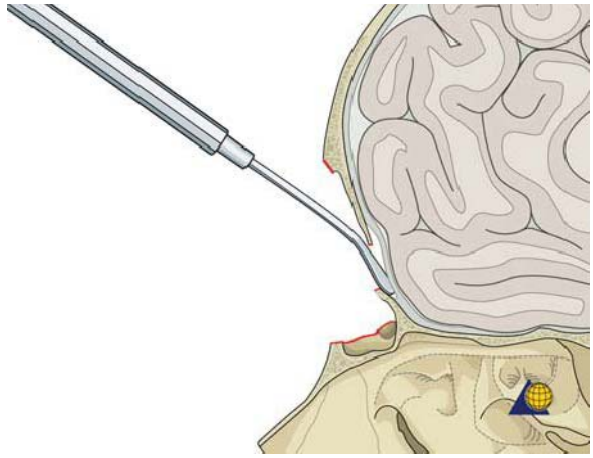


Figure 84.51 Illustration of dural elevation prior to removal of posterior table bone for a frontal sinus cranialization procedure. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

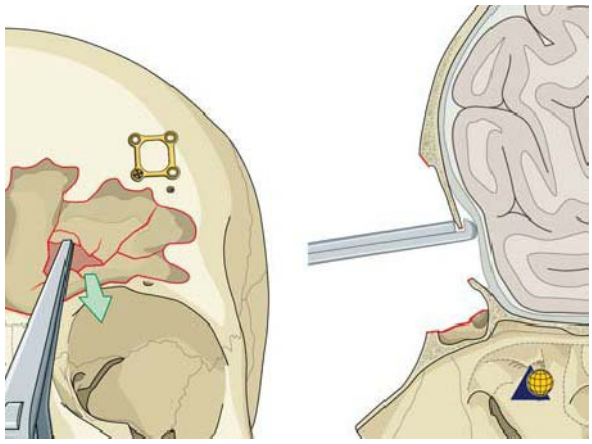


Figure 84.52 Illustration of bone removal with Kerrison rongeurs. The entire posterior table should be removed to complete the frontal sinus cranialization. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

bone (Fig. 84.52). A drill should be used to smooth the posterior table edge flush with the anterior sinus walls, floor, and anterior cranial fossa (Fig. 84.53). The frontal recess is occluded as previously described in "Frontal Sinus Obliteration." Simple dural lacerations can be repaired with interrupted 5-0 nylon sutures. More complex injuries may require neurosurgical debridement and closure with a pericranial flap. When a pericranial flap is used, a small bony defect must be fashioned just above the orbital rims to allow passage of the flap intracranially without strangulating it. The anterior table is then reconstructed using 1.0 to 1.3 microplates and mesh. The bony disruption of the anterior table can be so severe that posterior table fragments are required for reconstruction. The incision is closed as described under "Open Reduction and Internal Fixation."

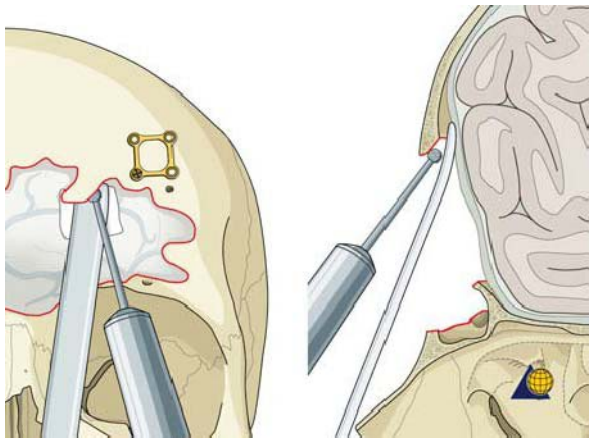


Figure 84.53 Illustration of a drill used to remove the remaining posterior table bone flush with the anterior cranial fossa. A malleable should be used to protect the brain. (From AO Surgery Reference Cranial Vault & Skull Base, www.aosurgery.org. Copyright by AO Foundation, Switzerland with permission).

SUMMARY

Optimal management of frontal sinus fractures remains a controversial topic. While there is a paucity of evidence to support a uniform approach to treatment, it is critical that each surgeon have a well thought out strategy for management of these injuries. The author provides an anatomically based, hierarchical treatment strategy for frontal sinus fractures. Differences in materials use for reconstruction, obliteration, or cranialization of the sinus are likely less important to a successful outcome than meticulous surgical technique. There is a long-term risk of mucocele formation in all patients sustaining frontal sinus fractures, even years after treatment. Patients must therefore be informed of this risk, educated about the signs and symptoms of a mucocele, and encouraged to actively participate in long-term follow-up.

HIGHLIGHTS

- The majority of frontal sinus fractures involve young males (average age 30 years) involved in high velocity injuries such as motor vehicle accidents (52%), assaults (26%), and recreation or industrial accidents (14%).
- A thorough history and physical examination is critical for patients with frontal sinus fractures. The majority of patients will have associated facial fractures and commonly have other non-head and neck injuries.
- The hierarchy of surgical management for frontal sinus fractures includes: management of any intracranial injury, avoidance of short- and long-term complications such as mucoceles, reestablishment of an aesthetic facial contour, and return of normal sinus function if possible.
- The gold standard for diagnosis is a thin cut (1.0 to 1.5 mm), axial CT scan with coronal, sagittal, and 3-D reconstructions.
- The appropriate treatment strategy for the management of frontal sinus fractures can be made by assessing *four* anatomic parameters. These parameters include the presence of: (a) an anterior table fracture, (b) a posterior table fracture, (c) a nasofrontal recess fracture, (d) a dural tear (cerebrospinal fluid leak).
- Nondisplaced (0 to 2 mm) anterior table fractures can be observed with little risk of long-term morbidity.
- Coronal incisions carry with them a moderate risk of alopecia. When recommending a coronal incision for mildly displaced fracture (2 to 6 mm), the risk of alopecia must be weighed against the risk of a cosmetic deformity if nothing is done.
- Patients with mildly displaced anterior table fractures that do not extend into the inferior orbital rim are potential candidates for endoscopic fracture treatment.

- Posterior table fractures are the result of higher velocity injuries and carry with them greater risk of long-term complications.
- If sinus obliteration is to be performed, it is absolutely critical that all sinus mucosa be meticulously removed to avoid long-term mucocele formation.
- Because mucoceles form very slowly, it is critical that the patient be informed of the associated symptoms, and that long-term follow-up is stressed.

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85 Pediatric Facial Fractures

Peter C. Revenaugh *Paul Krakovitz*

The last 25 years have seen dramatic changes in the diagnosis and treatment of facial fractures driven by advances in imaging and the advent of internal rigid fixation. Rapid acquisition of high-resolution images with three-dimensional (3-D) reconstruction techniques has facilitated more accurate definition of fracture patterns and precise preoperative treatment planning. Advances in biocompatible materials with high tensile strength, low profile, and absorbable characteristics have allowed rigid fixation of complex injuries with minimal morbidity. These refinements in technology, along with increased understanding of facial biomechanics and growth patterns, have rendered complex injuries consistently amenable to precise 3-D reconstruction. However, controversy still exists regarding the suitability of rigid fixation for the developing pediatric craniofacial skeleton.

Despite controversies, the fundamental principles of pediatric traumatology are similar to those in adults. Goals include stable restoration of preinjury architecture with minimal functional and aesthetic impairment. A unique challenge to pediatrics is the need to reconcile acute injury and functional limitations with the potential long-term growth consequences. Fortunately, there is an increasing wealth of literature in this arena and this knowledge can be used to formulate a reasonable treatment plan. The evaluation and treatment of pediatric facial trauma should include consideration for the differential injury mechanisms and patterns as well as the potential growth implications on the developing facial skeleton.

EPIDEMIOLOGY

Trauma is the leading cause of death and major contributor to long-term morbidity among children in the United States (1). There are approximately 15,000 deaths annually from trauma and 100,000 children are permanently disabled (2). The estimated national health care cost for the treatment of pediatric injuries is over $15 billion (2). Despite the high prevalence of pediatric trauma, facial fractures in this age group are relatively rare, accounting for 5% to 14% of all facial fractures (1,3,4). This percentage has remained stable despite advances in motor vehicle and sport safety and accounts for a significant health care cost at an average charge of $22,510 for pediatric patients hospitalized with facial fractures (4).

An age differential is generally noted, where patients younger than 5 years of age are less likely to sustain facial fractures. Younger male patients are disparately affected at a rate of 1.5 to 3.1:1 versus females (1,4,5).

Nasal bone fractures likely account for the most frequently fractured facial bone, but precise statistics are not available as the majority of nasal fractures occur in isolation and are treated in the outpatient setting. More routinely, large studies report fracture incidence based upon emergency department and hospital admissions. Mandible fractures comprise the majority of these fractures accounting for 20% to 50% of facial fractures in the pediatric age group (5,6). The condyle is the most vulnerable and hence, most commonly involved site in 40% to 70% of mandible fractures (1,6). Rarely seen in young children, fractures of other mandible sites increase as children approach adolescence, reflecting adult frequency and anatomic location. Dentoalveolar trauma and fractures occur often in children but due to the same limitations in data gathering, frequency may be higher than reported. Midfacial fractures are less common in children, but orbital fractures are the next most frequent midfacial fracture after nasal bone fractures accounting for 15% to 39% or pediatric facial fractures (1,5,7). Isolated zygomaticomaxillary fractures occur in 10% to 20% of patients (1,5). Even less commonly, complex midface fractures account for 5% to 10% of pediatric facial fractures. Panfacial and Lefort fracture patterns are rarer still and the scarcity and diverse fracture patterns highlight the challenge in gaining experience in the treatment of such injuries.

Pediatric maxillofacial trauma frequently involves associated injuries due to mechanism and force variability. An estimated 30% to 75% of children with facial fractures have additional injuries (3,8). Frequently, pediatric patients hospitalized with facial fractures have concomitant brain injuries (32.3%), skull base fractures (27.7%), cranial vault fractures (13% to 30%), ocular injuries (7.2%), and cervical injuries (3.3%) (1,3). Orthopedic, thoracic, and abdominal injuries are also encountered, reinforcing the need for comprehensive initial assessment of pediatric trauma patients. Further, it may be necessary to delay fracture management in lieu of neurologic stabilization. This delay can complicate future treatment in the rapidly healing pediatric facial skeleton.

EMERGENCY MANAGEMENT AND PHYSICAL EXAMINATION

Initial assessment of all patients who have experienced trauma should adhere closely to advanced trauma life-support protocols (Table 85.1). Airway management can be approached using a variety of methods based upon the patient's injury profile and mental status. For the majority of isolated maxillofacial injuries, adequate positioning of the patient is sufficient for airway management, given appropriate consideration for cervical injuries. In addition to positioning, oral suctioning to remove saliva, blood, and tooth fragments can be beneficial. In some severe cases of bilateral mandibular fracture with tongue retrodisplacement, manual traction or midline tongue traction suture can help maintain airway patency until definitive airway management.

Orotracheal intubation may be necessary in situations where positioning is inadequate to maintain the airway, there is neurologic impairment, significant oral bleeding, or complicated maxillary fractures. Again, cervical spinal injures should be considered and airway management would ideally follow proper stabilization of the spine.

If oropharyngeal or laryngeal injuries are present, intubation should be approached in the operating room with rigid instrumentation available. Emergent cricothyroidotomies or tracheotomies are avoided in favor of orotracheal intubation. However, elective tracheotomy may be beneficial in patients with panfacial fractures or when fractures are accompanied by severe neurologic injuries.

TABLE 85.1 EMERGENCIES PEDIATRIC FACIAL TRAUMA

Adherence to the Airway, Breathing, Circulation (ABCs)
Emergent tracheotomies and cricothyroidotomies are ideally avoided
Septal hematoma requires urgent drainage

TABLE 85.2 DIAGNOSIS AND EVALUATION

Injuries inconsistent with the history should raise suspicion of child abuse
Secondary survey proceeds in an orderly fashion; neurologic assessment, manual palpation, inspection of the neck, spine, eyes, nose, face, and oral cavity
Periorbital edema and hypoesthesia, ecchymoses, subconjunctival hemorrhage, diplopia, and mobility reduction are indicative of orbital injury
Suspected orbital trauma warrants an ophthalmologic evaluation
Trapdoor or "white-eyed" fracture can be subtle with limited supraduction mobility
Malocclusion is indicative of mandibular fracture
Intranasal examination is essential for septal injury, particularly septal hematoma
CT has revolutionized the evaluation of pediatric trauma

Once the patient has been stabilized according to trauma protocols, the secondary survey should proceed in an orderly fashion, keeping in mind that portions of the exam may be difficult to accomplish in an uncooperative or neurologically injured child (Table 85.2).

Full neurologic evaluation should be pursued, followed by examination of the neck and cervical spine. Attention to overall level of consciousness and cranial nerve integrity is crucial in this assessment. Particular attention to sensation of all divisions of the cranial nerve V and the motor function of the facial nerve are paramount. Ophthalmologic examination should focus on overall visual integrity, pupillary evaluation, range of motion examination, ophthalmoscopy, or presence of diplopia or ophthalmoplegia. Forced duction testing may be performed, usually under anesthesia in cases of suspected orbital trauma. Otoscopy may reveal hemotympanum or cerebrospinal fluid (CSF) otorrhea associated with temporal bone fractures. External auditory canal lacerations associated with mandibular condylar fractures or displacement may also be seen on otoscopy. Anterior rhinoscopy should focus on ruling out nasoseptal injuries, particularly hematomas and CSF rhinorrhea. Full oral examination is crucial to assess occlusion, dentoalveolar injuries, missing or broken teeth, tongue injuries, or palatal fractures associated with midface injuries.

The facial skeleton should be approached in a systematic fashion with observation followed by palpation. Facial asymmetry, ecchymosis including "raccoon eyes" or Battle sign, edema, periorbital edema, conjunctival chemosis, epistaxis, malocclusion, trismus, and gingival laceration all are signs of potential underlying fractures. Once the face has been thoroughly inspected, palpation of the buttresses follows, usually beginning at the zygomatic arches or supraorbital rims and proceeding caudally. Asymmetry, tenderness, mobility, or crepitus should be

noted wherever present. Areas of frequent fracture should be examined including the nasal bones, orbital rims, and malar eminences. Assessment of midface stability is accomplished with attempted movement of the premaxilla with one hand while stabilizing the head with the other hand. Maxillary buttressing can also be palpated intraorally. Bimanual palpation of the mandible should focus on loose teeth or tooth segments, and attempted elicitation of mobility in multiple vectors. Any missing teeth should be catalogued and considered as a potential source of airway foreign body. As with the facial skin, oral mucosa and all oral structures should also be inspected.

As time and witness availability allows, an accurate history should be obtained. Injury mechanism and assessment of velocity may predict potential fracture patterns or concomitant injuries. Any suspicious stories or inconsistent injuries should raise the threshold of concern for child abuse or nonaccidental injury.

RADIOGRAPHIC EXAMINATION

Computed tomography (CT) has revolutionized the diagnosis and treatment of facial fractures. Contemporary scanners allow rapid image gathering, ultrafine cuts (1 mm), multiplanar and even 3-D reconstructions for fracture identification and treatment planning, especially in the multiply injured children. Axial cuts provide a reasonable starting point for overall facial assessment and are particularly useful in the mandible, midface, nasal bones, and frontal sinuses. Coronal cuts are necessary for evaluating the orbital floor and may provide valuable information regarding the mandibular condyle. Sagittal cuts can provide additional information about the orbital floor, roof, and overall facial and mandibular projection.

Though CT is regarded as the "gold standard" for facial skeletal assessment, mandible panoramic x-rays (Panorex) are still useful in the evaluation of the isolated mandible fracture. Care should be taken to ensure condyle inclusion and the clinician should understand that Panorex may be inferior to helical CT in evaluation of the condyle or multiply fractured mandible (9). Plain films are now of little use in facial fracture workup and may delay diagnosis or miss facial fractures (5,10). However, nasal plain films are still commonly encountered in the emergency department setting. One should recognize the potential inadequacy of facial plain films and the subsequent need for CT in cases of nasal fracture where there is significant deformity and flattening of the dorsum or a history of significant contributing force. However, imaging in the vast majority of isolated pediatric nasal injuries is unnecessary.

ETIOLOGY/MECHANISM OF INJURY

The variable structural characteristics of the developing face and skull in relation to the mechanism of trauma determines the risk and pattern of facial fractures. Young children are generally spared from facial fractures due in part to their protected environment and minimal engagement in activities known to be risk factors for fractures. When considering all types of pediatric facial fractures, including nasal and dentoalveolar, childhood play may account for the greatest percentage (11). However, motor vehicle collisions account for the vast majority of serious facial fractures (1,5). The risk of serious facial fracture is doubled by inappropriate motor vehicle restraint in children (1,12). Falls, interpersonal violence, and sporting injuries are all common causes of fractures and vary in percentage based upon the age group of the patient. Bicycles have remained a common cause of pediatric facial fractures. Though helmets have contributed to a reduction in intracranial injuries and midfacial injuries, they do not protect against mandibular and dentoalveolar trauma (13). Fractures in young, especially preambulatory patients, or fractures of the mandible should be remembered as a possible indication of child abuse (3).

The anatomic development of the face is important to understand the different patterns of fracture seen between adults and children. At birth, the ratio of cranial to facial volume is approximately 8:1 with the face set in a recessed position. The relative protection of the skull contributes to a lower incidence of facial fractures, but a higher incidence of skull fracture and intracranial injury in young children (14). Facial growth generally occurs in a downward and forward direction and begins to outpace cranial growth after the second year of age. The orbit and brain near completion of growth by age 7, but facial growth continues well into the second decade of life. In the developing face, the bones have less mineralization with a greater proportion of cancellous bone, thinner cortices, and the sutures are not fused in infants. These factors, combined with the presence of multiple tooth buds and the lack of paranasal sinus development, make the infant craniofacial complex a solid yet elastic structure, resisting fracture. These factors also contribute to the higher proportion of greenstick fractures observed in pediatric patients. Likewise, suture ossification, sinus pneumatization, tooth eruption, and greater independence contribute to the transition from pediatric to adult fracture patterns.

FACIAL GROWTH AND TRAUMA

Understanding of craniofacial growth and its relation to trauma is limited. Coordination mechanisms of facial growth and the exact genetic and environmental contributions are unclear. A complete discussion of the various theories of facial growth and regulation is beyond the scope of this chapter. However, it is fairly accepted that facial skeletal growth and development consists of remodeling and displacement combined with inner table resorption and outer table deposition (15). Factors contributing to bony growth undoubtedly include finely regulated local and systemic factors as well as vector forces acting on the bones.



Figure 85.1 **A:** 3-D CT reconstruction of a 3-year-old child with mandibular hypoplasia, retrognathism, and right temporomandibular ankylosis. The child had a history of crush injury to the right mandibular condyle in the first year of life. **B:** 3-D CT scan of the child depicted in **(A)** shows a normal left condyle and an abnormal, hyperplastic right condyle with a foreshortened condylar neck ankylosed in the right temporomandibular joint.

The facial skeleton can be divided into two independent, yet related growth areas—the nasomaxillary complex and the mandible. Alterations in growth and remodeling within and between these areas due to trauma contribute to the deformities and dysfunction observed.

Mandible growth has long been associated with the condyle, although it is likely there are a series of growth centers that contribute to overall growth. As an area of continued growth throughout childhood the condyle seems to have an ability to remodel quickly (less than 12 months) under the strains of mastication (16,17). However, crush injuries to the condyle and injuries involving condylar head can lead to mandibular and maxillary growth asymmetries or ankylosis (Fig. 85.1) (18). Norholt et al. (19) demonstrated that younger children have fewer deformities following trauma suggesting that growth may compensate for the injury. Contrary, Rowe (2) found that injuries occurring before 3 years of age generally produced more severe deformities. Despite these apparent disparities, there is consensus that early return of mandibular mobility in pediatric patients is desirable to limit the risk of ankylosis and to stimulate normal growth and remodeling.

The nasomaxillary complex appears more sensitive to the effects of trauma on normal growth. This may be due to the multiple suture sites, limited functional restorative movement compared to the mandible, or the importance of the septum as a regional growth site. Numerous animal studies involving septectomies and septoplasties in the last three decades have continued the debate into the role of the septum as a growth center for the midface (20–22). Small case series and twin studies in humans have demonstrated midfacial hypoplasia following trauma to this area (23). Surgical manipulation of the nasoseptal area in the pediatric population carries the same concerns for midfacial or nasal growth alteration; however, evidence is limited (24). Unless functional limitation or gross deformity exists, minimal surgical manipulation of the area is recommended, especially in the area where the septal cartilage contacts the bony septum (25).

The potential effects of trauma on growth should be a counseling point with parents following injury and care should be taken wherever possible to minimize additional growth alteration risk during treatment. Minimizing additional risk would include careful restoration of the periosteum and other soft tissues with minimal periosteal elevation, attention to realignment of the septal cartilage where possible, and accurate reduction with correct suture realignment. Long-term follow-up for pediatric trauma patients is essential in identifying alterations in growth and initiating appropriate orthodontic treatment if necessary.

RIGID FIXATION

The role and best use of rigid fixation in children is still controversial, given the aforementioned concerns regarding facial growth and other potential complications of internal fixation (Table 85.3).

As with traumatic injuries, animal studies have investigated the potential growth retardation related to plating. Plating across suture lines and elevation of the periosteum has demonstrated restricted growth in several animal models (26,27). Laurenzo et al. (27) observed an equivocal amount of growth restriction between rabbits that had

TABLE 85.3 COMPLICATIONS FACIAL FRACTURES

The nose, nasoethmoidal complex, and maxilla are susceptible to growth abnormalities as a result of trauma
More severe types of pediatric facial trauma are associated with concomitant injuries— especially neurologic in up to 60% of patients
Fracture complications can include delayed sinus infections, malunion, malocclusion, TMJ dysfunction, and delayed growth disturbances
Inadequate treatment of upper and midfacial injuries may result in serious alterations of facial growth
Bone growth can cause translocation of metallic implants

trauma and those that had trauma and subsequent fixation. They concluded that plating offers no additional growth restriction beyond that of the initial trauma. Their group then reported that subsequent removal of the plates had additional detrimental effects to growth in rabbits (26).

Human studies have also demonstrated growth restriction in the setting of plated fractures (28). These data have caused some clinicians to recommend plate removal, although detractors would cite the animal evidence that removal may further traumatize growth centers and less than 8% of patients who are observed eventually require plate removal (28). Independent of growth considerations, metallic hardware can be complicated by palpability, hypersensitivity, bone atrophy, tooth bud injury, and potential interference with future imaging. Plate displacement, plate and screw migration (even intracranial), and plate isolation are also complications to consider when planning rigid fixation (29).

To avoid the complications associated with permanent plates and screws in the developing face, absorbable plating systems have been developed. The safety and efficacy of these systems have been established and this technology gained U.S. Food and Drug Administration (FDA) approval in 1996. High molecular weight polyalphahydroxy acids are the most commonly used craniofacial bioabsorbable materials including polylactic acid (PLA) (both L and D enantiomers), polyglycolic acid (PGA), polydioxanone (PDS), and their copolymers. Biodegradation of PLA and PGA occurs in two phases; a hydrolysis phase where water molecules cleave the larger macromolecules, and a metabolic phase where macrophages phagocytize the polymer fragments (30). Substantial strength loss occurs during the hydrolysis phase and the space occupied by the absorbable screws is eventually obliterated by bony ingrowth (30). During degradation, PLA and PGA are metabolized into carbon dioxide and water and eliminated through respiration whereas PDS degradation products are primarily excreted in the urine (30). Pure polymers have disadvantageous properties in regard to strength, degradation time, and local tissue reactions.

Currently available plating systems utilize copolymers of PLA and PGA allowing a variety of strength profiles and degradation times from 6 months up to 6 years (30). Physical and biomechanical studies have demonstrated that available absorbable plates provide flexural and tensile strength comparable to available titanium microplate systems (31). Ideally, plate resorption should occur after the 4 to 6 weeks necessary for full fracture healing and indeed, commercially available systems retain 60% to 80% of their strength at 10 weeks (30).

Complications observed with absorbable plating commonly include peri-implant edema, temporary visibility, and palpable hardware (30). Degradation appears to elicit only a mild foreign body reaction in the surrounding tissue. As in permanent fixation, some controversy exists regarding the potential growth restrictive properties of absorbable plating procedures. To date there have been few long-term studies to address this possibility.

Currently, resorbable plating systems are recommended for "non–load-bearing" areas of the upper face and midface. Although plating of mandible fractures and saggital split osteotomies have been described, their use in these contexts is still investigational in children with limited long-term data (32). The somewhat larger screws, thicker plates, and limited malleability of absorbable systems can limit use in areas of thinner skin or in severely comminuted fractures. As technology improves, changes in product properties and indications are expected.

While it has been demonstrated that open reduction and internal fixation (ORIF) for the treatment of mandibular and complex midface fractures is safe and efficacious, especially in children older than 13 years, the risks and benefits of internal fixation must be weighed prior to intervention (Table 85.4) (3).

Many minimally displaced or greenstick fractures can be managed conservatively. Management of moderately displaced fractures requires higher clinical acumen and can be guided by postreduction stability. However, in certain complex cases, or load bearing segments, rigid fixation cannot be avoided. Whether rigid or absorbable, plates should be as small as possible without compromising stability, as

TABLE 85.4 TREATMENT PEDIATRIC FACIAL FRACTURES

Orotracheal intubation is ideally accomplished after securing the cervical spine
Careful restoration and resuspension of injured soft tissue
Reduction of fractures into stable anatomic locations
ORIF is indicated in unstable fractures
Correct realignment of suture lines
Minimal periosteal elevation
3-D, stable fixation
Use of bone grafts in areas of bone loss
Mandibular fractures with normal occlusion and mobility treated with soft diet
Malocclusion or movement limitation treated with MMF or ORIF
Traumatic telecanthus associated with nasoorbitoethmoid fractures is best treated with transnasal wiring

short as possible, and ideally not placed over more than one suture. Periosteal elevation should be minimized and dissected tissues reapproximated precisely.

SURGICAL APPROACHES

Despite advances in rigid fixation, it is important to remember that many pediatric fractures can be managed with closed techniques. In cases of displaced or complex fractures where fixation may be necessary, much of the facial skeleton can be exposed through a single incision or combination of several incisions.

The upper third of the face can be approached through a coronal incision to access the upper orbital rims, forehead, and nasoorbitoethmoid (NOE) complex. Subfascial release of the temporalis fascia allows complete exposure of the zygomatic arches. Exposure of the orbital rims can be accomplished using a subciliary or more popularly a transconjunctival incision with or without a lateral canthotomy. The medial orbit and apex can be approached via a transcaruncular incision (33). For important realignment of the midfacial nasomaxillary and zygomaticomaxillary buttresses, an upper gingivolabial sulcus incision can provide access to the entire maxilla and zygoma with care taken to identify the infraorbital nerve. In the case of especially complicated fractures requiring wide exposure, a midfacial degloving approach can be used.

Fractures of the mandibular symphysis, body, and angle can be approached through a lower gingivolabial sulcus incision. Rarely, plating of ramus fractures or comminuted fractures of the angle and body can be reduced through an external approach.

As always, tenets of limited periosteal dissection with careful restoration of soft tissue should be observed. In complex fractures, accurate reestablishment of facial buttresses to provide preinjury occlusion, facial width, and height is fundamental.

NASAL FRACTURES

Visual examination of the pediatric nose reveals the differences in anatomy from the adult nose. Children have limited nasal projection and the projecting tissue comprises soft cartilage that is compliant to physical forces. As a result, the pediatric nose deforms readily, dissipating force across the maxillary soft tissues and lateral buttresses. Rarely are the nasal cartilages injured. However, the underlying septum is relatively rigid and prone to injury with trauma of significant force. Three types of septal injuries are observed in children. The perichondrium can be sheared from the septum creating a potential space for blood and resultant hematoma. Secondly, a dislocation of the caudal septum can lead to nasal deformity and obstruction. Lastly, separation of the bony and cartilagenous septum can be observed, leading to nasal obstruction and growth abnormalities.

Nasal bones have limited projection in young children and therefore are rarely fractured in this age group. Fracture risk increases with age and if present in younger children, they can be of the greenstick variety. In addition to limited projection, the nasal bones are not fused in the midline in young children, resulting in "open-book" fractures where the nasal bones are separated in the midline and splayed over the maxilla. Clinicians should have an index of suspicion for occult nasoorbitoethmoid fractures in children with fractures of the nose with "open-book" fractures or a history of direct trauma to the nasal bridge.

Initial examination is often of limited utility due to the presence of midface edema from force dissipation and the lack of external deformity. Several days of observation may be necessary before the true cosmetic deformity can be appreciated. Initial examination must focus on evaluation for septal injury and hematoma. Nasal obstruction and unilateral septal bulging are hallmarks of a hematoma. A septal hematoma will classically appear purplish and compress with manipulation but not resolve with decongestion. Untreated and even treated hematomas can lead to a variety of complications including a fibrotic septum or loss of cartilage and resultant saddle-nose deformity (34).

Treatment of a septal hematoma is best approached under anesthesia in the pediatric population. The hematoma is incised via a Killian incision, allowing exploration of the septum and limited reduction of cartilaginous fragments. Through-and-through quilting suture should reapproximate the mucoperichondrial flaps. Septal splints can be used for 2 to 3 days to prevent reaccumulation. Packing can be poorly tolerated and only advised if there is strong justification for its use. Perioperative antibiotics are recommended. Closed reduction can be accomplished in the same setting if dorsal nasal fractures are encountered.

If no hematoma is encountered and there is no notable nasal deformity, the patient can be reevaluated in 3 to 5 days once edema has resolved enough to reveal any deformity. If bony or septal injuries are discovered causing a fixed nasal obstruction or poor cosmesis, definitive management is recommended. Usually, closed reduction is sufficient. Greenstick fractures and septal fractures may require open approaches to adequately reduce. Injuries presenting 2 to 3 weeks postinjury may require open reduction due to rapid ossification. Timing of open reduction is debated and should take into account the deficit or defect, patient age, and potential for altered growth.

NEWBORN NASAL DEFORMITY

Occasionally newborns may be born with a grossly asymmetric nasal tip. Intrauterine positioning and trauma while traversing the birth canal are two potential etiologies. Classically, the septum is deviated to the same side of the nasal tip and the nasal dorsum is unaffected. Since neonates are obligate nasal breathers, nasal obstruction would be an indication for early septal relocation. Otherwise, the nasal tip and septum eventually straighten in the majority of cases and reassurance is all that is needed (35).

FRACTURES OF THE MANDIBLE

Fractures of the mandible account for 13% to 48.8% of pediatric facial fractures with increasing frequency as patients age (1,5,7). Concerns over the developing face and dentition dictate management decisions, which are somewhat different in pediatric versus adult patients. Although treatment modalities may differ, the overall goal is accurate alignment and reduction with restoration of preinjury occlusion.

Unique to the pediatric mandible are concerns presented by the developing dentition. Until age 2 there is incomplete eruption of the deciduous teeth. In this age group traditional methods of immobilization may be inadequate. Age 2 to 5 years, the deciduous incisors and molars have firm roots for fixation if needed. From age 5 to 9 there is mixed resorption of the deciduous roots and incomplete eruption of the secondary dentition. Once children are 10 to 12 years old, an adequate compliment of secondary teeth for fixation is present.

Maxillomandibular fixation (MMF) is used more sparingly in the pediatric population given concerns for joint ankylosis, tooth development, and general airway concerns. If deemed necessary, 2 to 3 weeks of immobilization in children less than 12 years of age is adequate. When used, differences in dentition phase may dictate MMF type. Patients who have no teeth or limited deciduous teeth, an acrylic splint can be fabricated using plaster casts of the upper and lower dentition positioned in estimated occlusion to cast the final splint. The acrylic splint can be secured using circum-mandibular and transnasal wires (Fig. 85.2). Alternatively, screws can be placed in the zygoma and inferior mandibular border and secured with monofilament suture. However, this is

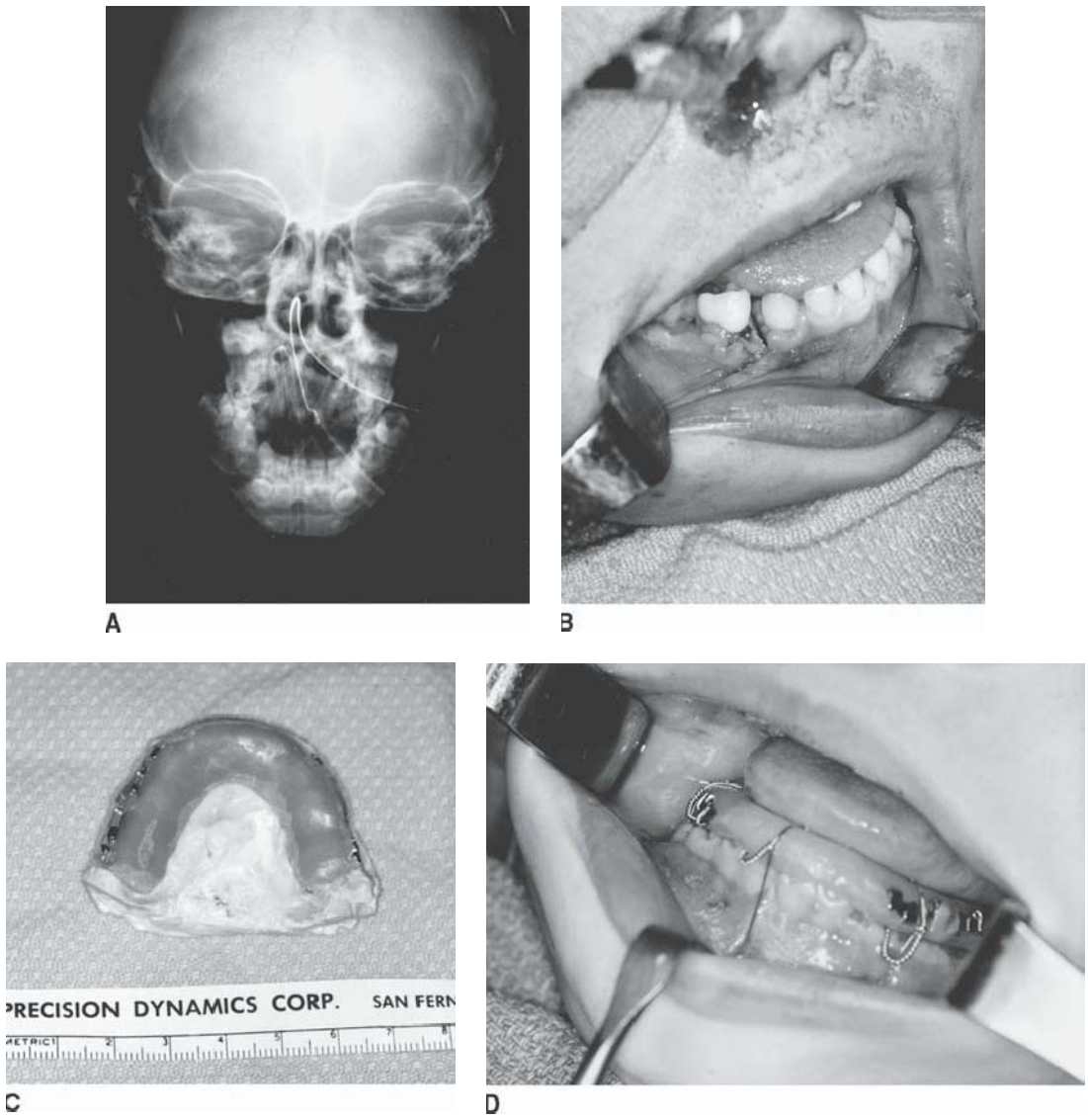


Figure 85.2 **A:** Towne view shows right parasymphyseal mandibular fracture in a 3-year-old girl. **B:** Clinical photograph shows the fracture depicted in **(A)**. **C:** Acrylic splint fabricated on a plastic cast of the mandible. The original impression of the mandibular arch was cut and the occlusion established to the maxillary impression before fabrication of the splint. **D:** Acrylic splint wired into place with circummandibular wires.

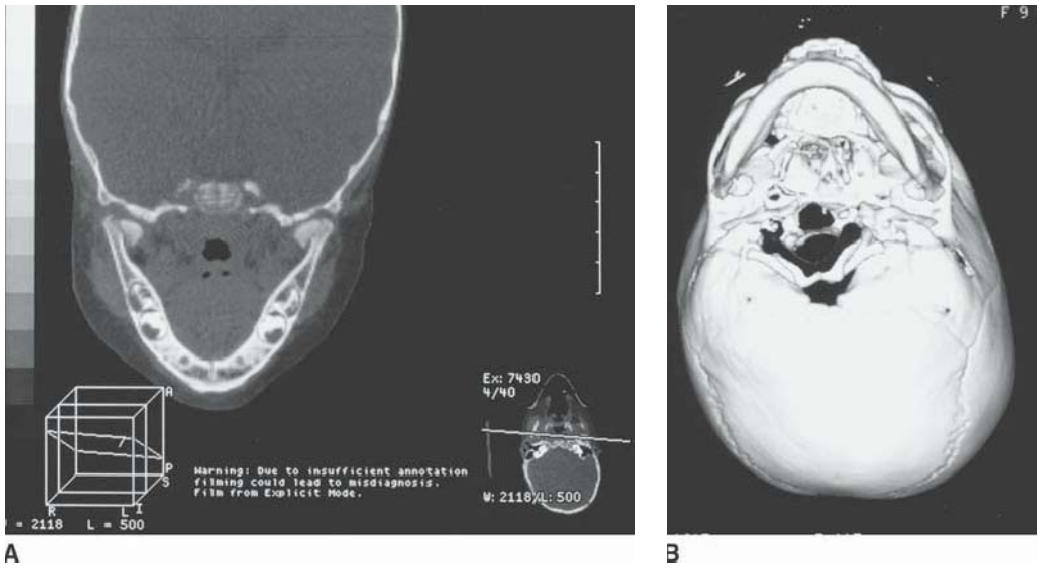


Figure 85.3 Coronal **(A)** and 3-D reconstruction **(B)** CT images of a 10-month-old infant with bilateral displaced subcondylar fractures. Coronal view shows symphyseal greenstick fracture of the lingual cortex. This child was treated expectantly.

inadvisable in older patients as the masticatory muscles may be strong enough to resist the fixation. Once patients are 2 to 5 years old, the deciduous teeth have firm enough roots for cap splints and arch bars. Arch bars may be difficult to secure, however, due to the shape of the teeth. If using MMF from age 2 to 5, augmentation of fixation may be obtained using pyriform aperture and circum-mandibular wiring. After 10 years of age, children generally have enough permanent dentition to securely place arch bars.

Consideration for the growing face cannot be overemphasized in fracture management. Complications of pediatric mandibular fractures in general can include malocclusion, malunion, nonunion, infection, tooth loss, and temporomandibular joint (TMJ) dysfunction. Greenstick fractures are common and teeth are often encountered in the fracture line and should not be removed unless devitalized (36). Prolonged MMF places the patients at risk for TMJ ankylosis, which can be difficult to treat and result in growth abnormalities.

FRACTURES OF THE CONDYLE

Fractures of the condyle account for the majority of mandibular fractures in children (6). These can be classified into three anatomic types: intracapsular crush fracture of the condylar head, high condylar fracture above the sigmoid notch, and low subcondylar fracture. The low subcondylar fracture is the most common type with many being greenstick fractures. Although the condylar head has rapid resorption capabilities, there is evidence to suggest that trauma to this growing area can result in growth arrest or functional or radiologic deformity in up to 20% of patients (37). Therefore, long-term follow-up and possible orthodontic intervention is advised.

Most clinical and experimental data support a conservative closed approach to the majority of condylar fractures. A primary clinical decision point is usually whether or not to immobilize the patient. Often, unilateral condylar fractures with normal range of motion and normal occlusion, a soft diet and movement exercises are all that is necessary. If there is good occlusion, but deviation with movement, arch bars with elastic guiding bands may be helpful. Commonly, an open bite may be a sign of unilateral or bilateral condylar fracture (Fig. 85.3). If there is an open bite, mandibular retrusion, or movement limitation, a short course (2 to 3 weeks) of MMF may be helpful followed by elastic bands if needed. Open surgical repair of the condyle is rarely indicated except in instances of displacement into the middle cranial fossa or severely restricted mandibular movement. Preauricular and submandibular approaches can be used.

FRACTURES OF THE ARCH OF THE MANDIBLE

Fractures of the arch of the mandible can range from greenstick fractures to displaced bicortical fractures and are commonly associated with fractures of other mandibular site in up to 30% of cases. Often, masticatory muscles exert unfavorable forces on fractures of the anterior arch causing displacement that can be carefully reduced under anesthesia.

Treatment of arch fractures ranges from soft diet to MMF or ORIF with miniplate fixation. Arch bar placement can be complicated by dentition stage and unfavorable splaying of the inferior border of the fracture. If rigid fixation is used, monocortical screws should be placed with cognizance of the underlying developing tooth buds

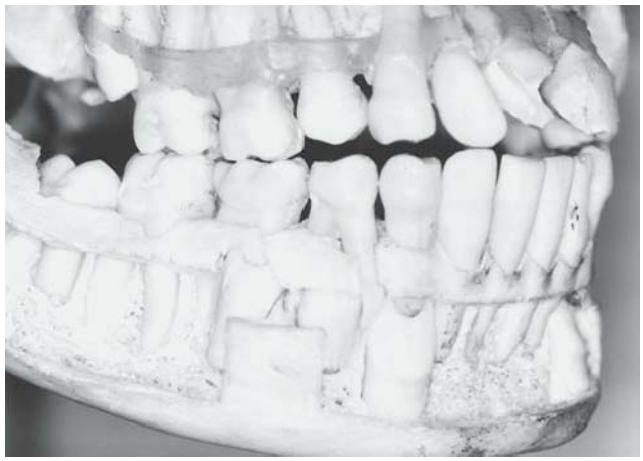


Figure 85.4 Proximity of the unerupted canine and bicuspid teeth to the lower margin of the mandible.

(Fig. 85.4). However, once children have a full complement of secondary dentition, adult treatment algorithms apply. Currently, absorbable plating systems are not FDA approved for mandible fracture treatment (30). Fractures of the body and angle commonly are of the greenstick variety, typically with normal jaw movement and occlusion. In these cases, soft diet and observation is appropriate. Conservative plate placement again should be observed if internal fixation is deemed necessary.

DENTOALVEOLAR FRACTURES

Dentoalveolar fractures are relatively common in pediatrics involving the incisors and canine teeth most often (38). Treatment of these fractures should occur on an emergent basis to stabilize the traumatized bone and teeth. Avulsion of primary teeth without bone is not serious, but it is often difficult to determine if a tooth is primary or secondary, so reimplantation of any avulsed teeth is a safe strategy. Acute treatment involves preserving and cleaning of the tooth with replacement in the socket in cooperative patients while arranging prompt dental consultation. If the child is uncooperative, the tooth can be placed in a saline solution, moist gauze, or submersed in milk until dental implantation. Every effort to implant within 1 hour of injury should be made to give the best chance for recovery. Treatment of the loss of multiple teeth or alveolar bone is challenging and may require MMF or miniplate fixation, generally with poor tooth survival rates (38).

FRACTURES OF THE MIDFACE

Fractures involving the midface, orbit, and nasoethmoidal region are rare in children and often result from significant forces with associated intracranial injuries. Injuries can range from isolated orbital blow-out fractures to severely comminuted fractures involving multiple facial buttresses. Severe facial edema, orbital ecchymosis, and malocclusion are signs of an underlying fracture. CT with multiplanar views is essential in diagnosis and treatment of midface fractures. Ophthalmologic examination should be undertaken with any fractures involving the orbit. Evaluation for vision loss, enophthalmos, exophthalmos, globe rupture, vertical dystopia, or elevated intraocular pressure is necessary. Sensory nerve integrity and intercanthal distance should also be inspected. Medial canthal stability and forced duction tests are generally reserved for patients under general anesthesia.

In midface fracture treatment, a multidisciplinary approach is necessary with the goal of therapy to establish facial symmetry, 3-D proportions, occlusion, and function. Taking into account the overall medical condition of the patient after a potentially severe trauma, fracture reduction should be attempted within 10 days. Pediatric bone can reossify rapidly, making future correction difficult. If necessary, acute reduction can be attempted through existing lacerations.

Lefort fracture patterns can be used to describe complicated midface fractures. However, these classifications are rarely adequate in pediatric midface fractures due to the variety of fracture patterns associated with variable paranasal sinus development. With high-velocity midface injuries, fractures of the palate instead of Lefort I patterns can be observed due to lack of maxillary sinus development and incomplete midline palatal fusion. Oblique fractures extending through the frontal bone and fractures of the cranial vault are also observed with upper midface trauma (39). Due to the variety of fractures, classification schemes to describe treatment implications have been proposed (11). Type I fractures are minimally displaced, Type II are moderately displaced with some areas of comminution. Type II injuries can involve multiple buttresses, but the fragments are recognizable and large enough to rigidly fix. Type III fractures are severely displaced with multiple areas of comminution involving buttresses where 3-D stabilization and bone grafting may be necessary for adequate reduction.

FRACTURES OF THE ZYGOMATICOMAXILLARY COMPLEX

Zygomaticomaxillary complex fractures generally do not occur under the age of 5 owing to the lack of maxillary sinus pneumatization. After this age, fracture patterns resemble those in adults although involvement of the orbital floor and rim can be observed more frequently in children (40). Greenstick fractures of the frontozygomatic suture and zygomatic arch with medial displacement of the malar fragment are commonly seen. In these cases, single-point fixation of the zygomaticomaxillary buttress may be adequate. More often, two- or three-point fixation is required and proper reduction should be confirmed with palpation at the zygomaticomaxillary, frontozygomatic, and even zygomaticosphenoid sutures. Fixation is often undertaken at the zygomaticomaxillary buttress through a

gingivolabial incision, and at the orbital rim and/or frontozygomatic suture through a subciliary or transconjunctival incision with lateral canthotomy. If exposure of the zygoma is necessary for complex or comminuted fractures, a hemicoronal incision can be added.

Isolated zygomatic arch fractures without displacement can be observed with institution of a soft diet. Minimally displaced fractures can be reduced via the intraoral route, a Gillie approach or even directly through existing wound or transcutaneously with a bone hook. Contingent upon reduction and stability, isolated zygomatic fractures may not require further fixation.

FRACTURES OF THE ORBIT, ORBITAL ROOF, AND FRONTAL BONE

Fractures involving the orbital and orbitoethmoid area can range from simple to quite complex and result in severe functional deficit and poor aesthetic outcomes. Thirty percent of orbital fractures are associated with other facial fractures (41). As with midface fractures, ophthalmologic consultation is imperative and consideration for intracranial injuries should be maintained, especially in cases of orbital roof, frontal bone, NOE, or bilateral orbital fractures. Assessment of visual acuity should be primary as optic nerve injury can result from apex fracture or extension of orbital wall buckling. Loss of visual acuity and the presence of an afferent pupil defect are hallmarks of optic neuropathy. Fractures of the orbital apex are exceedingly rare and usually associated with other nonsurvivable injuries due to the force required to injure this area. Attention should also be given to orbit position, extraocular movements, pupillary abnormalities, cranial nerve V integrity, and intercanthal distance.

Fracture patterns in this area tend to be age specific paralleling paranasal sinus development. Maxillary sinus pneumatization generally begins after age 5, when isolated orbital floor fractures are more often seen. The ethmoid air cells continually expand throughout childhood, reaching 70% of interorbital width by age 7 and frontal sinus development generally begins around age 6 (42).

ORBITAL FLOOR AND MEDIAL WALL FRACTURES

Due to lack of sinus pneumatization, isolated orbital floor fractures are infrequent in young children. In older children, they are more commonly seen as a result of play or sporting injuries. Coronal CT offers the best depiction of these fractures and ophthalmologic evaluation should be included in the work-up, but serious ocular injury occurs in less than 5% of isolated orbital blow-out fracture (43). Diplopia, enophthalmos, periorbital edema, echymosis, and infraorbital hypesthesia can be observed. Fracture patterns have been described as "trapdoor" or "saucer" patterns.

The *trapdoor* fracture is a linear orbital floor fracture, hinged medially that can allow herniation of orbital contents into the maxillary sinus (43). These are more commonly seen in the pediatric population, probably due to a higher incidence of greenstick fractures, where self-reduction occurs. Trapdoor fractures are also known as "white-eyed" fractures due to their subtle presentation. Extraocular mobility reduction with forced duction examination is diagnostic (44). CT may reveal linear fracture along infraorbital nerve but is not necessary for diagnosis. Urgent surgical intervention is indicated in cases of entrapment with oculocardiac reflex resulting in emesis, bradycardia, and/or arrhythmia (45). True entrapped fractures should be explored within 48 hours to reduce risk of permanent diplopia or symptomatic oculocardiac reflex (46).

Saucer fractures result in a depressed orbital floor with potential for herniation or orbital contents and resultant enophthalmos. Surgical intervention in nonurgent cases is based upon need for concomitant exploration with other fractures, significant enopthalmos (greater than 2 mm), extraocular muscle restriction on forced duction, symptomatic diplopia, or CT findings indicating large fracture (greater than 50% of the orbital floor or wall) (47). Patients not indicated for surgery can be observed for a period of days to weeks for resolution of edema or diplopia. The orbital floor can easily be exposed through transconjunctival or subciliary incision with delicate reduction of bone fragments. An array of repair materials has been cited throughout the literature. The more commonly described absorbable gelatin film can be used for reconstruction of floor defects and if necessary split calvarial bone for larger defects.

Medial orbital wall fractures rarely occur in isolation and are commonly denoted by orbital emphysema on CT scan (33). Surgical repair is indicated for fixed enopthalmos or entrapment of medial muscles. Exposure can be facilitated through transcaruncular or external ethmoid incision, with a transcaruncular approach offering a more inconspicuous scar (33).

FRACTURES OF THE NASOETHMOIDAL COMPLEX

Nasoorbitoethmoid fractures involve the central core of the face including the nasofrontal suture, nasal bones, medial, and inferior orbital rim. These fractures can range from minimal displacement to complicated comminution. CT is essential in operative planning with axial images demonstrating degree of posterior displacement into the ethmoid sinuses and coronal images displaying medial wall and orbital floor displacement (Fig. 85.5). Medial canthal tendon integrity should be investigated under general anesthesia with a hemostat inserted intranasally toward the medially orbital rim. Additionally, intercanthal distance should be measured to determine hypertelorism. Although there is

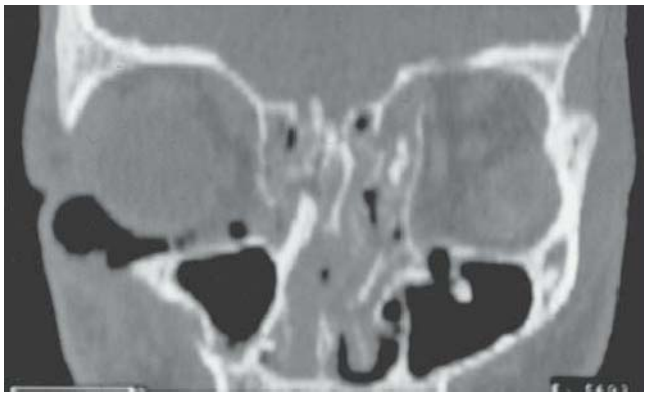


Figure 85.5 Coronal CT reconstruction of a complex nasoethmoidal fracture in a 12-year-old child. Disruptions of the nasomaxillary buttress are evident on the right, the medially orbital walls bilaterally, and the orbital floor on the left.

considerable variability in intercanthal distance between individuals, the average distance at age 3 is 25, 28 mm at age 12, and reaching 30 mm in adulthood (48). Five millimeter of widening is suggestive of a displaced fracture while 10 mm is diagnostic.

Status of the fragments can aid in treatment planning. Fractures can be categorized into three types based upon fragment status (49). In type I fractures the medial canthal tendon remains attached to a central fragment of bone, type II fractures display comminution of the central fragment without extending deep to the anterior lacrimal crest, and type III fractures are severely comminuted.

ORIF is the most reliable method of treatment with correction of the intercanthal distance paramount. Overcorrection may result in superior results versus undercorrection. Existing lacerations or bicoronal incisions can be used for intervention. Plating, wiring, and calvarial bone grafts for dorsal reconstruction may be necessary. Wiring can be accomplished by drilling bilateral holes in the anterior lacrimal crest just above and posterior to the anterior insertion of the tendon and in the posterior lacrimal crest just behind the insertion of the posterior limb of the tendon. Twenty-eight-gauge Kirschner-wire can be threaded through the holes and tightened to desired correction. Additional plate stabilization may be required and small screws can be used to anchor the wires if desired. Complications can include poor aesthetic outcome or rarely lacrimal system injury.

FRACTURES OF THE ORBITAL ROOF, SUPRAORBITAL RIM, AND FRONTAL BONE

Fracture of the orbital roof, rim, and frontal bone are more common in young children due to the large cranium to face ratio and nonpneumatized frontal sinuses. Typical history is of a blow to the brow with a late-developing hematoma. Other findings such as proptosis or dystopia can occur later and as with other orbital injuries, ophthalmologic consultation is required. While the orbit and the globe rarely suffer significant long-term damage, concurrent intracranial injuries occur in upwards of 86% of orbital roof fractures (3,50). This is especially true in older children where more significant force is required to fracture the orbital roof. Treatment of such injuries should be handled in a multidisciplinary fashion with neurologic injuries at the forefront.

A classification scheme based upon orientation of the fractured segments has been proposed (50). Type I fractures have comminution of the orbital roof without displacement, type II have displacement of the fragments toward the anterior cranial fossa whereas type III fractures have displacement inferiorly into the orbit. Most fractures of the orbital rim do not require operative intervention. Type III fractures have been associated with permanent exophthalmos, vertical dystopia and encephalocele and therefore repair via combined intracranial and extracranial approach with calvarial bone graft can be considered. A period of observation for 7 to 10 days for any resolution of dystopia or exophthalmos may be prudent in less severe injuries. However, long-term follow-up with imaging is recommended due to the appearance of late encephalocele. Hallmarks of orbital encephalocele are vertical dystopia, axial proptosis, and globe pulsation.

FRACTURES OF THE FRONTAL SINUS

Development of the frontal sinus occurs late in childhood; therefore, fractures are not common until adolescence. Isolated anterior table fractures can occur from sporting injuries, but overall, frontal sinus fractures results from high-impact trauma and in 70% of cases the posterior table is involved (51). Deformity of the anterior table must be addressed through reduction, which can be accomplished through bicoronal incisions. Careful assessment of the frontal recess should be accomplished both endoscopically and directly if possible. Posterior table reconstruction should be commenced based upon the same criteria as adults and often with neurosurgical consultation. Long-term follow-up with periodic imaging is crucial. Complications can occur both acutely and late, consisting of CSF leak, intracranial abscess, and mucopyelocele formation.

CONCLUSION

Pediatric patients suffer a somewhat different injury profile than adults with facial trauma. Basic tenets of traumatic stabilization should be observed followed by more directed evaluation and treatment. Under the age of 5 pediatric patients suffer fewer fractures and a higher proportion of greenstick fractures due in part to the elastic nature of the facial skeleton and the somewhat protected environment. As children age, fracture patterns begin to resemble those of adults with a higher proportion of mandible and midface

fractures. However, partly due to the rapid healing ability and constant growth, many fractures can be managed conservatively. When necessary, rigid fixation should consider potential facial growth abnormalities, but basic principles of proper, stable reduction should not be sacrificed. Continued evolution of absorbable plating systems may help reduce potentially deleterious effects of permanent rigid fixation. Overall, the evaluation and treatment of pediatric facial trauma should include consideration for the differential injury mechanisms and patterns as well as the potential growth implications of the developing facial skeleton.

HIGHLIGHTS

- Trauma is the leading cause of death and a major source of morbidity in children.
- Nasal fractures are the most common facial bone fractured in children. Mandible fractures are the most common facial fracture among children hospitalized for trauma.
- Facial growth and development is closely related to fracture patterns and the potential for future growth alteration.
- Midface and condylar fractures are associated with the greatest risk for growth disturbances.
- Conservative approaches to reduction are more desirable with ORIF reserved for fractures that cannot be stabilized by less invasive methods.
- If internal fixation is necessary under age 13, an understanding of tooth bud position and the role for monocortical screw placement is essential.
- In nasal injuries, septal hematoma should be ruled out and edema may require observation to assess for displaced bones.
- Nasoorbitoethmoid fractures should be suspected with high force traumas, dorsal nasal flattening, or CSF rhinorrhea.
- Associated neurocranial injuries are more common in the pediatric trauma patient and should be considered during the workup.
- If MMF is necessary, it should be limited to 2 to 3 weeks, followed by 6 to 8 weeks of elastic bands.
- Orbital fractures should consider muscular entrapment where early surgery is indicated. Observation may be appropriate in other isolated injuries.

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VI

Pediatric Otolaryngology

Margaretha L. Casselbrant *Charles M. Myer III*

Pediatric Otolaryngology

86

Stephen C. Maturo *Michael Cunningham*

The management of the otolaryngologic disorders of childhood traditionally has been and remains an integral part of the practice of general otolaryngology. Pediatric otolaryngology has evolved as a surgical subspecialty oriented toward the comprehensive otolaryngologic care specifically of children (1,2). The evolution of this subspecialty can be traced to developments within the fields of pediatrics and anesthesia and within otolaryngology itself (3). The establishment of freestanding children's hospitals or sections of general hospitals devoted solely to pediatric care reflected a growing appreciation on the part of the medical community that the problems of children differed from those of adults and required a different focus of diagnostic intervention and management (4). The patient population of these children's hospitals and pediatric wards changed over the years as the development of vaccines and newer generations of antibiotics led to improved control of acute infectious diseases. The focus of pediatric medicine gradually shifted to children with chronic illnesses, progressive noninfectious disorders, malignancies, and disabling or disfiguring handicaps. Patients with these much more complex conditions required the coordinated services of many subspecialty fields, including otolaryngology (5).

Concurrent technologic advances and a better understanding of the pathophysiologic characteristics of cardiorespiratory failure ushered in the modern era of anesthesia and intensive care unit medicine. The establishment of pediatric and neonatal intensive care units, the latter associated with advanced obstetric care hospitals, allowed the treatment and survival of younger and sicker infants and children. These children presented with a new array of medical and surgical problems of interest to the otolaryngologist, particularly regarding airway management.

Scientific advances within the field of otolaryngology–head and neck surgery further contributed to pediatric otolaryngology specialization. The development of fiber optic, illuminated, rigid endoscopes of appropriate size for use in infants and young children allowed safe operative assessment of congenital and acquired airway lesions. Small-diameter flexible endoscopes facilitated the dynamic examination of the upper airway in awake infants and children, and ultrathin versions of these scopes allowed lower airway evaluations even in intubated infants. Newer laryngoscopes and bronchoscopes were developed to allow unrestricted visualization of the pediatric airway for instrumentation and laser applications and to facilitate the delivery of inhalational anesthetic agents through standard endotracheal, Venturi jet, or spontaneous respiration techniques (6). More recently, airway-specific balloon technology and smaller microlaryngeal instruments have made minimally invasive endoscopic airway procedures a viable option.

Radiologic advances in computed tomography (CT), magnetic resonance imaging (MRI), and digital subtraction angiography added to the diagnostic acumen available for evaluating both congenital malformations and mass lesions. The management of extensive benign as well as malignant head and neck neoplasms in this age group has been greatly influenced by the application to children of angiographic embolization and microvascular surgical techniques, more precise radiotherapy protocols including proton beam and gamma knife technologies, and newer chemotherapeutic agents designed to decrease long-term maturation side effects.

Polysomnography studies enhanced the physiologic assessment of children with obstructive lymphoid hypertrophy. Immunologic antibody–antigen detection techniques facilitated the serologic diagnosis of various infections and the confirmation of inhalant atopy in young children. Novel laboratory studies have also helped aid in the diagnosis of immunodeficiency disorders commonly manifested in the upper aerodigestive tract. Electrodiagnostic techniques such as electroneurography, electromyography, brainstem auditory-evoked response testing, and otoacoustic emissions allowed more in-depth assessment of pediatric sensory

impairments. Lasers, cochlear implants, intraoperative radiologic guidance systems, and distraction osteogenesis techniques, to name a few, have all opened new avenues of therapeutic otolaryngologic intervention in children.

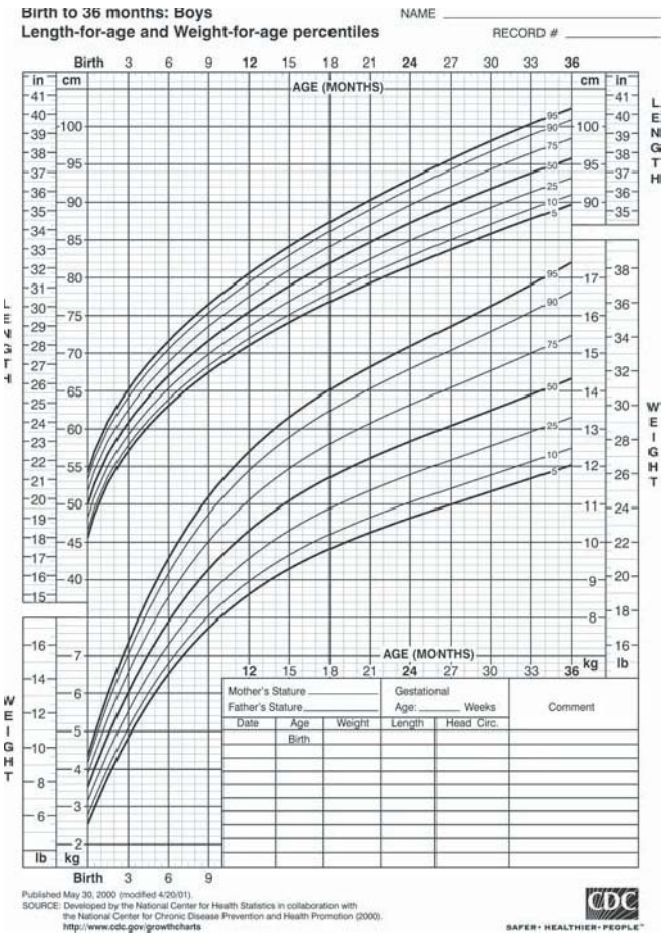
The application of these technical innovations to the care of children with acute and chronic otolaryngologic problems stimulated further clinical investigation and bench research activities, leading to the increasing fund of knowledge and expertise that now defines the subspecialty. Pediatric otolaryngology shares with geriatric otolaryngology a focus on a specific age group rather than on an organ system or category of disease (7). This chapter highlights otolaryngologic disorders specific to the pediatric population and relevant issues pertinent to caring for such children.

PATTERNS OF GROWTH AND DEVELOPMENT

Pediatric otolaryngology is the study of the disorders and diseases of the ears, nose, and throat as they relate to the growth and development of the head and neck structures (8). The clinical presentation and sequelae of any disease process are greatly influenced by the age and maturation of the afflicted person. Children differ anatomically and physiologically from adults, and they also change in these respects along a continuum from the neonatal/infancy period through the toddler, preschool, later childhood, and eventually adolescent years. Pediatric otolaryngology requires a working knowledge of the standard patterns of growth and development through this continuum so that deviations from normal can be recognized and age-appropriate diagnostic techniques and methods of management can be applied.

Measurement of the vital characteristics of somatic growth can provide information about a child's general state of health or illness regardless of the specific organ system of interest. Height and weight measurements of all children, supplemented by head circumference measurements during the first year of life, provide an early warning system for pathologic processes. Charts documenting serial measurements over months to years construct an accurate record of the child's general pattern of growth (Figs. 86.1 and 86.2), with deviations from normal being indicative of an intrinsic or extrinsic insult.

Different organ systems mature at different rates and at different times throughout infancy, childhood, and adolescence (Fig. 86.3). The rapid rate of neural tissue growth during fetal life explains the relatively large size of the neurocranium in relation to the face in the newborn. The face of



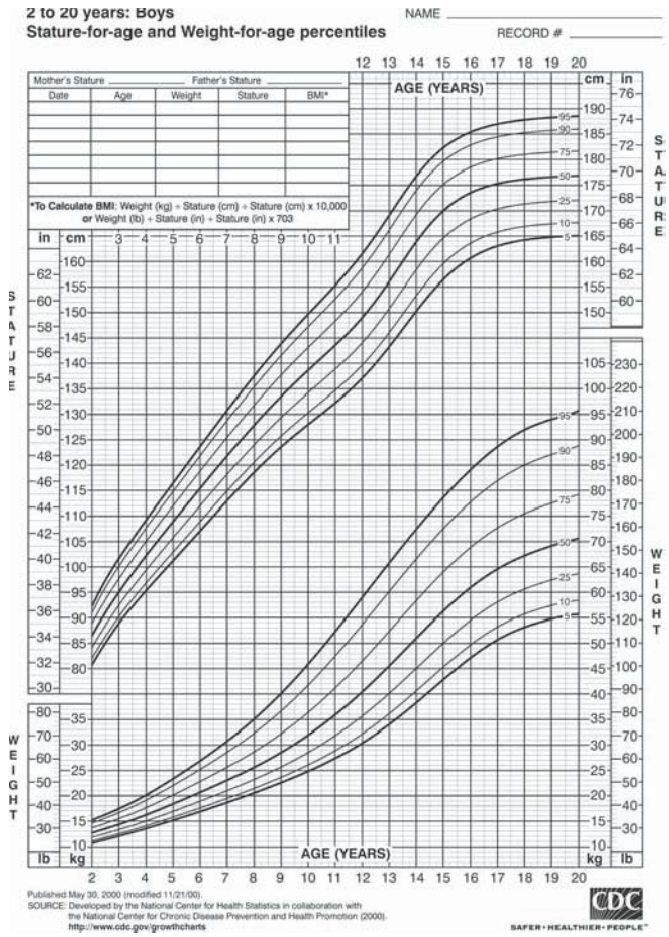


Figure 86.1 Physical growth in boys (Centers for Disease Control and Prevention).

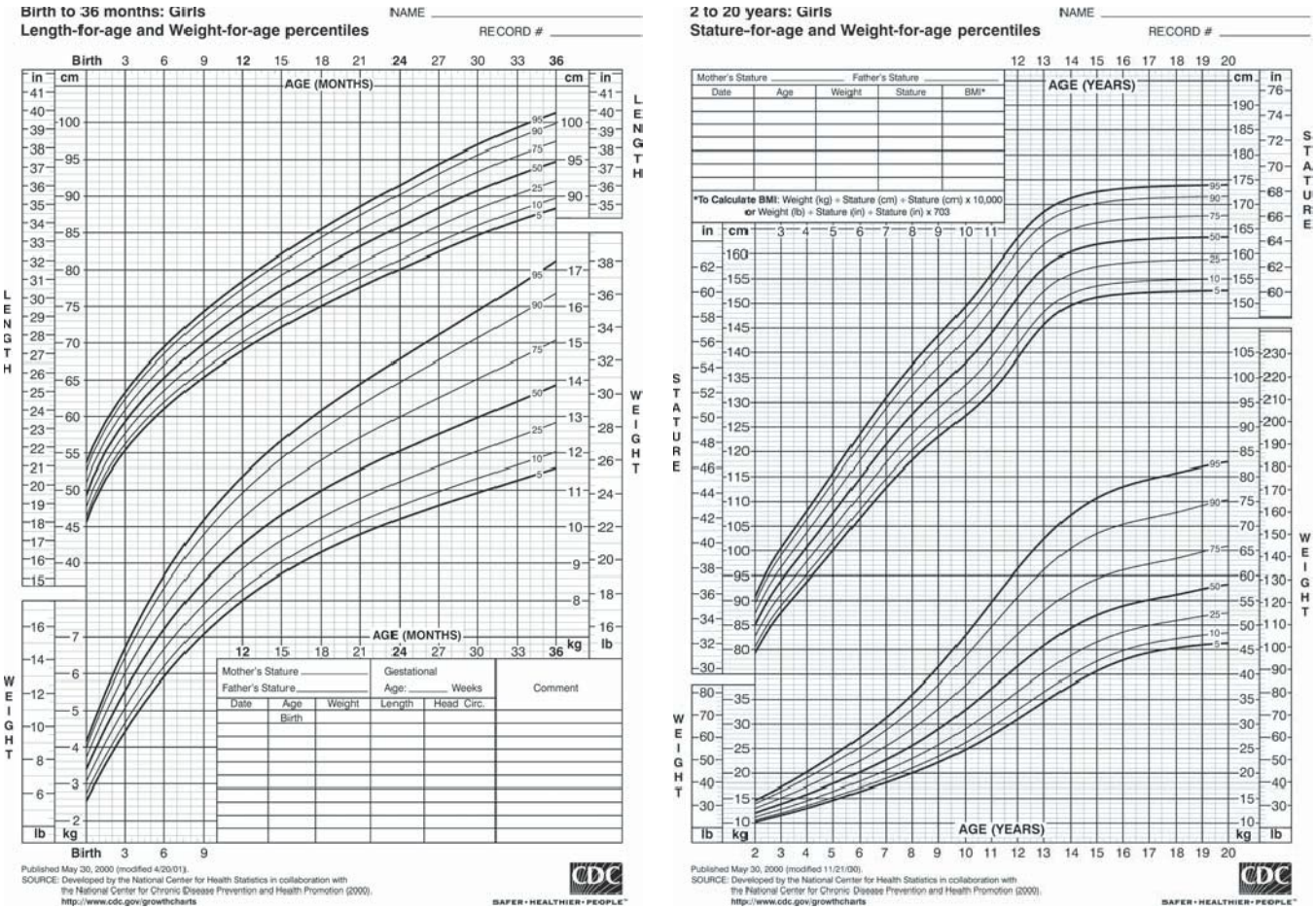


Figure 86.2 Physical growth in girls (Centers for Disease Control and Prevention).

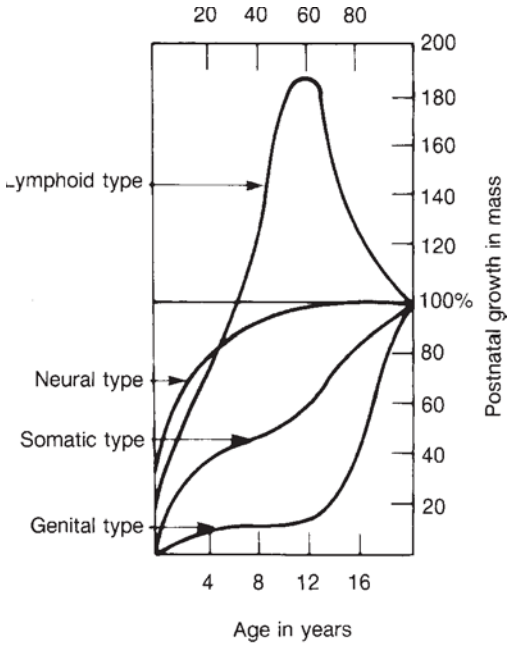


Figure 86.3 Postnatal growth of different anatomic systems with age.

the infant or young child is not a small image of the eventual adult (Fig. 86.4). The infant's forehead is prominent and the face comparatively round and diminutive. Elongation of the face occurs secondary to mandibular and maxillary growth in association with the eruption first of the primary and later of the permanent teeth. As this vertical growth continues throughout childhood, the relative proportion of facial to cranial mass gradually changes, and the narrower adolescent/adult facies eventually is achieved (Fig. 86.5). Associated with this progressive increase in facial height is a gradual change in the child's profile. The child's cheeks and chin are flat, the nose is diminutive, and the eyes appear comparatively large. With mandibular and maxillary growth, the chin and cheek bones become more prominent, and the growth of the nose and supraorbital rims decreases the relative orbital size.

The nares are small at birth and retain their roughly circular shape until puberty. The oval or oblong nares associated with the adult facies develop in association with the marked increased vertical growth of the nose during adolescence. Major forces in the vertical height and projection of the nose are the osseous and cartilaginous growth centers of the nasal septum and nasomaxillary pyramid.

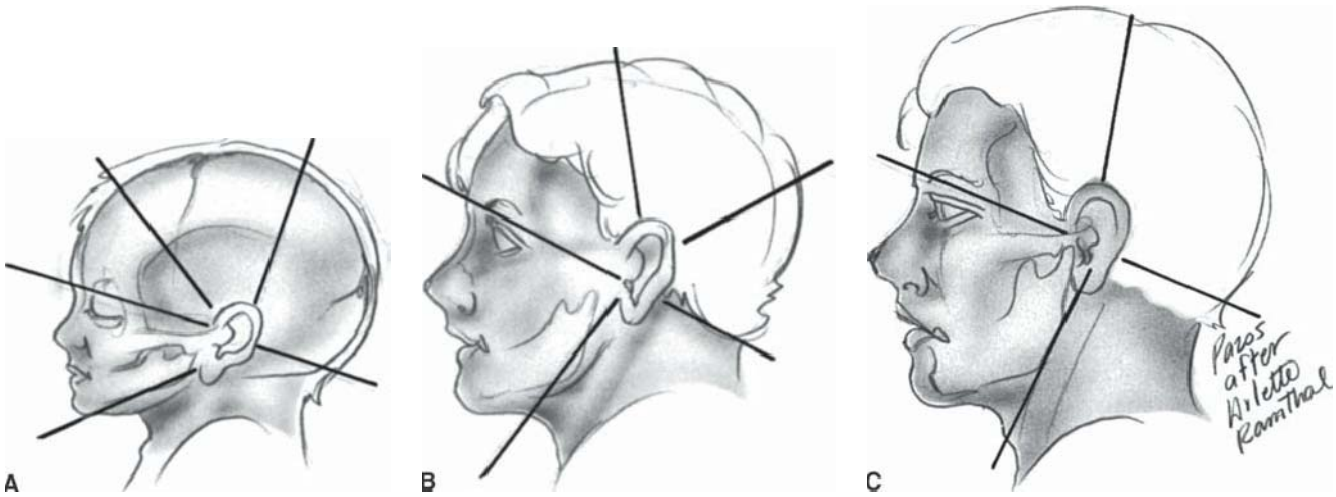


Figure 86.4 Changing facial configuration with age. **A:** At birth. **B:** Through 5 years. **C:** At 15 years. (From Stool SE, Marasovich W. Postnatal craniofacial growth and development. In: Bluestone CD, Stool SE, eds. *Pediatric otolaryngology,* 2nd ed. Philadelphia, PA: WB Saunders, 1990:18, with permission.)

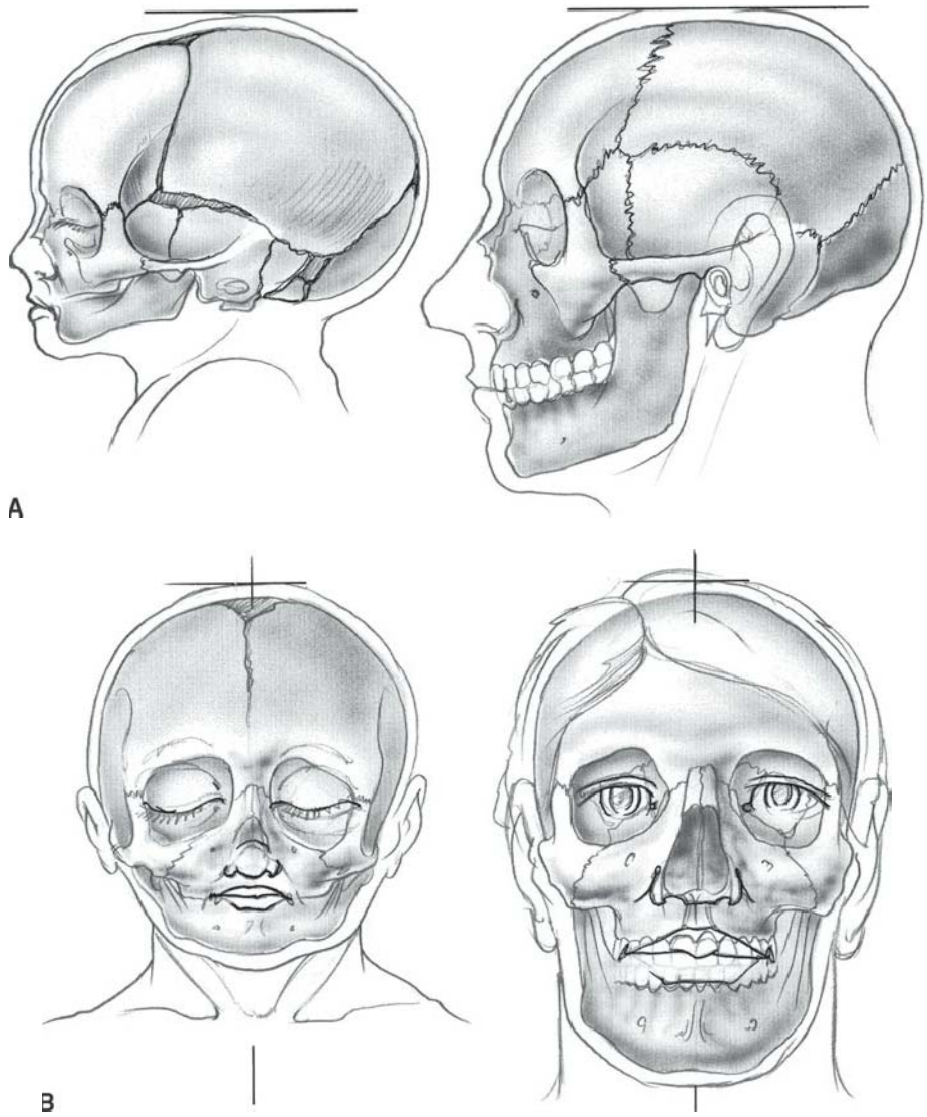


Figure 86.5 Infant and adult skulls for craniofacial skeletal comparison. **A:** Lateral views. **B:** Anteroposterior views.

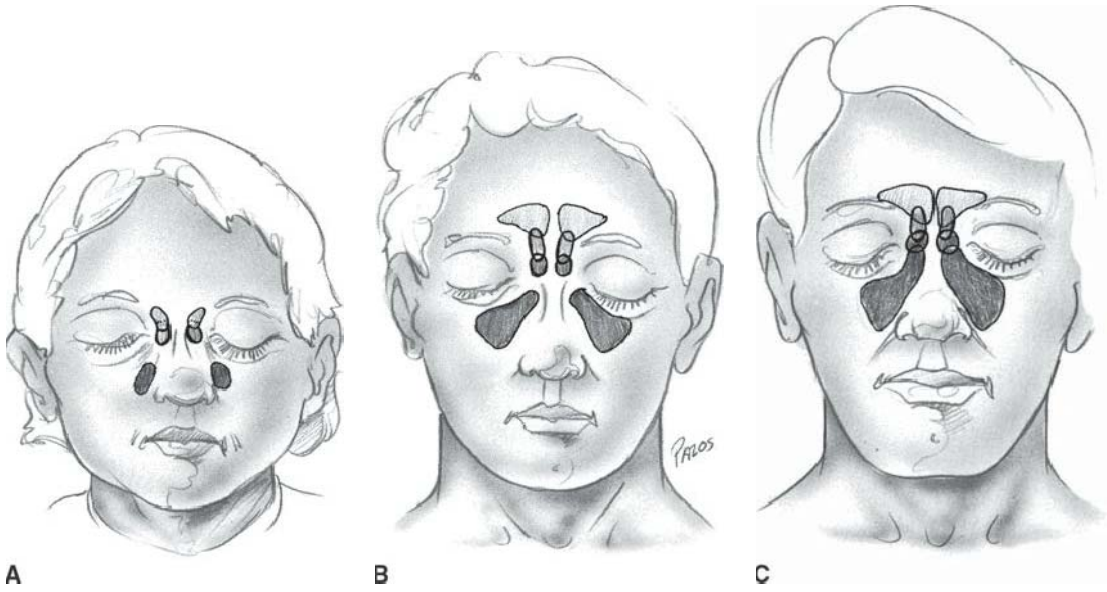


Figure 86.6 Paranasal sinus development. **A:** At birth. **B:** At 10 years. **C:** At 15 years.

Elective surgery on the nose usually is deferred until the adolescent years when full facial growth has been achieved. Exceptions to this rule include severe traumatic injuries or nasal deformities associated with congenital anomalies such as cleft lip and palate. Growth may further exaggerate the facial deformity in such cases.

Despite small anatomic nasal dimensions and increased airway resistance, infants are predominantly nasal breathers (the anatomic and physiologic explanations for this preferential nasal breathing pattern are discussed later in this section). Although the degree and duration of this reliance on the nasal airway for respiration vary with each child, complete nasal airway obstruction at birth is usually an airway emergency. Even unilateral obstruction can cause the newborn significant respiratory distress and secondary feeding difficulties. In older children, chronic nasal and nasopharyngeal obstruction, most frequently caused by lymphoid hypertrophy, may be associated with constant mouth breathing, abnormal tongue positioning, dental malocclusion, and suspected craniofacial growth changes. This so-called adenoid facies syndrome remains controversial from a cause and effect standpoint; its description, however, serves to highlight the potential sequelae of a single disease entity on an actively growing child.

The development of the paranasal sinuses is connected intimately with nasomaxillary and facial growth (Fig. 86.6). The maxillary and sphenoethmoid sinuses are present at birth, although their small size typically precludes their radiologic appearance (Table 86.1). Conspicuous growth in the maxillary sinuses begins by approximately age 3 years, but inferiorly directed expansion does not occur until eruption of the permanent dentition, when the child is 7 to 8 years of age. The floor of the maxillary sinus approximates the inferior meatus at age 8 years and reaches the level of the floor of the nose by 12 years of age. Adult size is reached by midadolescence. The ethmoid sinuses arise as evaginations of the nasal mucosa from the middle, superior, and supreme nasal meatuses. Although present at birth, significant pneumatization does not occur until the child is between 3 and 7 years of age. Final adult form typically is achieved by age 12 to 14 years. The sphenoid sinuses originate within the nasal cupola; they do not begin to pneumatize the sphenoid

TABLE 86.1 PARANASAL SINUS DEVELOPMENT

			Size (mL)			
	First Appearance	Birth	3 y	10 y	14 y	Age of Importance
Maxillary	3 wk fetal life	0.13	2.5	10.4	11.6	Birth
Ethmoid	6 mo fetal life	0.06	0.16	2.4	4.8	Birth
Sphenoid	3 mo fetal life	0.02	0.68	1.8	2.1	5 y
Frontal	1 y life		0.08	1.0	3.6	10–12 y

Modified from Schaeffer JP. *The embryology, development and anatomy of the nose, paranasal sinus, nasolacrimal passageways and olfactory organ in man.* Philadelphia, PA: Blakiston, 1920, with permission.

bone and become clinically significant until 4 to 5 years of age. Sphenoid development, although complete by midadolescence, is highly variable in terms of the final extent of sphenoid bone pneumatization. The frontal sinuses originate as outgrowths of the middle meatuses in the frontal recess regions. The frontal sinuses are typically not present at birth; growth begins during the third year of life and continues well into adolescence. Pneumatization is highly variable and is of limited clinical significance until the early adolescent years. The thin posterior table and floor of the frontal sinuses have important anatomic relationships to the anterior cranial fossa and orbital structures, respectively.

Discussion of paranasal sinus development is incomplete without mention of the ostiomeatal complex region, which represents the joint location of the maxillary sinus ostium, anterior ethmoid sinus ostia, and frontal recess in the region of the middle meatus. The channels into which these ostia open are bound by the ethmoidal bulla, the uncinate process, and the middle turbinate. Anatomic enlargement or mucosal hypertrophy of these three structures can significantly narrow these channels and obstruct maxillary–ethmoid–frontal sinus drainage. The relatively small size of the child's nose has traditionally made intranasal sinus surgery comparatively risky because of limited surgical exposure. Although still challenging, this situation has improved with the development of instruments and telescopes of appropriate size for the application of functional endoscopic sinus surgery directed at the ostiomeatal region in the pediatric population.

At birth, the pinna has an adult configuration and location, although the ears appear to rise in position as a result of the vertical growth of the lower third of the face. The pinna reaches near adult size at 4 to 5 years of age and obtains full adult size by age 9 years. The soft and pliable nature of the young child's ear cartilage also matures during this same period, which influences the timing of auricular reconstruction, specifically those procedures requiring cartilage manipulation.

The tympanic membrane is adult sized at birth, but due in part to incomplete ossification of the external auditory canal, lies in a nearly horizontal position, impairing its visualization on neonatal ear examination. The final vertical orientation of the eardrum is achieved with completion of canal ossification by approximately 2 years of age. Middle ear ossicular formation is complete at birth. Middle ear pneumatization is likewise near complete. The mastoid antrum, in contrast, enlarges significantly over the first years of life with generalized mastoid pneumatization and development continuing well into early childhood. Most postnatal mastoid growth occurs in a lateral and posterior direction, with a fully developed mastoid and styloid process not appearing until the child is about age 3 (Fig. 86.7).

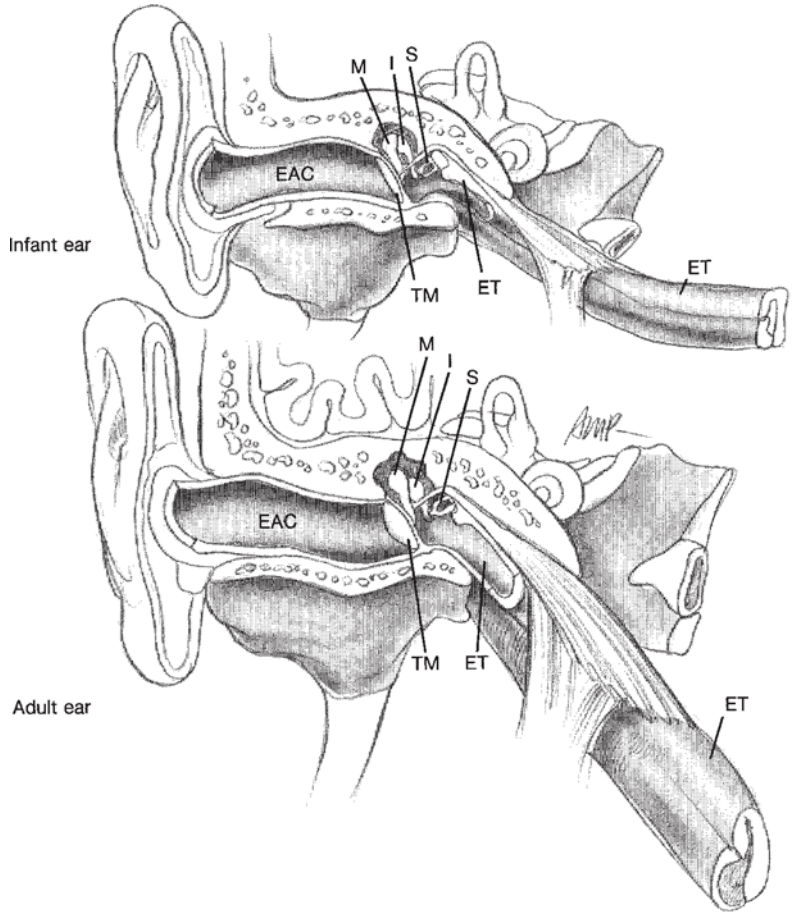


Figure 86.7 Comparison of infant and adult middle ear and eustachian tube development. M, malleus; I, incus; S, stapes; ET, eustachian tube; TM, tympanic membrane; EAC, external auditory canal.

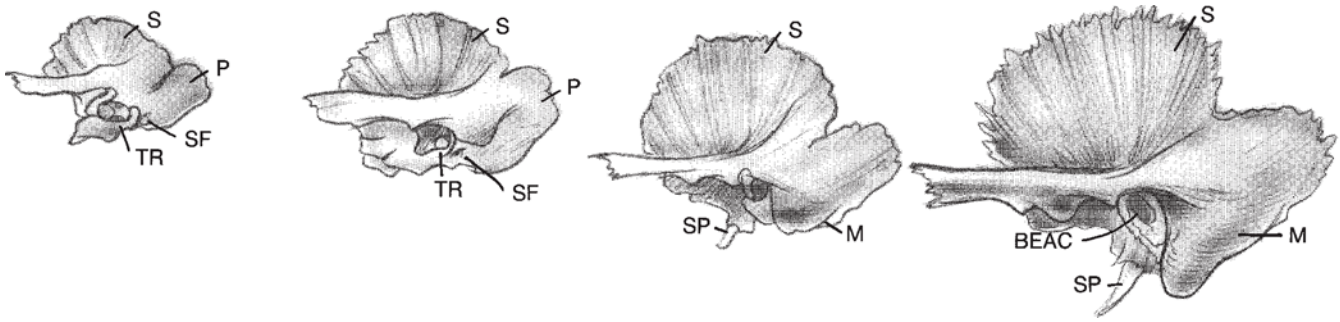


Figure 86.8 Postnatal temporal bone development. Note mastoid bony external ear canal and styloid process growth. BEAC, bony external auditory canal; M, mastoid; P, petrosa; S, squamosa; SF, stylomastoid foramen; SP, styloid process; TR, tympanic ring. (Adapted from Kenna M, Hirose K. Embryology and developmental anatomy of the ear. In: Bluestone CD, et al., eds. *Pediatric otolaryngology*, 4th ed. Philadelphia, PA: WB Saunders, 2003:136.)

The extratemporal portion of the facial nerve is relatively unprotected during this period of development, predisposing it to obstetric injury and potential iatrogenic injury during tympanomastoid and parotid surgery. The thin mastoid cortex at this young age also accounts for the potential subperiosteal postauricular spread of mastoid infection.

Eustachian tube development plays a prominent role in the predisposition of infants and young children to middle ear infection (Fig. 86.8). At birth, the eustachian tube is about 50% of its adult length and lies in a fairly horizontal position, entering the nasopharynx at the level of the hard palate. With growth, the eustachian tube lengthens, widens, and angles inferiorly, achieving its final nasopharyngeal position by the time the child is 5 to 7 years old. The petrous portion of the temporal bone, including the bony and membranous labyrinths, is formed completely at birth. The neonate should be fully functional from both a hearing and a vestibular standpoint.

The neonate's oral cavity is small and the comparatively large tongue fills it entirely, contributing significantly to the infant's status as a preferential nasal breather. The fully formed palatal structures provide the infant with velopharyngeal competence and the more superior cervical position of the larynx allows potential overlap of the epiglottis and the velum, establishing a nasopharyngeal airway during suckle feeding. The flow of milk or formula is channeled around the dorsum of the tongue and laterally around the epiglottis, protecting the airway. With mandibular growth, the oral cavity enlarges and the base of the tongue descends to its final hypopharyngeal position. The infant's suckle gradually changes to a more mature swallow pattern, which is functionally quite complex, consisting of an extremely well-synchronized series of oral, pharyngeal, and esophageal neuromuscular movements.

The larynx serves the infant immediately as a conduit for breathing. No other head and neck structure is initially so essential to life. The larynx additionally protects the lower airway by means of two mechanisms: glottic and supraglottic closure during swallowing and the cough reflex. The phonatory function of the larynx provides the infant with a means of expressing basic needs; this communicative function obviously increases in complexity and importance later in childhood.

The pediatric larynx has considerable anatomic differences from that of the adult. These differences involve the specific breathing and airway protection demands of suckle feeding in the newborn infant. The newborn neck is relatively short, and the infant larynx is positioned high, approximating the third or fourth cervical vertebra at rest and rising to the height of the first or second cervical vertebra with swallowing (Fig. 86.9). As discussed previously, this high position allows overlap of the epiglottis with the soft palate. With growth of the neck, the larynx gradually descends to its adult position opposite the fifth cervical vertebra. The still relatively high childhood position of the larynx is highlighted by the ease with which the epiglottis can be visualized on oropharyngeal examination in many children.

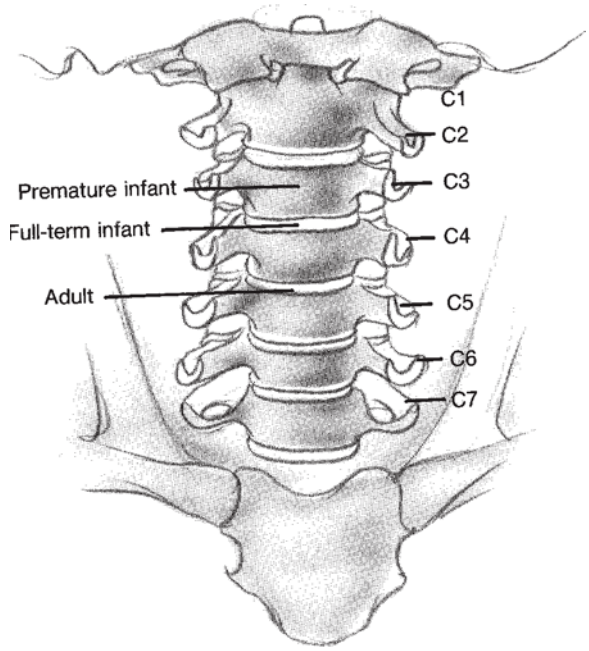


Figure 86.9 Comparative neck positions of the infant and adult larynx (glottic level).

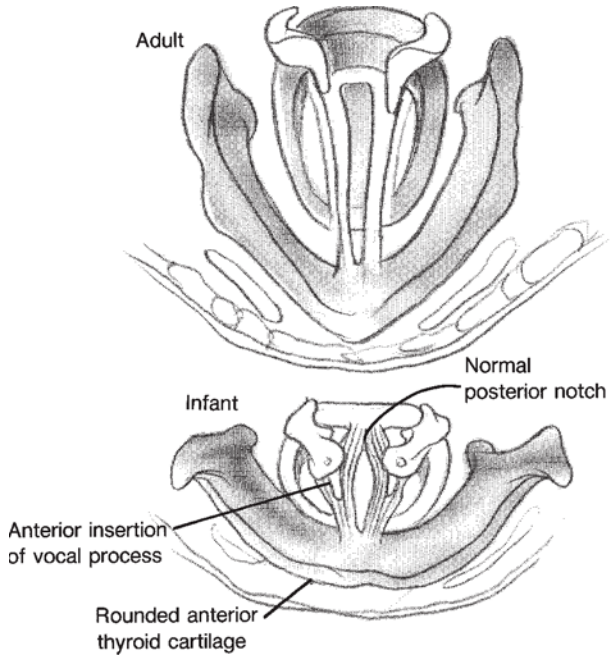


Figure 86.10 Endoscopic view of infant and adult demonstrating the comparatively large arytenoids and rounded thyroid cartilage configuration in the infant compared with those of the adult larynx.

The predisposition of the infant airway to obstruction is related to its absolute small size, the pliability of its constituent connective tissues, and some intrinsic anatomic features. The infantile epiglottis is furled or omega-shaped and the arytenoids are relatively large, covering a significant percentage of the posterior glottis (Fig. 86.10). This anatomic configuration contributes to the entity of laryngomalacia. In the infant, the cricoid cartilage is smaller in diameter than the length of the true vocal cords, making the subglottic region the narrowest portion of the pediatric airway. The resultant funnel-shaped internal dimension (Fig. 86.11) has important consequences for the young child in terms of both the sequelae of inflammatory airway edema and the effects of endotracheal intubation.

The infant larynx grows rapidly in terms of both width and length in the first 3 years of life, which may obviate the need for airway intervention in certain congenital anomalies. Laryngeal growth then slows until adolescence, when there is a rapid increase in all airway dimensions. The adolescent growth spurt of the cricoid and thyroid cartilages also changes the angulation of the true vocal cords as they insert into the anterior commissure region. This contributes, in part, to the voice changes associated with puberty.

Of additional anatomic importance is the comparative underdevelopment of the thyroid cartilage in the infant. The thyroid cartilage is relatively flat without a vertical midline prominence (Fig. 86.12) and tends to be overlapped by the hyoid bone because of the high laryngeal position. The cricoid cartilage is also small, and the cricothyroid membrane is more of a slit than a true palpable space. The standard landmarks for tracheotomy and cricothyroidotomy are not very demonstrable, making the emergent performance of either of these procedures difficult in the newborn infant. Endotracheal intubation is a far preferable choice of airway maintenance in acute emergencies in young children.

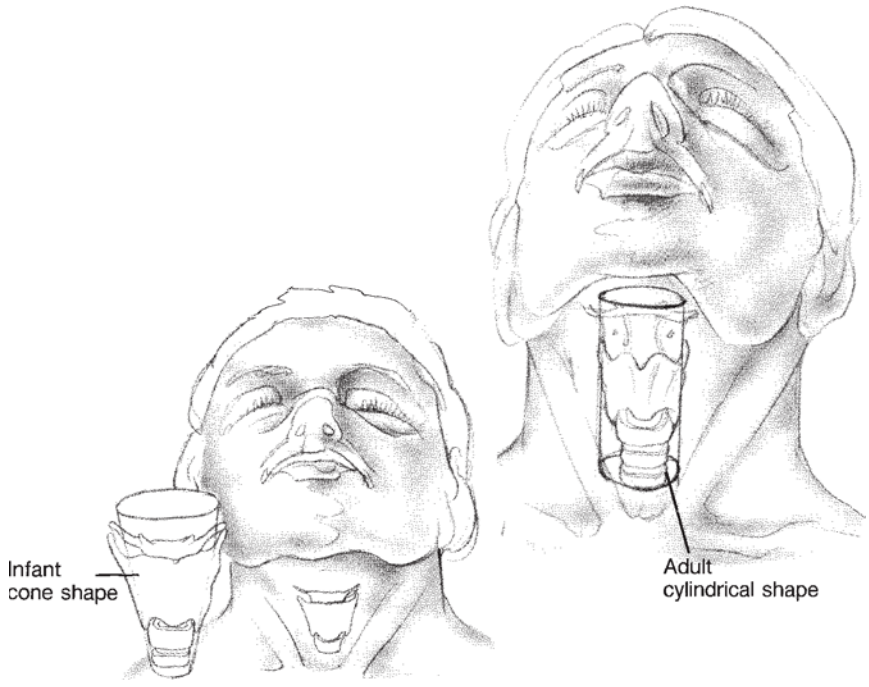


Figure 86.11 Narrowing cone-shaped internal dimension of the infant larynx is due to the smaller diameter of the cricoid cartilage compared with that of the glottis. These glottic–subglottic dimensions approximate one another in the adult larynx.

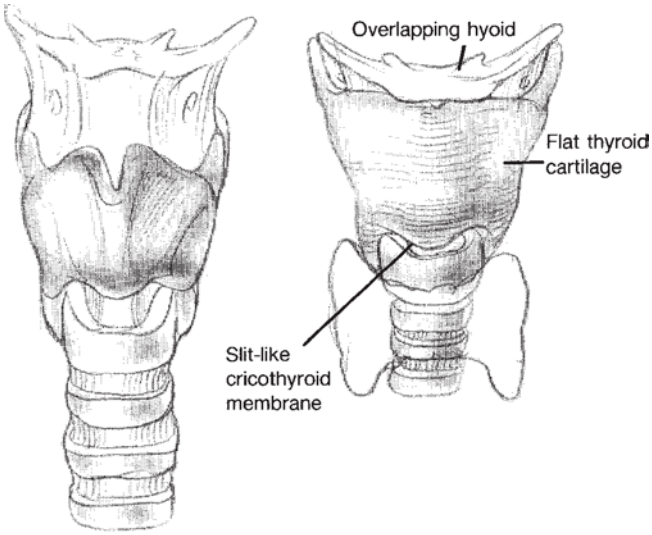


Figure 86.12 Anterior view demonstration of the flat infantile thyroid cartilage and overlap by the hyoid cartilage above and over the cricoid cartilage below. These cartilage elements separate with increasing age.

The neck of the infant and young child also differs from that of the adult in the prominence of the cervical lymphoid tissue. The cervical lymph nodes increase in size proportionally to the growth curve for the body's lymphoid tissue in general (Fig. 86.3). The variability of cervical lymphadenopathy palpable on routine pediatric neck examination can make the decision regarding when to perform a nodal biopsy a diagnostic challenge. Children at risk for significant pathology include those with supraclavicular adenopathy, worrisome clinical symptoms such as persistent fever or weight loss, and local fixation of the node(s) to the overlying skin or underlying deep tissues. The retropharyngeal and parapharyngeal lymph nodes are of additional importance in young children. Suppurative lymphadenitis in these regions can rapidly progress to abscess formation with aerodigestive tract compromise and sepsis risk.

CONGENITAL MALFORMATIONS

Diagnosis and management of congenital malformations of the head and neck structures are an integral part of the practice of pediatric otolaryngology. Children with these conditions require a thorough otolaryngologic and general pediatric assessment to ensure that their head and neck anomaly is not a manifestation of an underlying craniofacial or systemic syndrome. The discovery of additional syndromic manifestations can be of prognostic importance, altering surgical or long-term care plans, and also be of potential use from a genetics and family planning standpoint. A comprehensive list of all congenital malformations of the head and neck is beyond the scope of this chapter. A brief review of several of the more common lesions highlights the diversity of a pediatric otolaryngology practice.

Auricular Malformations

The complex origin of the middle and external ear from the first two branchial arches lends itself to varying degrees of sporadic malformation. Minor malformations include preauricular pits and tags. Although typically an isolated finding in normal-hearing children, preauricular tags may be associated with ossicular malformations and secondary conductive hearing loss. Preauricular pits can occur in the presence of renal disease and mixed conductive/sensorineural hearing loss in children with branchial-oto-renal syndrome. Not all children with preauricular pits or tags require formal audiologic or renal ultrasound examinations; such evaluations, however, should definitely be performed in those with additional congenital anomalies and in those with a family history of hearing loss or renal disease (9,10).

Major auricular malformations are microtia and atresia. These may be isolated entities, or they may occur in the setting of a generalized craniofacial disorder, such as Goldenhar syndrome. Intervention in these children is typically dictated by the unilaterality or bilaterality of the condition, the child's hearing status, and the feasibility or desirability of cosmetic or hearing restoration. Such children may develop acute otitis media (AOM) in the rudimentary ear space of the microtic ear, and they have an increased risk of developing cholesteatoma in the atretic ear canal. The normal ear in unilateral cases must be monitored closely for otitis media with effusion (OME) and secondary hearing compromise. Comprehensive care of children with these conditions includes parental counseling, detailed audiologic assessment with amplification if needed, and surgical intervention including auricular reconstruction, atresia repair, or bone-anchored hearing aides.

Nares Malformations

Choanal atresia is representative of a major malformation in nares development that, when bilateral, usually causes immediate respiratory compromise in the newborn. Modified oral airways or endotracheal intubation provide acute airway relief until definitive surgical management is possible. High-resolution CT scanning is a requisite part of the preoperative evaluation of these patients. Their operative management has been enhanced greatly by the application of endoscopic surgical techniques. Osseous as well as membranous atresias may be approached in transnasal or combined transoral–transnasal fashion, rendering the classic transpalatal approach near obsolete. Choanal atresia needs to be additionally recognized as one potential manifestation of the CHARGE syndrome. Such children have a propensity for additional airway and systemic anomalies that may dictate neonatal tracheotomy to be the most appropriate initial treatment measure, delaying choanal atresia repair until the child is older. CHARGE syndrome also highlights the importance of a thorough

cardiology evaluation in most children with syndromic abnormalities prior to committing to a surgical procedure. The long-term effect of successful choanal atresia repair on midfacial growth and future velopharyngeal function is still unknown. Debate also continues on the necessity of nasal stents and the application of mitomycin-C for improved surgical outcomes (11).

Less severe malformations of nares development include pyriform aperture stenosis and choanal stenosis. These cause varying degrees of nasal obstruction. Most affected neonates can be treated conservatively with artificial airways or topical steroid drop preparations to decrease nasal mucosal hypertrophy. Such measures often must be continued through the infant's preferential nasal breathing period. Surgical intervention to enlarge the nasal passages is required in a small percentage of pyriform aperture stenosis patients typically via a sublabial approach. Children with pyriform aperture stenosis are also at risk for associated holoprosencephaly (central mega-incisor syndrome) and their overall evaluation should include central nervous system imaging (12).

Midline Malformations

Encephaloceles, gliomas, and dermoids are congenital midline nasal masses whose typical manifestations are signs and symptoms of nasal obstruction. Their greatest risk is that of potential central nervous system infection, either spontaneously or from inappropriate surgical intervention. The complementary use of both CT and MRI is recommended as the preoperative evaluation of such lesions. Surgical resection via a transnasal endoscopic approach, an external lateral rhinotomy or open rhinoplasty, or an anterior craniofacial resection using the combined skills of both the otolaryngologist and the neurosurgeon provides definitive treatment.

Malformations of the Oral Cavity

Oral cavity malformations frequently occur in association with mandibular or maxillary hypoplasia. Such malformations can be isolated entities, may be one component of a specific craniofacial disorder as in Treacher Collins syndrome, or may be one of multiple manifestations of a systemic process as in Stickler syndrome. One of the more common presentations is the association of retrognathia, glossoptosis, and soft palate cleft in Robin sequence. Many children with mandibular and maxillary malformations have airway and feeding problems. Interventions vary from positioning strategies and special feeding techniques to surgical procedures such as tongue–lip adhesion, tracheostomy and gastrostomy in severe cases. Such treatments historically would be continued until facial growth and neuromuscular maturation were adequate to prevent further airway obstruction. This expectant approach has been supplanted in recent years by the application of distraction osteogenesis and craniofacial reconstruction techniques early in life to many of these children (13). The long term beneficial and deleterious effects of these advanced techniques on occlusion, dental formation, and facial nerve integrity are just beginning to be elucidated (14).

The oral cavity is also one of the more frequent sites of presentation of congenital lymphatic and venous vascular malformations (15). Such vascular malformations of the tongue and floor of mouth often cause airway obstruction, swallowing dysfunction, and speech impediment. Spontaneous drainage (weeping), mucosal bleeding, secondary infection, and intralesional hemorrhage are also common. Facial deformity and malocclusion may result from soft tissue and bony dysmorphisms. Treatments vary, depending upon whether the goal is to stabilize superficial manifestations or to physically reduce tongue size for functional and cosmetic purposes (16–18).

Cleft lip and palate are the most common malformations of the head and neck region. In some medical centers, the pediatric otolaryngologist has the primary responsibility for the surgical repair of these anomalies; in other centers, the otolaryngologist functions in a consultant role as a member of a multidisciplinary team. Children with cleft palate have a higher incidence of middle ear disease and are at increased risk for speech and articulation issues, particularly due to velopharyngeal insufficiency.

Airway Abnormalities

Congenital anomalies of the airway pose a particular diagnostic and therapeutic challenge. The most common laryngeal anomaly is laryngomalacia, which in some respects is a variant of normal neonatal supraglottic development (8). Historically attributed to flaccid supraglottic cartilage formation or redundant supraglottic soft tissues, more recent research suggests that immature sensorimotor integration and tone may be the more significant underlying etiology (19). The characteristic clinical manifestation of laryngomalacia is inspiratory stridor, which usually resolves spontaneously by 18 months of age. Infrequently, laryngomalacia can cause dyspnea, feeding difficulties, and failure to thrive. In such instances a supraglottoplasty is performed, in which the obstructive aryepiglottic folds are divided and the redundant supraglottic soft tissues are removed. This procedure provides immediate relief of respiratory distress in the majority of such infants, with limited risks relative to aspiration and supraglottic scarring. In severe cases of laryngomalacia recalcitrant to supraglottoplasty, a tracheotomy may be required; such children often have additional airway or associated systemic anomalies.

Congenital subglottic stenosis also may represent a severe variant of normal tracheal airway development. The time-honored standard of care for infants with this malformation was tracheotomy pending further airway diameter growth. Anterior laryngotracheal decompression with cartilage augmentation, or cricotracheal resection in severe

cases, offers a more immediate and potentially efficacious form of therapy in these children.

Hemangiomas and vascular malformations can also compromise the airway of neonates and infants. The management of subglottic and laryngotracheal hemangioma has historically involved a combination of systemic or intralesional steroid therapy, bypass tracheostomy, laser excision, or open resection. More recently, the use of oral propranolol is changing this treatment paradigm (20,21). Intrinsic laryngotracheal vascular malformations are best managed via microscopic suspension laryngoscopy and tracheoscopy with laser debulking; aerodigestive tract compromise secondary to extrinsic vascular malformation compression is alternatively often approached transcervically (22,23).

Laryngeal cleft is an uncommon and potentially devastating congenital aerodigestive tract anomaly because of the risk of repeated aspiration. A high index of suspicion with careful endoscopic examination of the posterior commissure region is required for the diagnosis of laryngeal cleft. The surgical treatment of laryngeal cleft isolated to the supraglottis or glottis can be by either a microendoscopic or anterior laryngofissure approach; more extensive laryngotracheoesophageal clefts often require a lateral cervical and thoracotomy approach performed by a joint otolaryngology, pediatric surgery, or cardiothoracic surgical team.

Congenital tracheal anomalies include tracheal stenosis and tracheomalacia. Congenital tracheal stenosis can be focal or segmental and is usually due to complete tracheal rings. Focal segmental stenosis is amenable to resection and reanastomosis. Long segment tracheal stenosis is best treated with a slide tracheoplasty procedure. Tracheomalacia can be caused by inherent tracheal cartilage weakness or due to external compressive forces such as vascular compression or mediastinal masses. The tracheal segments affected can be focal or diffuse regardless of the underlying etiology. Intrinsic tracheomalacia causing failure to thrive, apparent life threatening events, or cyanotic spells presents a difficult challenge; therapeutic options include tracheotomy with continuous positive airway pressure support, tracheal stents, and tracheal resection or augmentation in severe cases. Tracheomalacia due to external compression is best treated by identifying and relieving the external force. Aberrant vascular structures that can cause tracheal compression include double aortic arch, right aortic arch with aberrant left subclavian artery, aberrant left or right subclavian artery, innominate artery compression, pulmonary artery sling, and absence of pulmonary valves (24,25). The workup of such children may include airway fluoroscopy, barium swallow, operative endoscopic evaluation, and a dynamic airway assessment in the form of pulmonary function testing with flow volume loops if age appropriate. The latter studies have expanded the clinical indications for surgical treatment of such children to include moderate to severe exercise intolerance. Magnetic resonance angiography has replaced arteriography as the radiologic study of choice in assessing both the anatomic degree of airway compression and the vascular structures involved. Postoperative pulmonary function studies remain indispensable for children in whom residual tracheobronchomalacia is clinically suspected.

Malformations of the Neck

Congenital malformations of the neck are a comparatively rare but interesting group of childhood neck masses that typically present in the first two decades of life. Such congenital lesions may present as an asymptomatic cervical mass or may become acutely apparent when secondary infection occurs. Most of these lesions arise from developmental arrest of the fetal branchial or thyroid descent systems. Branchial anomalies include an array of cysts, sinuses, and fistulae. Thyroid anomalies include both thyroglossal duct cyst and ectopic thyroid. Anatomic location on physical examination often suggests the underlying system of origin. Definitive treatment necessitates complete excision of the lesion, including any identifiable external tracts to the skin or internal tracts to the aerodigestive system.

Over 50% of lymphatic vascular malformations occur in the head and neck region (26). The cervical site of presentation is important. The majority of infrahyoid lymphatic vascular malformations are macrocystic and extrinsic to the laryngotracheal airway, whereas suprahyoid lymphatic vascular malformations are more likely to be microcystic and intrinsically involve the upper aerodigestive tract. Treatment approaches are based on the anatomic structures involved, the severity of the symptomatic presentation, and whether or not the lymphatic vascular malformation is macrocystic, microcystic, or a combination of both. A conservative approach is advised because one must keep in mind that vascular malformations are benign lesions. Complete removal may not be feasible; rather a fine balance between lesion excision and maintenance of form and function is often the ultimate goal (27).

SENSORY IMPAIRMENTS

Of the sensory impairments relevant to the pediatric otolaryngologist, hearing loss is of the greatest importance. Inadequate speech and language development is typically the clue to an underlying hearing impairment in an otherwise healthy child. The otolaryngologist and the primary care physician must be well versed in the expected developmental milestones of receptive and expressive language to recognize such delays (Table 86.2). In the face of a normal otologic and audiologic assessment, alternative etiologies for inadequate language development such as mental deficiency, dyslexia, dysarthria, or one of the disorders of the autistic spectrum need to be sought.

Most hearing loss in children is mild, transient, and conductive in nature, occurring secondary to AOM or OME. More severe permanent conductive hearing losses are

TABLE 86.2 LANGUAGE MILESTONES FOR INFANTS AND CHILDREN FROM BIRTH THROUGH 2 YEARS OF AGE

Age (mo) at Which Behavior Should Be Established	Receptive Language Behavior	Expressive Language Behavior
1	Random activity arrested by sound	Random vocalization; primarily vowel sounds
2	Appears to listen to speaker; may smile at speaker	Vocal signs of pleasure; social smile
3	Looks in direction of speaker	Cooing and gurgling; smile in response to speech
4	Responds differentially to angry vs. pleasant voice	Responds vocally to social stimuli
5	Responds to own name	Begins to mimic sounds
6	Recognizes words like "bye-bye," "Mama," and "Daddy"	Protests vocally; squeals with delight
7	Responds with gestures to words such as "up," "come, and bye-bye"	Begins to use word like sounds and some jargon
8	Stops activity when own name is called	Imitates sound sequences
9	Stops activity in response to "no"	Imitates intonation pattern of speech
10	Accurately imitates pitch variations	First words appear
11	Responds to simple questions ("where is the dog?") by looking or pointing	Jargon well established
12	Responds with gestures to a variety of verbal requests	Announces awareness of familiar objects by name
15	Recognizes names of various parts of body	True words heard embedded in jargon, often with gestures
18	Identifies pictures of familiar objects when they are named	Uses words more than gestures to express desires
21	Follows two consecutive related directions ("pick up your hat and put it on the chair")	Begins combining words ("Daddy car," "Mama up")"
24	Understands more complex sentences ("after we get in the car we'll go to the store")	Refers to self by name

Courtesy of Beery QC. Center for speech, language and voice pathology, eye and ear Institute of Pittsburgh, with permission.

attributable to congenital anomalies of the external and middle ear. Almost all conductive hearing losses are potentially amenable to surgical correction.

Approximately 1 in 1,000 children is born with a severe to profound sensorineural loss. An equal number of children will develop profound sensorineural hearing loss by late adolescence. This incidence of sensorineural deafness is increased markedly in specific populations.

Most children with congenital or neonatal-acquired hearing losses should now be identified due to the establishment of universal newborn hearing screening as the standard of care. Such early identification screening programs are feasible because of technologic refinements in brainstem auditory-evoked response and otoacoustic emissions testing. The earlier institution of amplification, ideally between 6 weeks and 3 months of age, is the goal of such screening programs. The more frequent recognition of deafness and hearing impairment in children also places a greater responsibility on the pediatric otolaryngologist to understand the relevant genetics of hearing loss and the diagnostic potential of genetic testing. This is particularly true of nonsyndromic sensorineural hearing loss and the utility of screening for connexin mutations.

Multichannel cochlear implantation has proved beneficial for children with profound bilateral sensorineural hearing loss who are unresponsive to conventional amplification. Such benefits include improved auditory and speech production abilities and enhanced psychological and social integration. Strategies for assessing auditory function and aided benefit in such children must be balanced against the time-sensitive nature of cochlear implantation. This is particularly true in young children before age 1 year, and in the postmeningitic bilaterally deafened population in whom the potential development of labyrinthitis ossificans heightens concern about the need for earlier rather than later implantation. In addition to implant placement at younger age, a current trend in cochlear implantation is bilateral implantation, the results of which suggest an improvement in auditory abilities when compared to a single implant. Although initially thought to be a contraindication to implant placement, current data demonstrate that children with a history of AOM, OME, and those with tympanostomy tubes in place do not have a higher incidence of postoperative complications (28,29). Recent guidelines also stress the importance of appropriate immunizations to decrease the risk of otitis media and meningitis; all cochlear implant candidates should receive age-appropriate doses of pneumococcal and *Haemophilus influenzae* type B (HiB) conjugate vaccines and appropriate annual immunization against influenza (30).

Vertiginous disorders in the pediatric and adolescent age group are unusual. Both audiologic screening and radiologic imaging of such children are extremely important to rule out potential central nervous system lesions or predisposing temporal bone anomalies. Benign paroxysmal vertigo of childhood and other pediatric migraine equivalents are variants of a spectrum of vertebrobasilar circulatory dysfunction. The vestibular testing of children, particularly postural and vestibulo-ocular responses, is in its infancy. The role of peripheral vestibular and central sensory organizational deficits in the overall motor development of children remains undetermined.

Facial paralysis in children, in contrast to that in adults, is less often idiopathic and more typically represents any of a diverse number of identifiable etiologies. A careful physical and laboratory evaluation is necessary to rule out potential infectious, inflammatory, traumatic, neoplastic, or syndromic causes. Electrodiagnostic testing using electroneurography can be performed accurately in children. Advances in microsurgical techniques have made cross facial nerve grafting and free muscle transfer procedures available to children; case series with long follow-up periods reveal very adequate aesthetic and functional results with no apparent adverse effects on the developing facial skeleton (31–33).

Vocal fold paralysis is a common cause of stridor and hoarseness in infants and children. Unilateral pediatric paralysis most often occurs secondary to iatrogenic injury or cardiac abnormalities; bilateral paralysis is usually of neurogenic or idiopathic etiology. Any infant or young child with bilateral vocal fold paralysis requires a detailed neuroradiologic workup, specifically MRI, to rule out posterior fossa abnormalities. Bilateral and unilateral vocal fold paralyses present different problems in diagnosis and management. Bilateral vocal fold involvement typically results in life-threatening airway compromise, whereas hoarseness and weakness of voice are the characteristic features of unilateral paralysis. Although historically tracheotomy has been the treatment of choice for neonates and infants with bilateral vocal fold paralysis, in select patients tracheotomy can be avoided if adequate observational monitoring can be assured. Surgical techniques to permit decannulation in children with bilateral vocal fold paralysis include arytenoidectomy or cordotomy by endoscopic or external approach, lateralization arytenoidopexy, and expansion laryngotracheoplasty either via an open or endoscopic approach. When performed conservatively, such procedures can improve the airway with limited voice compromise. Reinnervation techniques using nerve or muscle pedicle graft implantation into one or both posterior cricoarytenoid muscles continue to be investigated as voice-preservation methods. Aspiration or severe dysphonia secondary to unilateral true vocal fold paralysis that remains refractory to speech and swallow therapy also has surgical options. These include laryngoplasty with various bioinjectables, medialization thyroplasty techniques, and unilateral reinnervation procedures. Such procedures (other than reinnervation) are most safely performed in older children and adolescents where the risks of subsequent airway compromise are lessened. An overall conservative approach to the treatment of true vocal fold paralysis is recommended in children in light of the increased likelihood of spontaneous recovery or excellent compensation, especially in idiopathic and neurogenic cases. Definitive voice procedures in children may obtain more optimal results if delayed until postpuberty or young adulthood.

Pediatric otolaryngologists also evaluate children who demonstrate severe sialorrhea secondary to poor oromotor control and impaired swallowing. Most of these children have underlying neurodevelopmental issues, particularly cerebral palsy. When behavioral and medical management techniques fail, several options exist. Submandibular and parotid gland botulinum toxin injections have become increasingly popular as a successful minimally invasive method, although repeated injections are usually necessary. More invasive surgical procedures include rerouting of salivary flow by submandibular or parotid duct relocation, cessation of salivary flow by submandibular and parotid duct ligations, and bilateral submandibular gland excisions. These procedures are offered individually or in combination as definitive means of removing the major sources of saliva production both at rest (the submandibular glands) and during meal stimulation (the parotid glands). In those children with sialorrhea causing life threatening aspiration, laryngeal separation may be an option.

INFECTIOUS DISEASES

Otitis Media

Otitis media is one of the most common childhood illnesses. Evidence-based, multispecialty, clinical practice guidelines exist providing recommendations to primary care physicians regarding the management of children with uncomplicated AOM (34). The focus of such guidelines is appropriate diagnosis and initial therapy, including a period of watchful waiting with appropriate pain control in children of a certain age with less severe symptoms, applicable antibiotic choices in those who warrant treatment, and preventive measures. Pediatric otolaryngology intervention is sought when AOM remains refractory to medical management, responds to treatment but is frequently recurrent, becomes complicated by additional otologic or intracranial manifestations, or is superimposed on persistent OME.

Similar clinical practice guidelines provide evidence-based recommendations on the diagnosis and management of OME (35). Underlying conditions that predispose children to OME are of particular importance to the pediatric otolaryngologist, as are the suspected long-term ill effects of bilateral and even unilateral middle ear effusion on eventual speech-language development and cognitive

function. The relative therapeutic roles of tympanostomy tube placement and adenoidectomy in the management of both AOM and OME are fairly well established, with studies indicative of improved quality of life in children so treated (36).

Streptococcus Pneumoniae Vaccination

The addition of the *Streptococcus pneumoniae* conjugated vaccine to childhood immunization schedules over the past decade has resulted in significant success. Studies indicate that infant immunization with this heptavalent pneumococcal conjugate vaccine has decreased the incidence of invasive pneumococcal infections like meningitis by more than 90% and noninvasive infections like AOM by approximately 10% (37). The former has had the secondary beneficial effect of a decreased incidence of meningitis-related sensorineural hearing loss similar to that observed following HiB vaccination.

Rhinosinusitis

The diagnosis and treatment of rhinosinusitis in the pediatric population underwent revolutionary change with recognition of the ostiomeatal complex as the primary site of involvement of most inflammatory sinus disease. Obstruction of this area leads to blockage of drainage from the frontal, maxillary, and ethmoid sinuses. Systematic nasal endoscopy and high-resolution CT have markedly increased the ability to diagnose disease in this region. Functional endoscopic sinus surgery is performed in children who fail maximal medical and appropriate surgical therapy like adenoidectomy, or who suffer from complications from severe sinus infections such as a subperiosteal abscess. The beneficial role of endoscopic sinus surgery is particularly well established in selected populations of children such as those with primary immunodeficiency disorders, ciliary dyskinesia syndromes, and severe atopic disorders such as allergic fungal sinusitis. Although concern remains, there have been no documented adverse long-term effects of functional endoscopic sinus surgery on human facial growth, yet minimalist surgery removing only the least amount of obstructive tissue is recommended to avoid possible long-term facial aesthetic changes. Within the past two decades the frequency of sinus surgery in children has decreased; this reflects the realization that pediatric sinus disease should be viewed as primarily a medical condition where allergy, immunodeficiency, and reflux mechanisms need to be considered and maximally treated prior to proceeding with operative intervention. Image guidance technology is also being selectively used in children with abnormal anatomy or whose disease process involves the skull base, orbit, and frontal or sphenoid sinuses (38). Intraoperative image guidance has been demonstrated to decrease the risks associated with the surgical removal of both congenital nasal anomalies and benign and malignant skull base lesions, as well as to enhance the safe management of complications from sinusitis such as subperiosteal abscess (39). Newer developments such as balloon sinuplasty appear to be applicable to children but long-term efficacy remains to be determined (40,41).

CYSTIC FIBROSIS

Children and young adults with cystic fibrosis are another special group of patients. Chronic pansinusitis is an almost universal problem in this population, with a variable incidence of obstructive nasal polyposis. Medical therapy offers limited benefit in the treatment of cystic fibrosis polyps. Wide antrotomy of the maxillary, sphenoid, and frontal sinuses, if age appropriate, combined with ethmoidectomy using an endoscopic microdebrider technique has proved efficacious. Initial treatment success as characterized by relief of nasal airway obstruction must be judged relative to the likelihood of postoperative polyp recurrence.

ADENOTONSILLAR SURGERY

The pediatric otolaryngologist shares with his or her general otolaryngology colleagues many of the common ear, nose, and throat procedures performed on children, particularly adenoidectomy, tonsillectomy, and the combination thereof. As a subspecialty field, pediatric otolaryngology has attempted to better define the clinical indications for these common operations, and to investigate alternative ways of performing these procedures in order to decrease risk and improve patient outcome (42).

Chronic or recurrent streptococcal pharyngotonsillitis remains one of the predominant indications for adenotonsillectomy, particularly in older children and adolescents. Adenotonsillectomy has historically been shown to be effective in treating severely affected individuals with repeated bacterial throat infections (43,44). Additional infectious indications for adenotonsillectomy include those children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, characterized by obsessive compulsive and tic disorders exacerbations in the presence of documented streptococcal infection, and those with PFAPA syndrome, defined by a combination of periodic fever, aphthous stomatitis, pharyngitis, and adenitis presumably of viral or autoimmune etiology (45).

Obstructive sleep disorders secondary to adenotonsillar hypertrophy account for the majority of pediatric adenotonsillectomy cases. The etiology of sleep disordered breathing is multifactorial, with craniofacial airway dimensions, oromotor muscle tone, and the rapid increase in pharyngeal and palatine lymphoid tissue size over the first several years of life playing major contributory roles. In the United States a childhood obesity epidemic is also contributing to increased rates of sleep disordered breathing. Clinical practice guidelines exist regarding the diagnosis and management of childhood obstructive sleep

apnea syndrome (46). The efficacy of tonsillectomy, with or without adenoidectomy, in the relief of obstructive sleep apnea is well established by studies incorporating preoperative and postoperative polysomnography monitoring (47,48). Significant improvements in quality of life have been documented following adenotonsillectomy in children even with less severe degrees of obstructive sleep disorder (49,50). The establishment of sleep laboratories and sleep disorders centers in coordination with pediatric pulmonary and neurology colleagues has aided greatly the understanding of the pathophysiology of this disorder and enhanced the perioperative care of severely afflicted patients. Children with craniofacial disorders such as Down syndrome and achondroplasia, or those with severe hypotonia as a result of cerebral palsy and other neuromuscular disorders, may have obstruction that cannot be reversed by adenotonsillectomy alone. Pharyngoplasty, tongue base reduction, lingual tonsillectomy, and even tracheotomy may be required in such children.

The predominant performance of adenotonsillectomy as an ambulatory procedure has focused attention on surgical techniques, methods of hemostasis, and perioperative management. Conventional extracapsular tonsillectomy with electrocautery dissection or cold dissection and snare techniques has been compared with intracapsular tonsillotomy or partial tonsil excision utilizing microdebridement or radiofrequency ablation. Postoperative pain and hemorrhage have been the principal outcome factors assessed. The perioperative use of antibiotics or steroids, the local and systemic administration of narcotics and other analgesics, the postoperative use of nonsteroidal anti-inflammatory medications, and the alteration of anesthesia and hydration practices in an attempt to decrease the incidence of adverse postoperative sequelae and reduce the risk of postoperative sedation all continue to be subjects of investigation (51,52).

SPEECH AND VOICE

The development of speech and voice in children has a significant impact on social and educational development. The inability to communicate clearly affects the psychological and emotional well-being of the growing child. The societal impact is evident into adulthood where adults with speech problems were found to be in a lower income group at a rate 1.5 times greater than controls (53).

The prevalence of voice disorders in the pediatric population ranges between 3% and 10% (54,55). Etiology varies depending on age of presentation. One of the more common causes of dysphonia in an infant is vocal fold immobility as previously discussed. Vocal fold nodules are the most common cause of hoarseness in preschool and school age children, yet one cannot overlook more serious potential pathologies such as juvenile onset recurrent respiratory papilloma. Another group of children with abnormal voice and speech patterns are those with velopharyngeal insufficiency, particularly common following cleft palate repair and occasionally manifest status post adenoidectomy (56–58). Functional voice disorders, rather than organic pathology, are more prevalent in the adolescent population (59). Functional or muscle tension dysphonia is characterized by an altered voice or, in some cases, aphonia in an individual with a normal laryngeal and neurologic evaluation. An alternative diagnosis, paradoxic vocal fold motion disorder (PVFMD), is commonly defined as the adduction of the vocal cords during inspiration resulting in dyspnea and shortness of breath. It should be noted that some practitioners also include inappropriate adduction during expiration as a reasonable exam finding in PVFMD.

The majority of children with speech and voice disorders can be helped with a multidisciplinary team approach that involves pediatricians, otolaryngologists, pulmonologists, gastroenterologists, speech–language pathologists, teachers, and psychologists. Treatment options depend on the specific diagnosis but include an array of behavioral, medical, and surgical therapies.

SPECIAL ISSUES

Children are not cared for in isolation. All pediatric otolaryngology encounters are modified to some degree by the close identification of the parent(s) and other family members with the child. The family is the major source of the clinical history of the young child and complements the history obtained from older children. A family member is often needed to hold the infant or toddler during the head and neck examination. The vigor with which this is pursued must balance the need to examine the child adequately with the need to maintain the confidence and trust of the family. Although much of the physician's encounter is spent in discussion with the child's caregiver, one should not lose focus on the child as the patient.

Treatment recommendations must consider family dynamics and the role of secondary caretakers in daycare or school settings. This may influence medication dosage schedules or modes of administration. Deferring to the child's preferences for one flavored medication over another or for an available liquid or chewable form may greatly improve compliance. Acquiring surgical consent for children from parents or other primary caretakers typically requires a great amount of time and counseling. Special problems in this regard include legally separated families, in which case instructions must be provided individually to both parents, and foster care families, in which case the social service or judicial system is the child's guardian.

The ill child who requires frequent office visits, hospitalization, or surgery places numerous stresses on the family unit. Extended families with grandparents or other relatives within the home are rare today. In families with two working parents, economic and social sacrifices are necessary so that at least one parent is present with the child throughout

the course of treatment. This poses an even greater burden on single parent families. In cases of prolonged hospitalization, the intervention of social services is often of great help. Strong consideration also should be given, when appropriate, to home nursing care; the discharge to home of a newly tracheotomized child is one prime example.

One of the facets of pediatric otolaryngology is the care of children with multiple medical problems. These children have complicated disease processes requiring the subspecialty expertise of many caregivers. Pediatric medical and surgical subspecialists often join to establish multidisciplinary groups to coordinate the care of these patients. Some of the more common of these groups include craniofacial syndrome, cleft lip and palate, and vascular anomalies clinics, cochlear implant teams, aerodigestive, speech, and swallowing centers, and head and neck tumor boards. Maintaining the economic viability of such multidisciplinary teams in the current health care environment will require outcomes data demonstrating that such improved patient access and enhanced physician to physician communication optimizes care.

Technologic advancements have resulted in a significant increase in the frequency of performance of imaging studies in children, especially CT scans. CT scans account for 70% of medically related radiation doses to the general population, and given data that one-third of pediatric CT scans are performed in the first decade of life, there is significant concern regarding the theoretical increased risk of cancer in children undergoing such imaging (60,61). The FDA has recommended that CT settings be optimized for pediatric patients using the ALARA (as low as reasonably possible) principle, that multiple phases in contrast studies be avoided, and that inappropriate CT referrals be minimized (62). Special attention particularly needs to be given to those children who require frequent imaging, with greater consideration of alternate modalities such as MRI. Although the issue of CT radiation risk is complicated and nuanced, as with any diagnostic or therapeutic study, discussing the necessity, risks, and benefits with the child's caregiver is of utmost importance (63).

The administration of anesthesia, especially in the child undergoing a first-time procedure, is often of equal or greater concern to the family than the operation itself. These fears can be decreased significantly by the use of preoperative anesthesia consultations and educational programs coordinated by a hospital-based child life therapist. Such programs require the family to attend a preoperative hospital session during which the parent(s) and child are prepared for what will occur on the day of surgery. Most institutions also allow one parent to enter the operating room and remain at the child's side during the induction of anesthesia in age-appropriate elective cases.

The long-term physiologic effects of anesthetic medications themselves on the developing pediatric neural system have garnered significant attention over the past decade in academic journals and the lay press. There is considerable debate among pediatric anesthesiologists and neuroscientists about the effects of anesthetics on children. Animal studies have demonstrated anesthetic induced neuronal cell death, and there is anecdotal evidence from infant studies that early anesthesia exposure may be associated with altered neural development (64–67). Long-term randomized studies to determine if early anesthetic exposure increases risk of developmental impairment are now underway and should provide more specific and higher quality data (68,69). At present the unknown long-term effects of anesthesia should simply be considered as another variable when deciding about the risks and benefits of possible surgical intervention.

Preoperative guidelines also have changed in recent years relative to the need for prolonged fasting. Increased knowledge concerning fluid and electrolyte maintenance in infants and young children has suggested that only a few hours of absolute fasting is necessary and that clear fluids offered up to 2 hours before planned induction do not increase the child's risk of pulmonary aspiration. Over a decade's worth of data have also reinforced the safety guidelines that allow shortened fasting periods for breast milk (3 hours), formula (4 hours), and light meals (6 hours). This change in practice both avoids the anesthetic risks of induction in a hypovolemic child and creates a much more humane preoperative period for the child and family.

The family must be informed of the immediate care needs of the postoperative child, especially in outpatient surgery cases in which the presence of two caretakers may be necessary for the trip home afterward. The rise of ambulatory surgery over the past decade, especially in the realm of tonsillectomy surgery where inpatient stays decreased by 54% from 1996 to 2006, is of obvious importance to pediatric otolaryngologists (70). The anesthesia team plays a special role in the ambulatory surgery setting. The use of sedative, antiemetic, and anesthetic agents can be varied to result in a more alert, less systemically ill, postoperative child.

CONCLUSION

The subspecialty of pediatric otolaryngology has grown from that of a few individual otolaryngologists in the 1960s to the degree that most major medical centers in this country now have several pediatric otolaryngologists on their full time staffs. An increasing percentage of community–based otolaryngologists also devote their careers principally or solely to pediatric otolaryngology. Pediatric otolaryngology fellowships currently exist at many academic otolaryngology institutions, and attempts are underway to formalize and uniformly accredit pediatric otolaryngology fellowship training from a didactic instruction, clinical responsibility, and research experience standpoint (71,72). These fellowships produce otolaryngologists committed to caring for the ear, nose, and throat disorders of children. The work of these individuals will continue to benefit their own pediatric patients directly, and their

accomplishments will indirectly strengthen the comprehensive management of otolaryngologic diseases in children for our specialty overall.

HIGHLIGHTS

- The subspecialty of pediatric otolaryngology focuses on a specific age group rather than a single organ system or category of disease. It is best defined as the study of the disorders of the ears, nose, and throat relative to the growth and development of the head and neck structures.
- Marked anatomic, physiologic, and behavioral changes occur along the continuum from infancy through childhood and adolescence into adulthood. The clinical presentation of any otolaryngologic disease process is greatly influenced by the age and maturation of the afflicted person.
- Children with congenital malformations of the head and neck require a thorough general pediatric assessment to ensure that their otolaryngologic anomaly is isolated and not a manifestation of a systemic syndrome. The discovery of additional syndromic anomalies could change both acute and chronic treatment plans significantly.
- Refinements in endoscopic instrumentation have influenced multiple aspects of pediatric otolaryngologic care. This is particularly true in the diagnosis and management of congenital and acquired airway lesions and the surgical treatment of paranasal sinus disease.
- Of the sensory impairments of relevance to pediatric otolaryngology, none is of greater significance than hearing loss. Otolaryngologists who care for children must be knowledgeable about the expected developmental milestones of receptive and expressive language from both a diagnostic and rehabilitative standpoint.
- Universal newborn hearing screening programs are designed to identify children with congenital or neonatal-acquired hearing loss. The goal of such screening programs is the institution of amplification, when needed, between 6 weeks and 3 months of age.
- Refinements in angiographic embolization, microvascular techniques, and craniofacial approaches have broadened the definition of resectability without deformity in many children with extensive benign or malignant head and neck neoplasms.
- Bilateral and unilateral vocal fold paralysis present different problems in diagnosis and management. An overall conservative approach to treatment is recommended in light of the increased likelihood of adequate compensation in children, especially in idiopathic and neurogenic cases.
- Sleep disordered breathing accounts for the majority of pediatric adenotonsillectomy cases. Significant postoperative improvement in quality of life is documentable in children even in the absence of polysomnography-confirmed apnea.
- Continued research is needed in such dedicated pediatric arenas as the genetics of hearing loss, the neuromaturation of the auditory and speech pathways, and the potential adverse effects of imaging radiation and general anesthesia on the developing child.
- Multidisciplinary collaboration likely improves the care of medically complex children. Creative coordination among all parties involved will be necessary to prove this to be the case in an era where health care delivery will likely undergo significant change.
- Children are not cared for in isolation. All pediatric otolaryngology encounters are influenced to some degree by the close identification and vested interest of the parent(s) and other family members with the ill child.

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87 Congenital Aerodigestive Tract Anomalies

Christopher T. Wootten *Charles M. Myer III*

EMBRYOLOGY AND PATHOPHYSIOLOGY OF THE UPPER AERODIGESTIVE TRACT

The aerodigestive tract includes an array of organs and tissues with specialized roles that begins at the nares and lips proximally and ends at the stomach and bronchioles distally. Despite the disparate anatomy, these organs and tissues are united around three common functions: feeding, breathing, and voicing. Disease at any level of the aerodigestive tract often affects all three functions. Congenital malformations of the upper aerodigestive tract usually relate to errors in the embryonic phase of development. Dividing anomalies by anatomical region provides organizational structure to the differential diagnosis and aids in the formulation of a focused and cost-effective diagnostic algorithm. A comprehensive list of congenital aerodigestive tract diseases by anatomical location is given in Table 87.1. Aerodigestive embryology is reviewed below.

Nasal and Nasopharyngeal

The stomodeum is surrounded by the frontonasal prominence superiorly, the maxillary processes laterally, and the mandibular processes inferiorly. Normal nasal development occurs during weeks 4 through 12 of intrauterine life. Within this timeframe, the foramen cecum provides communication between the prenasal space and the anterior neuropore. The nasal placodes, which are two small thickenings in the frontonasal prominence, burrow to form nasal pits (Fig. 87.1). This invagination process in the fifth week creates ridges of tissue around the pits called the lateral nasal prominences laterally and the medial nasal prominences medially. The nasolacrimal ducts develop as ectodermal thickenings that become buried in the mesoderm of the nasal pits between the lateral nasal prominence and the maxillary process. This buried ectoderm eventually canalizes from superiorly to inferiorly. The lateral nasal prominences form the nasal alae. Posteriorly, the nasal pits develop into the pouches of the nose and paranasal sinuses that reside above the oral and buccal cavities. The nasobuccal membrane separates the nasal and oral–buccal spaces, and eventually this membrane ruptures and obliterates (1). Several gene products have been identified that play regulatory roles in posterior nasal development, including PTPN14 (2), TBX22 (3), and CHD7 (mutated in greater than 50% of patients with CHARGE syndrome) (4).

Oral

As early as the third week, the branchial arches are demonstrated surrounding the foregut and primitive oral cavity, or stomodeum. The stomodeum is separated from the developing nose by the nasobuccal membrane and from the developing foregut by the buccopharyngeal membrane, the latter corresponding to the region of the palatine tonsils. The mandibular arch begins to grow anteriorly around the third week, enlarging the stomodeum. The mandibular arch subdivides into a maxillary and mandibular process, and the paired maxillary and mandibular processes from each side eventually fuse in the midline along neural crest cell migrations (5). Recalling nasal development, the lateral and medial prominences finalize interaction with the developing maxillary process, creating the philtrum and medial lip (from the fused medial nasal prominences) and the lateral upper lip (from the maxillary prominences). As palatal development occurs, the deepening nasal pits become separated from the developing oral cavity and tongue. Oral–nasal patterning of the palate as well as some aspects of oral cavity and tongue development (e.g., the development of taste buds) is under sonic hedgehog (Shh) regulation (6–10). Palatal development

TABLE 87.1 TYPES OF CONGENITAL AERODIGESTIVE TRACT ANOMALIES BY ANATOMIC ZONE

Nose/Nasopharynx	Oral	Oropharyngeal	Hypopharyngeal/ Laryngeal	Tracheobronchial/ Esophageal
Pyriform aperture stenosis	Median mandibular cleft	Vallecular cyst	Branchial fistula	TEF
Facial clefts	Micrognathia	Lingual thyroid	Choristoma	EA
Nasolacrimal duct cysts	Cleft lip	Lingual thyroglossal duct cyst	Pharyngeal bands	Complete tracheal rings
Hemangioma	Cleft palate	Teratoma	Hemangioma	Tracheomalacia
Teratoma	Midpalatal cyst of infancy	Maxillary duplication	Vascular malformation	Deficient tracheal rings
Dermoid	Nasolabial cyst	Persistent buccopharyngeal membrane	Cricopharyngeal bar	Tracheomegaly
Glioma	Nasopalatine duct cyst	Hamartoma	Laryngomalacia	Tracheal agenesis
Encephalocele	Labial frenulum	Glossoptosis	Vocal cord paralysis	Bronchogenic cyst
Choanal atresia	Oral synechia	Macroglossia	Subglottic stenosis	Tracheal bronchus
Thornwaldt cyst	Lip pits	Leiomyoma	Posterior glottic stenosis	Laryngotracheal stenosis
Epulis	Astomia	Desmoid fibromatosis	Laryngotracheal cleft	Epidermolysis bullosa
Salivary gland anlage tumor	Microstomia	Branchial fistula	Bifid epiglottis	Tracheal pouch/tracheocele
Hamartoma	Congenital macrostomia	Pharyngeal bands	Epiglottic cyst	Hemangioma
Proboscis	Ankyloglossia	Ectopic parotid tissue	Laryngeal saccular cyst	Vascular malformation
Ossifying fibroma	Median rhomboid glossitis	Ectopic carotid	Laryngocele	Chondroma
Pyogenic granuloma	Fissured tongue	Vascular malformation	Laryngopyocele	Chondrosarcoma
Infantile myofibromatosis	Macroglossia	Hemangioma	Epiglottic agenesis	Esophageal duplication cyst
Hemangiopericytomas	Lingual thyroid	Pharyngeal auricle	Epiglottic hypoplasia	Esophageal stricture
Lipoma	Lingual thyroglossal duct cyst	Encephalocele	Laryngeal web	Dysphagia lusoria
Chondroma	Microglossia		Laryngeal atresia	Broncho–biliary fistula
Chordoma	Aglossia		Submucous laryngeal cleft	Tracheal web
Schwannoma	Epidermoid cyst		Laryngoptosis	
Pleomorphic adenoma	Dermoid cyst		Subglottic hemangioma	
Rhabdomyosarcoma	Lymphoepithelial cyst		Hamartoma	
Soft tissue sarcomas	Mucocele		Sulcus vocalis	
Birth trauma	Ranula		Laryngeal cyst	
	Bohn nodule		Pachyonychia congenita	
	Natal teeth		Ectopic thymic cyst	
	Epulis			
	Choristoma			
	Lymphatic malformation			
	Hemangioma			
	Proteus syndrome			

is complex, and the numerous steps involved are detailed elsewhere in this text.

Oropharyngeal

Posteriorly, the tongue develops from multiple branchial arch contributions. Around the fourth week, four regions fuse to form the tongue: paired lateral lingual swellings (first arch derivatives), a midline lingual swelling (first arch derivative), and a hypobranchial eminence (second, third, and fourth arch derivatives). The first arch-derived tongue lies anterior to the buccopharyngeal membrane and constitutes the oral tongue that represents the anterior two-thirds of the tongue's length. In contrast, the portion of the tongue derived from the hypobranchial eminence becomes the oropharyngeal, or posterior one-third of the tongue. As the four zones of the tongue fuse, the lateral lingual swellings override the midline lingual swelling, which comes to be known as the tuberculum impar. Immediately posterior to the tuberculum impar is a V-shaped sulcus (the sulcus terminalis) that separates the tuberculum impar from the hypobranchial eminence, now known as the copula. In the midline of the sulcus terminalis is a zone known as the foramen cecum, which is the origin of the mesodermally derived thyroid gland (Fig. 87.2) (5).



Figure 87.1 Lateral and frontal drawing of a human embryo around 5 weeks. *1*, lateral nasal prominence; *2*, medial nasal prominence; *3*, maxillary process; *4*, mandibular process; *5*, stomodeum. Adapted from Nelson, 1953.

Hypopharyngeal and Laryngeal

Posterior to the hypobranchial eminence (inferior in postnatal life), the larynx appears as a thickening along the ventral aspect of the foregut around 28 days. The caudal portion of the hypobranchial eminence (also known as the furcula of His) gives rise to an epiglottic anlage by 33 days.

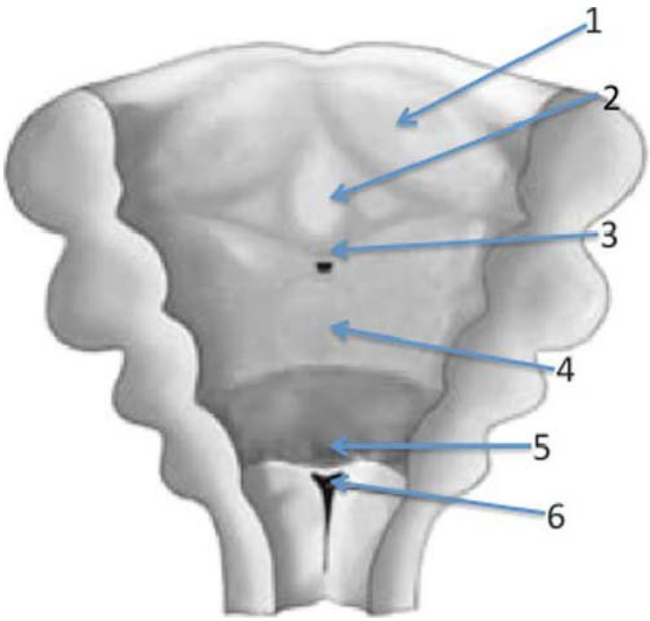


Figure 87.2 Posterior coronal illustration depicting the developmental anatomy of the tongue around the fifth week of development. *1*, lateral lingual swelling; *2*, tuberculum impar; *3*, sulcus terminalis; *4*, hypobranchial eminence (copula); *5*, epiglottic anlage; *6*, glottic inlet.

Paired fourth branchial arches contribute to the epiglottis and the aryepiglottic folds, but the hypobranchial eminence may also have unpaired midline derivatives. By 48 days, the vallecular space is well-defined enough to distinguish the epiglottis from the tongue (11). Inferiorly, the respiratory primordium develops an outpouching from the floor of the pharynx that begins to proliferate posteriorly. This laryngotracheal complex becomes continuous with the ventral lung buds. Obliteration of the ventral lumen of the primitive laryngopharynx gives rise to the epithelial lamina of the larynx. The pharyngoglottic duct is located dorsal to the epithelial lamina, and the laryngeal cecum (primitive vestibule) is located anterior to it. The epithelial lamina recanalizes to open into the laryngeal cecum and allows the pharyngoglottic duct to unite with the cecum, forming the vestibule (from the cecum) and the interarytenoid notch/posterior glottis (from the pharyngoglottic duct) (12). Beneath these epithelial movements, mesenchymal contributions from the paired fourth and sixth branchial arches comprise the cartilaginous framework of the larynx and its supporting nerves and vessels.

Tracheobronchial and Esophageal

Again, around 28 days, the anterior foregut begins to partition into a dorsal esophagus and a ventral trachea that connects to simultaneously developing ventral lung buds off the primitive foregut. The molecular mechanisms driving this early partition include the localized expression of *Nkx2-1* (*Tif1*) in the ventral wall of the anterior foregut, while Sox2 expression predominates dorsally. Patterning of *Nkx2-1*/Sox2 expression is in turn signaled by the expression of Bmps, noggin, Fgfs, Shh, and Wnts in the surrounding mesenchyme. Abnormalities in these mesenchymal signals can result in failure of foregut separation and abnormal differentiation of the epithelium and mesenchyme, including tracheal agenesis (13). Tracheoesophageal separation is a dynamic process that involves inward movement of lateral mesodermal ridges. This infolding proceeds in a posterior to anterior (inferior to superior, postnatally) direction according to the classic model of tracheoesophageal embryogenesis. Alternative theories depict a series of cranial and caudal folds along the evolving tracheoesophageal septum, and epithelial proliferation and apoptosis may play a role in the division of the trachea and esophagus as well (14). As the trachea is separating from the esophagus, the tracheal mesoderm is differentiating into C-shaped cartilage rings anterolaterally. Contrasting mesenchymal development occurs along the newly formed posterior tracheal wall where strips of smooth muscle are formed. The development of smooth muscle posteriorly and cartilage anteriorly at regular intervals is guided by differential expression of Fgf10 and Shh (15). Likewise, Fgf10 plays an essential role alongside Fgfr2 in the branching morphogenesis of the lung buds (13). By the end of intrauterine life, the trachea averages 5.7 cm in length, having 18 to 20 cartilaginous rings. Mesenchymal differentiation

within the esophagus results in a muscular layer of striated muscle in the upper one-third and smooth muscle in the lower two-thirds of the tube (16).

DIAGNOSIS

Prenatal Diagnosis of Aerodigestive Tract Disease

For many individuals, the diagnosis of aerodigestive tract disease begins in the prenatal phase. A "Triple Test" is available in the first trimester and combines a measurement of nuchal thickness on ultrasonography, maternal age, gestational age, and maternal serologic measurements of PAPP-A and beta hCG to predict the risk of trisomy 21, 18, and 13 as well as Beckwith-Wiedemann syndrome in the developing fetus (17,18). Second trimester screening can add serologic evaluation of inhibin-A and alpha-fetoprotein, constituting a "Penta test" which, when considered alongside the first trimester combined screening results, provides a more sensitive prenatal diagnosis of aneuploidy and neural tube defects (19,20). Invasive measures, such as chorionic villus sampling (CVS) in the late first trimester of pregnancy and amniocentesis in the second trimester, may identify individuals with chromosomal anomalies that place them at risk for postnatal problems, including aerodigestive tract dysfunction. Later in the second trimester of pregnancy, biometric measures of oral, oropharyngeal, and laryngotracheal structures can be obtained using four-plane sonography techniques. Individuals followed over time with ultrasonography demonstrate not only anatomic but also physiologic development, as increasingly complex orofacial, lingual, pharyngeal, and laryngeal movements indicate the evolution of suckling behavior. Further, children with genetic abnormalities identified through a Triple/Quad/Penta test, CVS, and/or amniocentesis demonstrate suckling dysfunction on prenatal ultrasonography compared to individuals without disease (21) (Fig. 87.3).

Because ultrasound is anatomical, physiologic, and noninvasive, it is currently the most important and commonly used means to diagnose aerodigestive disease prenatally. However, the application of fetal MRI is widening, and several reports exist documenting the utility of prenatal MRI in the diagnosis of aerodigestive tract anomalies that may predict respiratory embarrassment at delivery (Fig. 87.4). At many institutions, protocols are being developed to employ high-quality ultrasonography and fetal MRI in a complementary fashion to determine which patients should be offered *ex utero* intrapartum treatment (EXIT) to establish an airway (22). The utility of prenatal MRI likely will continue to evolve (23,24).

Postnatal Diagnosis of Aerodigestive Tract Disease: General Principles

As with any disease process, the diagnosis of congenital aerodigestive tract disease begins with a history and physical examination. Even in the management of an emergent airway obstruction, some modicum of historical information and physical observations guide the clinician to the appropriate urgent intervention. When evaluating a stable patient with congenital aerodigestive tract disease, a comprehensive history and physical examination may be obtained alongside flexible endoscopy and selected

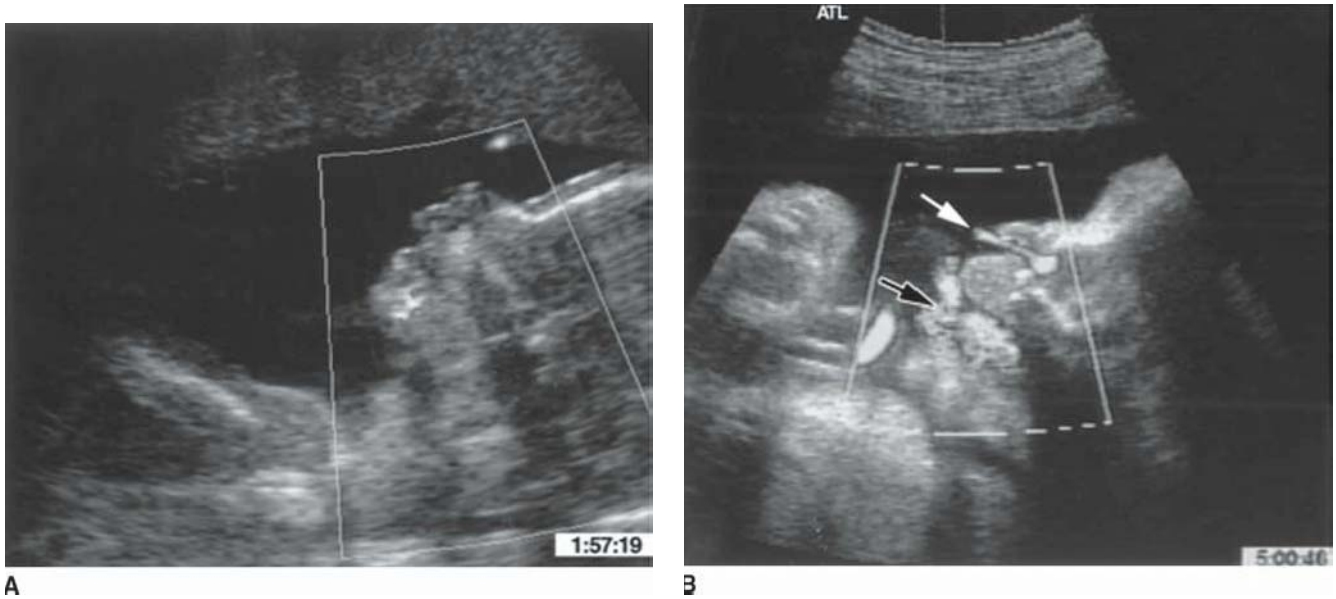


Figure 87.3 Parasagittal fetal ultrasound around 19 months depicting the fetus (**A**). Power Doppler imaging demonstrates amniotic fluid flowing through the mouth and nose (**B**) during swallows (black arrow) and respiration (white arrow). From Miller JL, Sonies BC, Macedonia C. Emergence of oropharyngeal, laryngeal and swallowing activity in the developing fetal upper aerodigestive tract: an ultrasound evaluation. *Early Hum Dev* 2003;71(1):61–87, with permission.

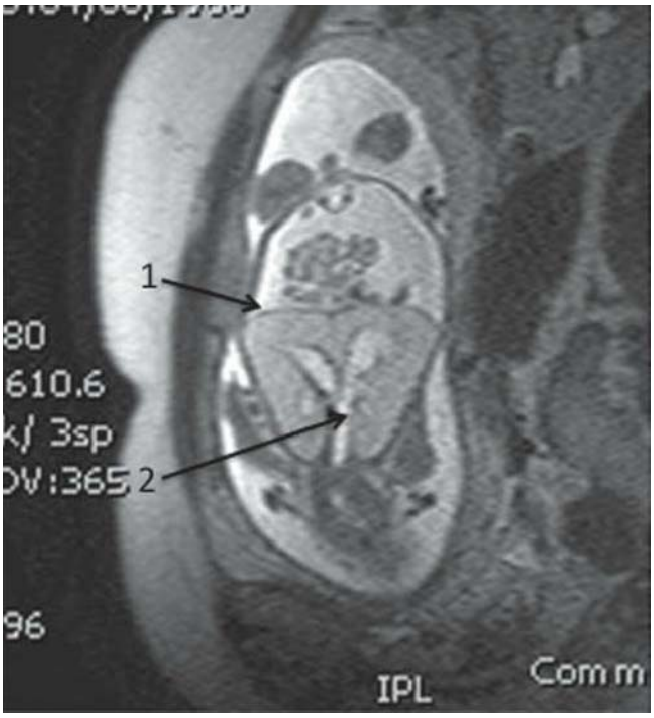


Figure 87.4 Fetal T2 FSE coronal MRI demonstrating (*1*) flattened diaphragms and (*2*) a dilated distal tracheobronchial tree. The 22-week fetus is inverted in this image.

imaging. In an unstable patient, diagnosis and management often occur at the same time in the operating room in the process of securing a safe airway.

The functions of the aerodigestive tract include breathing, feeding, and voicing. Aerodigestive disease frequently affects more than one of these functions simultaneously, and a useful history not only focuses in on the diagnosis but also accounts for the variety and degree of disabilities the patient is experiencing. Noisy, rapid, and/or labored breathing is representative of respiratory dysfunction. Adventitious breath sounds include stertor, snorting, snoring/sonorous breathing, stridor, wheezing, and coughing. When these signs are present on inspiration, the airflow limitation is usually above the level of the vocal folds. Biphasic stridor is classically glottic or subglottic, while expiratory stridor originates below the larynx. The timing, severity, relapsing and remitting factors, effects of positional changes and effects on feeding must be clarified, and such useful historical information may be obtained from the family, nursing staff, respiratory therapists, speech pathologists and the primary physician team managing the patient. For safe feeding to occur, the infant must have a reasonably slow respiratory rate to allow suck–swallow–breathe coordination, and nasal breathing is required for this coordinated effort until around the eighth month of life. How breathing is affecting feeding, the technique (breast, standard bottle, specialized feeder/nipple) and position of feeding, the consistency of oral intake and any signs of choking, coughing, wet sounding respirations, desaturations, and the presence or absence of pneumonia are all important questions to ask. Spitting up and emesis are also important to ascertain, as retrograde esophageal movement may lead to aspiration of refluxate or point to a pharyngoesophageal anomaly. Finally, the quality, quantity, and volume of voicing must be determined.

The physical examination of the infantile aerodigestive tract must account for the unique craniofacial relationships in the infant. The head is relatively large while the neck is relatively small in circumference and short in length. The midface is flattened, and the retropalatal and retrolingual airspaces are relatively compressed compared to their adult counterparts (25). In fact, the tip of the epiglottis may touch the tip of the soft palate during deglutition, indicating the high position of the infant's larynx in the neck. The inferior margin of the cricoid cartilage is at C2 in the newborn and at C7 in the adult. With this in mind, the physical examination again focuses on the presence and degree of respiratory, feeding, and communication difficulties being experienced by the patient. The examination begins by noting the patient's color, body position, and apparent level of distress. Respiratory rate, effort, and sound are all noted, as are the presence, location, and severity of retractions. The presence of labored breathing with retractions is more serious than of loud breathing without effort or retractions. As less and less air movement occurs, the patient may become quieter as a consequence. The clinician should also note pulse oximetry data and whether the patient is receiving supplemental oxygen. The cry should be assessed for hoarseness, breathiness, or aphonia. Observing the infant during a feeding gives useful insight into suck–swallow–breathe coordination, signs of aspiration, and the overall safety of oral feeding.

The history and physical examination often point to the diagnosis of congenital aerodigestive tract disease, but additional diagnostics commonly are called upon to both confirm the diagnosis and stage the extent of comorbidities. A significant minority of patients have multiple congenital aerodigestive abnormalities (26). In a stable patient, after a detailed history and physical examination, a common next step is flexible nasopharyngoscopy and laryngoscopy. With an appropriately sized flexible scope (around 2.2 mm outer diameter or smaller), nasopharyngoscopy is well tolerated and safe without topical anesthetic (which might confound a flexible endoscopic evaluation of swallowing [FEES]). Flexible endoscopy allows the examiner to diagnose the nature of the disease, the level(s) of disease, and any dynamic airway collapse. The position of the patient matters in flexible nasopharyngoscopy. The larynx is best visualized when the patient is in a seated position as it allows the pharynx to open and the larynx to fall forward. However, neonates do not assume a seated position, and flexible endoscopy in their typical supine, side-lying or reverse-Trendelenburg position will best recapitulate obstruction and aerodigestive tract dysfunction as they experience it (Fig. 87.5). Concomitant administration of dyed liquids, purees, and solids allows the examiner to assess swallowing safety and dysfunction endoscopically (FEES). Importantly, what is seen on flexible endoscopy

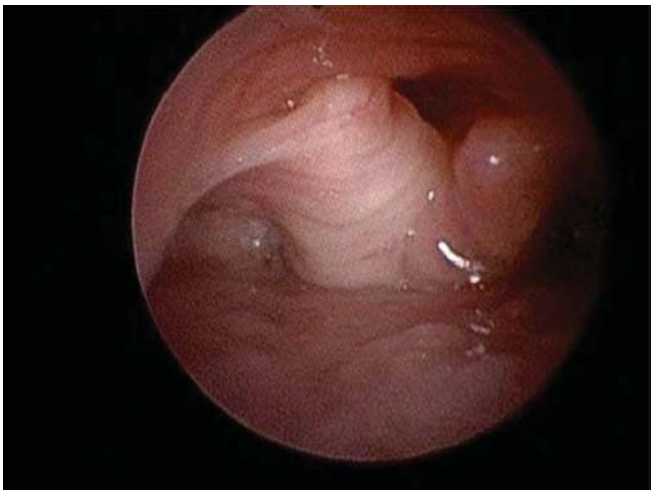


Figure 87.5 Flexible endoscopic view of the larynx in a supine infant demonstrating laryngomalacia secondary to bulky, obstructing supra-arytenoid tissue.

may also guide airway management when the patient undergoes treatment in the operating room.

In addition to flexible endoscopy, radiographic studies provide diagnostic and staging information in the stable patient. Plain films of the neck in anterior–posterior and lateral planes highlight the soft tissue relationships around the air column. However, most clinicians prefer the anatomical detail, multiplanar information, and surgical roadmap provided by computerized tomography (CT). Indeed, CT scanning is the initial imaging modality of choice for craniofacial, nasal, nasopharyngeal, oral, and oropharyngeal aerodigestive diseases (27–29). MRI also provides exceptional anatomical detail, but its added cost and absolute need for sedation render MRI less frequently employed. Dynamic radiographic studies continue to be useful in the diagnosis of aerodigestive diseases, and while airway fluoroscopy is of historical interest, cine MRI allows the clinician to determine anatomical levels of airway collapse under a plane of anesthesia that simulates sleep in patients with sleep-disordered breathing (30,31). Finally, a videofluoroscopic swallow study (VFSS or modified barium swallow study) remains an indispensable tool to diagnose dysphagia, make treatment recommendations, and occasionally directly see the effects of aerodigestive tract anomalies on swallowing (32).

Following an appropriate history and physical examination supplemented by appropriate imaging, rigid airway endoscopy is the gold standard in the diagnosis of aerodigestive tract disease. Nasal and nasopharyngeal lesions require nasal endoscopy/nasopharyngoscopy, whereas oral, oropharyngeal, hypopharyngeal, laryngeal, tracheobronchial, and esophageal diseases are diagnosed by microlaryngoscopy, bronchoscopy, and esophagoscopy. Diagnostic airway endoscopy requires careful preparation and adequate equipment to deal with expected and unexpected scenarios in the management of the patient's airway. The otolaryngologist must communicate with the anesthesia team their goals and expectations from the evaluation. Most rigid airway endoscopy in the operating room is performed with the patient anesthetized but spontaneously breathing. This allows a greater margin of safety as the patient is capable of unassisted gas exchange, and there is greater time to examine the airway before desaturation requires bagging or intubation. In this technique, topical anesthetic must be sprayed on the larynx and tracheobronchial tree to reduce laryngospasm and coughing. In neonates, 0.5% to 2% plain lidocaine typically is used. The exact technique of rigid airway endoscopy varies from surgeon to surgeon. Battery-powered intubation laryngoscopes (e.g., Miller, Phillips, or Wis-Hippel blade) and operating laryngoscopes with external light sources are both useful to examine the oral cavity, oropharynx, hypopharynx, and larynx. The operating laryngoscopes can be suspended for a two-handed stable examination and intervention as needed. Magnifying telescopes (Hopkins rod telescopes) are commonly used to enhance the examination and allow digital photo/video documentation. These scopes can be used independently with an intubation laryngoscope or with an operating laryngoscope. Alternatively, an operating microscope can be used with suspension laryngoscopy to evaluate and treat the larynx. Tracheobronchoscopy can be performed with a bare telescope passed through the glottis or with a ventilating bronchoscope containing a telescope. Advantages of the latter are obvious—the bronchoscope may be connected to the anesthetic circuit and the patient ventilated while the examination is taking place. However, the limiting factor in tracheobronchoscopy is the size of the patient's airway, and a much larger (and higher optical resolution) bare telescope can be passed into a small airway without the sheathing ventilating bronchoscope (Fig. 87.6). Operative rigid endoscopy is also the platform from which airway management, biopsies, and endoscopic therapies take place.

Postnatal Diagnosis of Aerodigestive Tract Disease: Specific Levels of Dysfunction

With an overview of aerodigestive disease diagnosis in mind, specific levels of aerodigestive tract dysfunction are detailed below. Key symptoms uncovered in a careful history, significant findings on physical examination, and other typical diagnostic results are highlighted.

Nasal and Nasopharyngeal

The symptoms and signs of nasal obstruction are sonorous or snorting inspiratory breath sounds with mild to moderate obstruction progressing to cyclic cyanosis relieved by crying and mouth breathing with complete nasal obstruction. Affected infants are poor feeders due to interruption of the suck–swallow–breathe mechanism. Voicing may be hyponasal. Flexible nasal endoscopy may note a tight anterior nasal valve secondary to congenital nasal pyriform aperture stenosis (CNPAS), an anomaly within the nasal passageway, or pooled secretions in the posterior



Figure 87.6 A 2.5 ventilating bronchoscope (**left**) and a 1.9 mm outer-diameter Hopkins rod telescope (**right**) can be mated to provide a magnified endoscopic assessment of the tracheobronchial tree. Alternatively, the telescope may be passed into the airway without the sheathing bronchoscope.

nasal passageway secondary to choanal stenosis or atresia. A high-resolution maxillofacial CT scan with axial, coronal, and sagittal reconstructions and/or three-dimensional (3-D) reconstruction is the single most useful radiographic study in the evaluation of congenital nasal anomalies because of its superior bony/soft tissue resolution (33,34). Rigid nasal endoscopy adds little to the diagnosis, but it is a platform from which both diagnosis and treatment can be instituted.

The symptoms and signs of congenital nasopharyngeal anomalies are largely the same as nasal ones. One exception is cysts or tumors (such as teratomas) that exert a mass effect on the nasal surface of the soft palate. In these instances, if the soft palate is stented open by a mass descending behind the palate, voicing is hypernasal secondary to velopharyngeal incompetence. If the entire nasopharyngeal space is obliterated, the cry is muffled. Again, flexible endoscopy is an indispensable diagnostic tool, especially as the scope tip can be rotated to evaluate all recesses of the nasopharynx, and a flexible nasopharyngoscope may be twisted through a stenotic choana. In these respects, flexible endoscopy is superior to rigid in the nasopharynx. As with nasal lesions, a high-resolution maxillofacial CT scan with axial, coronal, and sagittal

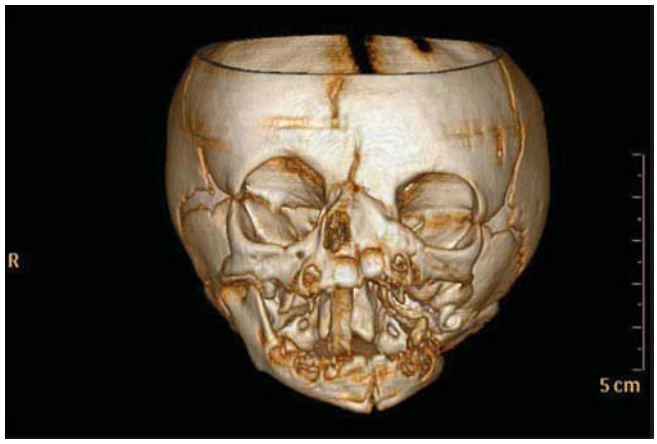


Figure 87.7 3-D reconstruction of a noncontrast-enhanced maxillofacial CT scan in a patient with unilateral left-sided hemiarhinia. A nasal trumpet is descending through the right nasopharynx.

reconstructions and/or 3-D reconstruction is the most useful radiographic study in the evaluation of congenital nasopharyngeal anomalies (Fig. 87.7) (33,34).

Oral

Congenital aerodigestive tract anomalies affecting the oral cavity are heterogeneous, ranging from abnormal bands, such as upper labial frenulum, ankyloglossia, and intergnathic bands, as seen in popliteal pterygium syndrome (35,36) to cleft palate to macroglossia, as seen in Beckwith-Wiedemann Syndrome (Fig. 87.8)



Figure 87.8 Beckwith-Wiedemann syndrome causing macroglossia in a neonate.

(37,38). The symptoms and signs of minor anomalous bands largely relate to feeding, as the inability to evert the upper lip or protrude the tongue may preclude effective breastfeeding. Airway and voicing are unaffected. Similarly, cleft palate (without micrognathia and/or relative macroglossia) is mostly a feeding problem at birth. In contrast, microstomia, intergnathic bands, micrognathia with relative macroglossia, absolute macroglossia and intraoral tumors produce drooling, gasping during feeding, muffled cry, and obstructed breathing patterns. When no oropharyngeal obstruction is present, quiet breathing through the nose may be unaffected. Nasopharyngoscopy rules out oropharyngeal extension, but the majority of the salient physical exam can be accomplished through direct observation with a tongue depressor and a headlamp. Consistent with the heterogeneous nature of congenital oral anomalies, there is no single imaging modality that is required or preferred for diagnosis. When the physical examination alone is insufficient, mandibular or dentigerous anomalies may be evaluated best with a panorex. Relationships between the upper and lower jaws and the encompassed soft tissue are best shown on a maxillofacial CT scan, while intrinsic soft tissue lesions (such as lingual masses) achieve best delineation on MRI (39). For vascular malformations, MRI adds the benefit of vascular phases that provide additional diagnostic sensitivity (MR angiography [MRA] and MR venography (40)).

Oropharyngeal

Moving inferiorly, the oropharyngeal space becomes the common aerodigestive tract in the nasal-breathing neonate. Symptoms and signs of congenital oropharyngeal anomalies include wet stertorous breath sounds, inspiratory stridor, snoring, gasping, discomfort and possibly cyanosis with feeding, and a muffled cry. Patients often breathe better in the prone position (which is also true for patients with stridor of a supraglottic etiology). Aspiration is likely with larger lesions due to suck–swallow–breathe interruption. Flexible endoscopy is essential to the diagnosis of oropharyngeal congenital anomalies because it provides a dynamic assessment of breathing, the management of secretions, and any effects the oropharyngeal lesion is exerting on the larynx—particularly with vallecular cysts that tend to drive the epiglottis into the glottic inlet (41). With oropharyngeal lesions, imaging may not be necessary. Important relationships to define are mostly soft tissue relationships, and MRI provides the best resolution. However, increased speed, decreased cost, and the possibility of avoiding sedation often support the use of a contrast-enhanced CT, which provides adequate anatomic delineation, particularly for cystic anomalies. Both for diagnosis and for airway management, rigid microlaryngoscopy and bronchoscopy are indicated if the oropharyngeal lesion abuts the larynx/hypopharynx.

Hypopharyngeal/Laryngeal

Anomalies of the hypopharynx produce dysphagia, muffled voicing, and airway obstruction by interfering with the esophageal inlet and/or the patency and movement of the larynx. Stridor is inspiratory, and the abnormal collection of hypopharyngeal secretions may lead to wet sounding respirations. Similarly, a large lesion of the hypopharynx, which directs secretions and oral intake into the larynx, produces coughing and aspiration. Flexible endoscopy is essential to diagnose the lesion and to assess its dynamic effects on the management of secretions, swallowing, and breathing. As with oropharyngeal lesions, imaging may be unnecessary, but a contrast-enhanced CT and MRI both provide adequate anatomic detail to resolve hypopharyngeal lesions. Dysphagia is common with hypopharyngeal anomalies, and VFSS is necessary to complete the workup in most instances (Fig. 87.9) (32). Microlaryngoscopy, bronchoscopy, and esophagoscopy complete the evaluation, and postcricoid lesions are evaluated specifically by lifting the larynx with the laryngoscope blade during a comprehensive exam.

The larynx has three cardinal functions: (a) an airway protection mechanism during swallowing, (b) a respiratory conduit, and (c) a phonatory source. These functions are carried out over a relatively small area, and their success depend on intact sensation and movement (glottic abduction, adduction, and laryngeal elevation), laryngeal patency, and the ability of thin, crisp vocal folds to be pulled together and driven by an adequate subglottic air column. The symptoms and signs of aerodigestive disease in the

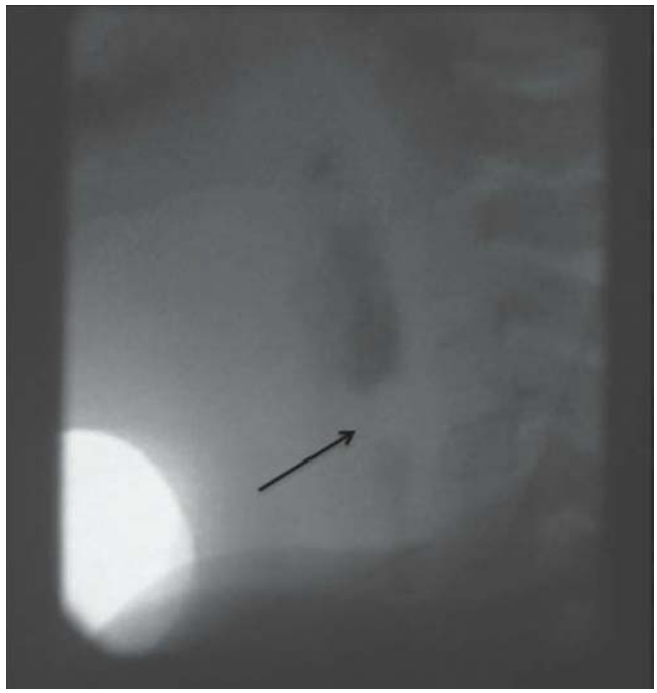


Figure 87.9 Sagittal video-fluoroscopic swallow study demonstrating bolus restriction by a cricopharyngeal bar (*arrow*) in the hypopharynx. Image courtesy of Gwen Provo-Bell, M.S., SLP-CCC.

larynx include dysphagia and aspiration with or without coughing and recurrent aspiration pneumonias. Stridor is present and is classically described as inspiratory when the lesion is supraglottic or glottic and biphasic when the lesion is subglottic. Stridor may progress to retractions and cyanosis. When stridor is absent at birth but appears in the first few weeks or months of life, laryngomalacia is the most likely cause, although subglottic hemangiomas also usually present with some delay. Vocal dysfunction due to laryngeal disease may be muffled or coarse if there is a large supraglottic lesion, hoarse, breathy, or aphonic if the disease is glottic, and hoarse and breathy if the disease is subglottic.

Ancillary diagnostic techniques are important in the workup of congenital laryngeal disease. Flexible laryngoscopy is indispensable, and the examiner should note pooling of secretions (denoting sensory dysfunction or a mass) (42), masses, tracts or mucosal abnormalities or vocal fold movement abnormalities. The examiner should attempt to differentiate between a fixed or neurologically paralyzed glottis and a glottis restricted by scarring. Vocal folds resting in a paramedian position may be paradoxically drawn inwards during inspiration. In contrast, expiratory adduction of the vocal folds or medial rotation of the supraglottic larynx suggests that motor input is intact. Dynamic collapse of the larynx with respiration should be noted as well. If possible, the subglottis should be assessed for stenosis, mucosal changes (cysts, inflammatory changes, exudates) and for masses, such as a subglottic hemangioma. Some authors routinely pass the flexible nasopharyngoscope through the vocal folds to obtain an anatomical and dynamic view of the trachea as well (43), although many voice concerns for laryngospasm, desaturation, and patient distress. A FEES exam adds an important dimension to flexible laryngoscopy, and patients with laryngeal dysfunction may demonstrate laryngeal penetration, aspiration, and hypopharyngeal residue (44). With FEES, the examiner is also able to ascertain whether the patient's unique laryngeal anatomy contributes to or protects against dysphagia and aspiration, potentially valuable in surgical planning. A VFSS provides complementary data, and all patients with congenital laryngeal disease benefit from this functional radiographic exam. Plain films of the neck in posterior-anterior and lateral planes remain useful to quickly diagnose swelling or mass effects in the larynx and particularly the subglottis. However, the phase of respiration must be considered, as an adducted glottis may masquerade as a swollen and inflamed conus elasticus on PA views—the so-called steeple sign. If greater anatomical detail is needed, one must recall that the neonatal larynx is nonossified. Therefore, MRI provides the best resolution of intrinsic laryngeal disease. However, CT scanning is less expensive, faster, and may not require sedation. The anatomical detail on CT is good, and contrast can be added to highlight inflammatory lesions such as saccular cysts and third or fourth branchial arch anomalies that may surround the larynx. With the exception of mild laryngomalacia, most congenital aerodigestive tract diseases affecting the larynx are best evaluated by rigid microlaryngoscopy and bronchoscopy (Fig. 87.10). Clear advantages over flexible endoscopy include improved optical resolution, the ability to splay the posterior glottis in the search for a laryngeal cleft, and the ability to palpate the cricoarytenoid joints and interarytenoid space in the case of vocal fold movement abnormalities. The subglottis may also be completely evaluated and sized during a rigid endoscopic evaluation.

Tracheobronchial and Esophageal

When considering the diagnosis and management of congenital tracheobronchial and esophageal disease, one must consider the benefits of a multidisciplinary approach. Many of the larger children's hospitals around the globe use multispecialty clinics involving otolaryngology, gastroenterology, pulmonology, speech pathology (to assess both voicing and swallowing), and others to provide comprehensive, concentrated diagnosis, and management of aerodigestive tract diseases (32). While the tracheobronchial tree and the esophagus remain under the purview of the otolaryngologist, the other specialists possess unique equipment, training, and perspective to supplement the evaluation and to benefit the patient.

The symptoms and signs of tracheobronchial dysfunction pertain more to airway limitation than problems with swallowing or voicing, although safe feeding may become difficult with labored breathing. Patients exhibit expiratory stridor that may be accompanied by increased use of intercostal musculature. Mild, though significant, tracheomalacia may resemble reactive airways disease (asthma), and infants may be placed unnecessarily on bronchodilators that tend to increase respiratory rate and effort. With agitation, the stridor of tracheomalacia becomes worse because the trachea is being collapsed by thoracic compression, and it is being drawn together by an increasingly fast column of air moving out of the bronchi. In these conditions, stridor may progress from an expiratory wheeze to a coarse, honking sound. Reflex apnea results from complete tracheal collapse (45). Tracheal stenosis secondary to complete tracheal rings tends to be less dynamic. The tracheal lumen is extremely small, and the adhesive property of water in the saliva coats the airway and enhances obstruction. Respirations are usually wet sounding in both the inspiratory and expiratory phases with labored breathing and low-normal oxygen saturations. Flexible endoscopy to the level of the glottis rules out concomitant laryngomalacia or vocal fold immobility. Plain films of the trachea may demonstrate congenital stenosis or tracheomalacia, or both. However, an inspiratory film of a patient with tracheomalacia is usually normal in appearance. Newer dynamic imaging protocols using multidetector CT and cine MRI can capture and quantify dynamic collapse of the airway (30,46). Additional advanced imaging modalities are high-resolution CTA or MRA, which

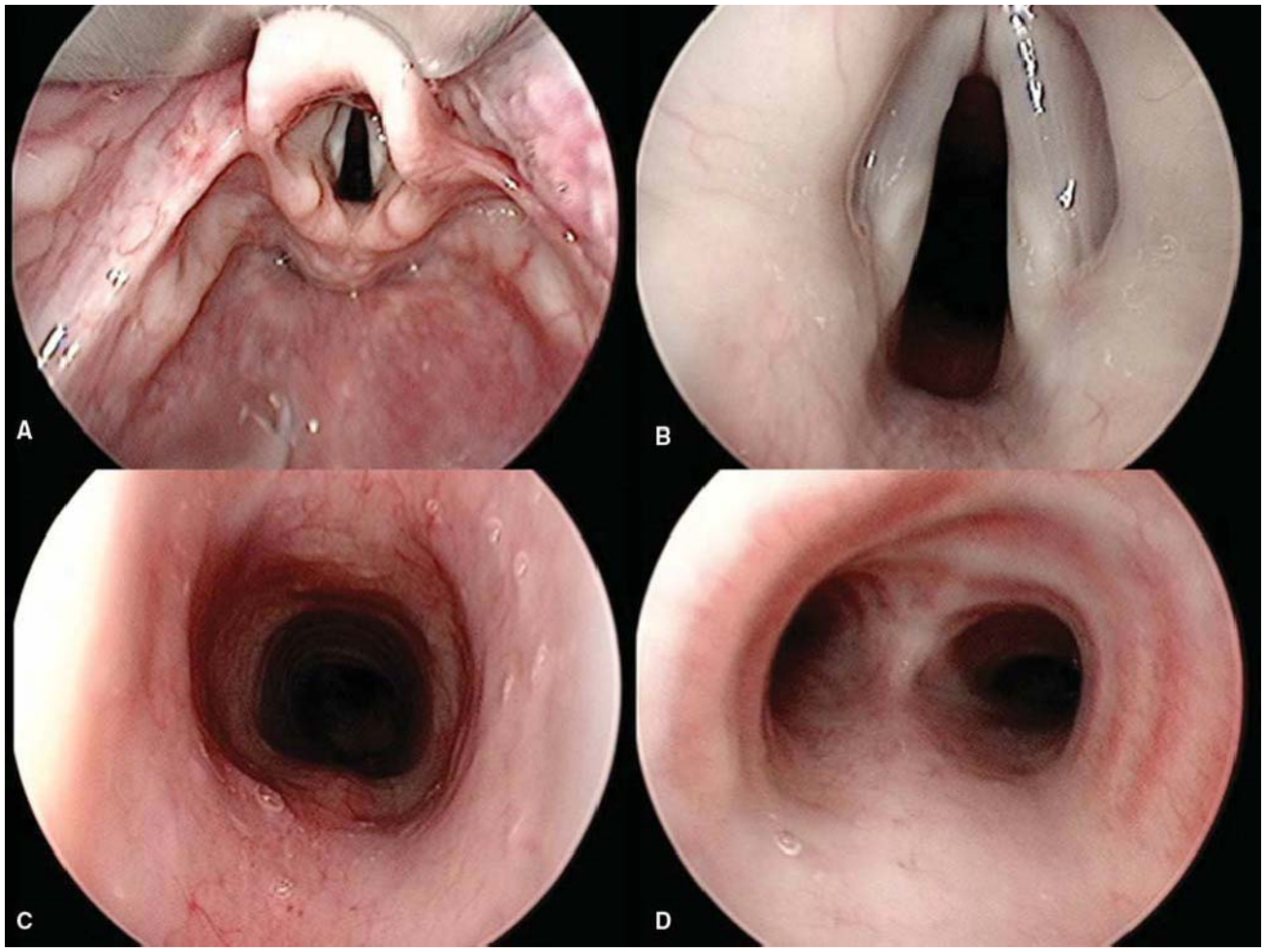


Figure 87.10 Endoscopic photos of the supraglottic larynx (**A**), glottis (**B**), subglottis (**C**), and trachea (**D**) in a 2-year-old without airway pathology in whom an airway foreign body was being excluded. Normal anatomy is seen throughout.

demonstrate the low cervical and mediastinal vascular anatomy surrounding the trachea. Either of these studies can delineate tracheomalacia secondary to innominate artery compression, aortic compression, vascular rings, a pulmonary artery sling, or some combination thereof, and further surgical therapies such as aortopexy may be guided by these findings (47). Additionally, congenital tracheal stenosis secondary to complete tracheal rings is frequently associated with mediastinal vascular anomalies that may require simultaneous repair (48). A final benefit of CTA or MRA is the demonstration of complete tracheal rings provided on 3-D reconstruction. Rigid tracheobronchoscopy is required to confirm the diagnosis of congenital tracheal anomalies, but as alluded to earlier, flexible bronchoscopy under a spontaneous ventilatory plane provides complementary and highly useful information about dynamic airway lesions, such as tracheomalacia and bronchomalacia (Fig. 87.11). Often, the pulmonology service performs this evaluation in the same operating room setting, and bronchoalveolar lavage is simultaneously performed to diagnose inflammatory pathologies.

Congenital esophageal diseases may be due to intrinsic abnormalities in the esophageal lumen, developmental arrest, external mass effects, or problems with tracheoesophageal separation (16). Partitioning abnormalities along the tracheoesophageal septum, such as



Figure 87.11 Rigid endoscopy demonstrating tracheomalacia secondary to vascular compression imposed by the innominate artery in an infant.

a laryngotracheoesophageal cleft or tracheoesophageal fistula (TEF), potentially interfere with both feeding and respiration. Classically, the affected infant may choke with feeding with clefts and fistulas, and gastric distention with air may occur with certain types of fistulas. With time, failure to thrive, aspiration pneumonia and bronchiectasis occur. H-type TEFs produce the subtlest symptoms. In contrast to tracheoesophageal problems, there are a variety of intrinsic esophageal abnormalities. A cricopharyngeal bar produces dysphagia and aspiration with rapid swallowing sequences or immediate regurgitation, whereas esophageal diverticula produce delayed rumination. Awake flexible nasoesophagoscopy has not been utilized in the evaluation of infants and children, and radiographic evaluations are the most useful ancillary studies. A contrast-enhanced esophagram (barium swallow) demonstrates the anatomy within or impinging upon the esophageal lumen. A VFSS adds to this a real-time sagittal and coronal assessment of swallowing from the oral cavity to the stomach. Not only does VFSS assess the various phases of swallowing, but it also allows evaluation of the effects of consistency modification in the patient with dysphagia (32). When an extra-esophageal mass or diverticulum is suspected based on contrast-enhanced esophagram or VFSS, a contrast-enhanced CT or MRI provides excellent anatomical detail and clearly demonstrates mediastinal vascular anatomy. Both rigid and flexible esophagoscopy provide direct assessment of the esophageal lumen and allow biopsies to be taken. In the multidisciplinary model of aerodigestive disease diagnosis, a pediatric gastroenterologist performs esophagogastroduodenoscopy.

TREATMENT

General Principles of Treatment

The following section highlights select congenital aerodigestive tract anomalies, their embryology, presentation, diagnosis, and treatment. Congenital aerodigestive diseases often produce dysfunction in more than one realm of the aerodigestive tract. Accordingly, any treatment rendered must account for its impact on feeding, breathing, and voicing. Sometimes, treatment in one area improves function in other areas, but the opposite may be true. As an example, improving voicing by vocal fold medialization also improves swallowing by closing an incompetent glottis. However, closing the glottis renders the respiratory conduit smaller, and dyspnea may ensue. In contrast, correcting choanal atresia improves nasal respiration and allows the suck–swallow–breathe sequence to be optimized. Voicing is only subtly affected as hyponasality improves. The treating physician must bear in mind these principles when managing unique aerodigestive problems. The specific disorders detailed below serve as a guide, and their treatment principles may be extrapolated to less common disorders.



Figure 87.12 Transoral view of a hemangioma involving the left hemipalate in an infant with mild feeding difficulties.

Nasal and Nasopharyngeal

Pyriform aperture stenosis obstructs the nasal airway anteriorly, and choanal stenosis or atresia obstructs it posteriorly. In the nasal space between the pyriform aperture and the choana, a variety of intranasal masses creates airflow resistance. These include nasolacrimal duct cysts, which are treated by endoscopic marsupialization, hemangiomas (Fig. 87.12), nasolabial cysts, and defects of the anterior neuropore that lead to dermoids, gliomas, and encephaloceles. Masses intrinsic to the nasal passageway should be approached sublabially or endoscopically if the pathology of the congenital mass is benign and medical management (including propranolol for hemangiomas) has failed (49,50). The anterior neuropore lesions all require surgical management that includes resection of the descending mass. Because a concomitant anterior skull base repair may be necessary (51,52), the opinion of an experienced neurosurgeon is valuable prior to undertaking resection of an anterior neuropore defect from a solely endoscopic approach. The management of nasal pyriform aperture stenosis and choanal atresia is described below.

Congenital Nasal Pyriform Aperture Stenosis

CNPAS is a rare anomaly that occurs secondary to bony overgrowth of the nasal process of the maxilla, and it is frequently accompanied by a solitary median maxillary central incisor (SMMCI) (53,54). While CNPAS may occur in isolation, hypertelorism, a flat nasal bridge, and the central mega-incisor are clinical features of premaxillary dysgenesis associated with holoprosencephaly (55). Pituitary disorders and dental and facial anomalies also are part of this spectrum. The pyriform aperture is the narrowest part of the nasal cavity, and small changes in the cross-sectional area significantly affect airflow. Newborns present with symptoms of snorting, gasping, and respiratory distress that are

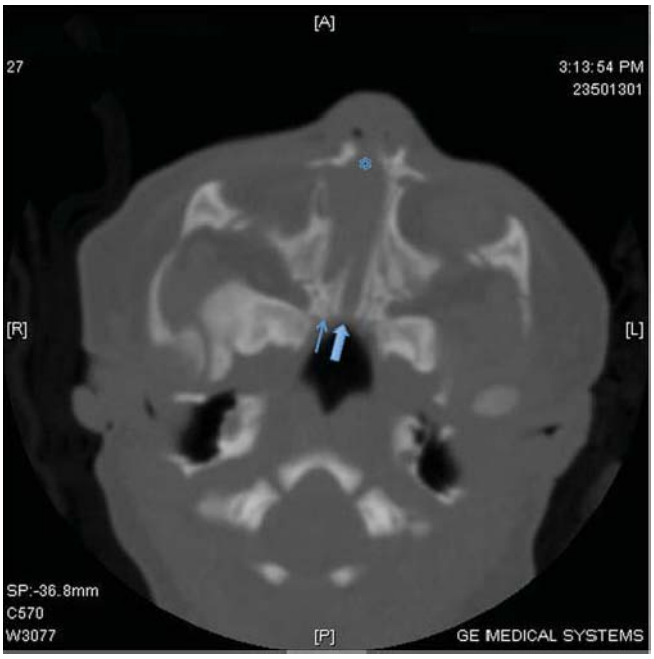


Figure 87.13 Maxillofacial CT in the axial plane without contrast demonstrating CNPAS (*asterisk*) and choanal atresia that is bony on the right side (*small arrow*) and bony-membranous on the left side (*large arrow*).

relieved by crying. Failure to pass a nasopharyngeal catheter may result in a misdiagnosis of choanal atresia. The diagnosis of CNPAS is established by physical examination and is confirmed by a maxillofacial CT (Fig. 87.13). At the level of the inferior meatus, the intermaxillary width is normally greater than 10 mm; a distance less than 8 mm strongly suggests CNPAS (56). By contrast, the height of the nasal cavity and cross-sectional area of the choana are not altered. If a SMMCI is discovered on imaging, a complete endocrine workup should be considered due to the risk of concomitant pituitary dysfunction (55). Nonoperative management begins with topical vasoconstrictive drops and/or intermittent use of a nasal trumpet. If the patient remains symptomatic, definitive repair is accomplished through a sublabial approach that exposes the inferior and lateral pyriform aperture. The bony space is enlarged with a drill, taking care to avoid damage to the maxillary tooth roots. The need for postoperative stenting up to 4 weeks is variably reported in the literature, though some stent only long enough for the skin flaps to be established again (54,57–59). As with stents placed at any level in the aerodigestive tract, granulation tissue may form beneath and at the ends of the stent. Systemic steroids, topical steroids, antibiotics, saline rinses, and mitomycin-C application are employed as indicated to reduce granulation and subsequent scar propagation.

Choanal Atresia and Choanal Stenosis

Choanal atresia results from failure of the nasobuccal membrane to recanalize in the embryonic phase of intrauterine development. The resulting atresia is either bony (around 30%) or a mixture of bony and membranous tissue (around 70%) (33). If the nasobuccal membrane recanalizes incompletely, choanal stenosis results. Two-thirds of choanal atresia is unilateral. If bilateral disease is encountered, there is a 75% chance that other congenital anomalies will be discovered, including anomalies that make up the CHARGE (coloboma, heart defect, atresia of the choana, retardation of growth and development, genitourinary anomalies and ear abnormalities) syndrome (60). Mutations in the CHD7 gene (8q12.2) cause more than half of CHARGE cases (4). Patients with unilateral choanal atresia or choanal stenosis have snorting and labored breathing that is improved with crying. The presentation of these conditions may be delayed and include mouth breathing, recurrent sinusitis, chronic rhinorrhea, otitis media, and speech problems. In contrast, bilateral choanal atresia presents at birth with agitation progressing to cyclic cyanosis that is relieved with crying. On anterior rhinoscopy, the occluded nasal cavity is typically filled with thick, tenacious secretions. The inability to pass a 6 Fr catheter beyond 3 cm into the nose raises the possibility of choanal atresia, and flexible endoscopy after suctioning confirms a blind-ending nasal passageway. A maxillofacial CT scan with axial, coronal, and sagittal reconstructions clarifies the type of atresia (bony or bony-membranous) or stenosis, the thickness of the lesion, and its relation to the overlying skull base (33,34). Specifically, a choanal space that is less than 6 mm across in the coronal plane is consistent with choanal stenosis (61). Complete blockage indicates atresia (Fig. 87.14).



Figure 87.14 Maxillofacial CT in the axial plane without contrast demonstrating right-sided choanal atresia and left-sided choanal stenosis.

Choanal stenosis may be managed with topical vasoconstrictive agents, dilation, and/or nasal trumpets, while bilateral atresia requires a formal repair. Unilateral atresia also requires formal repair, but topical vasoconstrictive agents and other less-invasive measures in the nonatretic passageway may allow unilateral atresia repair to be postponed for some time. Historically, transpalatal techniques were used to canalize the nasal passageways with a drill (62). Interference with palatal growth as well as palatal fistula is a concern with this approach. Currently, most surgeons opt for transnasal endoscopic repair whenever nonoperative measures fail—immediately for bilateral choanal atresia and within the first few months of life for unilateral atresia (63). Endoscopic repair begins with perforation of a thin portion of the atretic plate with urethral sounds, followed by sequential rigid or balloon dilation and resection of the posterior vomer. The intruding pterygoid plates, which are the lateral bony boundaries of the stenosis, may be reduced with a drill. Remaining inferior to the posterior end of the middle turbinate reduces the risk of skull base violation. Postoperative stenting for up to 6 weeks is reported in the literature (Fig. 87.15) (64–66).

Oral

Because of the heterogeneity of tissues found in the oral cavity (epithelial, salivary, dental, special sensory, muscular, and bony), congenital oral lesions take on many forms. Suprahyoid venolymphatic vascular malformations commonly affect the floor of mouth, and the treatment algorithm for such vascular malformations depends on the size of the constituent cysts and their location (64–66). A discussion of gnathic and odontogenic conditions is beyond the scope of this text. One common condition, ankyloglossia, and one representative mass, lingual choristoma (foregut duplication cyst), are examined below.

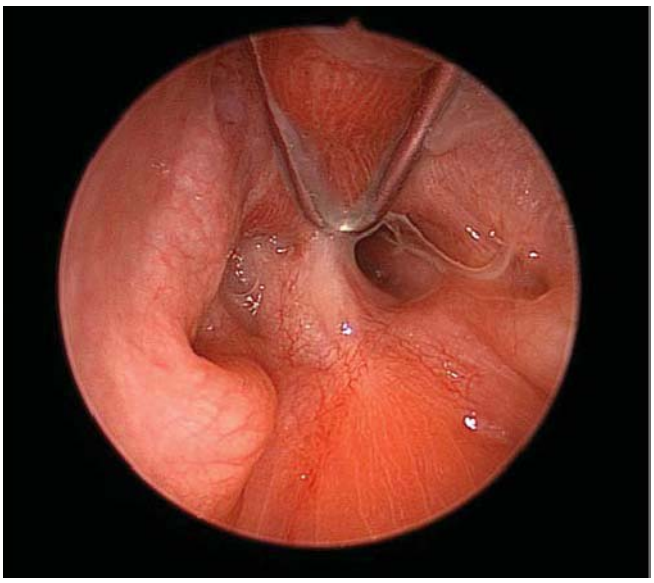


Figure 87.15 A 120-degree endoscopic view of the atretic choana in the same patient.

Ankyloglossia

Ankyloglossia, or tongue-tie, is a first branchial arch anomaly that results from persistence of the embryologic band connecting the anterior tongue with the medial surface of the developing mandible (67). A variation of ankyloglossia known as "posterior tongue tie" represents a densely adherent genioglossus. In this case, the problem is posterior and submucosal to the typical thin anterior band causing tongue restriction. Symptoms of ankyloglossia are poor feeding, particularly breastfeeding, in infancy and articulation problems in childhood. Respiratory symptoms are nil. The diagnosis is made by lifting the tongue from the floor of mouth and pulling it forward. If the tongue cannot protrude at least 2 mm beyond the mandibular alveolar ridge (or mandibular incisors) and/or if the tongue cannot contact the palate, treatment is warranted (5). A posterior tongue-tie is diagnosed by palpating the ventral midline tongue attachment for a dense, shortened band anchoring the tongue to the floor of mouth in an infant with feeding difficulty. In the neonate or young infant, a frenulectomy is performed at the bedside or in the office with proper patient restraint. Local anesthetic can be topically applied (benzocaine jelly) and infiltrated into the midline floor of mouth and midline ventral tongue (0.5% lidocaine with epinephrine 1:200,000). The frenulum is cross-clamped with a straight hemostat and sharply divided. Some surgeons will suture the wound. A posterior tongue-tie is treated by cross-clamping the tight band on the ventral tongue. The band is divided by dissecting into the ventral attachment until the tongue becomes mobile and a diamond-shaped wound is produced (68,69). Recurrence of ankyloglossia is relatively rare.

Lingual Choristoma

Lingual choristomas are sometimes termed "foregut duplication cysts," and the variable lining of the cysts may belie a heterogeneous origin (5,70). When gastric mucosa is found within the cyst, the pathophysiology may be heterotopic gastric tissue buried within the developing tongue (71). Alternatively, several authors propose that lingual choristomas are a duplication of the foregut with early arrest in development and secondary incorporation by the tongue. The cysts from two patients analyzed by Burkart et al. (72) were lined by a squamous epithelium with foci of dermal appendages and lymphatic tissue that pointed to a branchial origin, recalling that the tongue is formed anteriorly by fusion of first arch mesenchyme and posteriorly by arches 2 to 4. The symptoms and signs of lingual choristoma are those of any lingual mass, and the differential includes dermoid cyst, lymphatic or venolymphatic vascular malformation, hemangioma, teratoma, mucocele, ranula, epidermoid cyst, and lymphoepithelial cyst (70). The mass may produce symptoms ranging from

none to obstruction of the oral cavity with inability to handle secretions and poor suck–swallow–breathe coordination. On physical exam, the tongue may demonstrate a mass or submucosal asymmetry. Large masses force the tongue posteriorly and superiorly toward the oropharynx. Movement may be impaired. Flexible nasopharyngoscopy is important to delineate any concomitant oropharyngeal obstruction or glossoptosis that may alter airway management, and a nasal trumpet will offer significant relief in these circumstances. The oral cavity lends itself to physical diagnosis, but for any deep mass a contrast-enhanced CT or MRI provides the necessary anatomical detail. Lingual choristomas are fluid filled and concentrate contrast on CT or appear bright on T2 weighted MRI (Fig. 87.16) (39,72). The management of most lingual masses is surgical, although macrocystic lymphatic malformations are amenable to sclerosis (73). Choristomas always are managed surgically to correct the anatomical defect to confirm benign pathology. If the lingual mass effect is significant, flexible transnasal intubation in the operating room is a convenient means to secure the airway. Most oral tongue choristomas occur near the ventral reflection of the tongue onto the floor of mouth, and the incision is placed at this reflection (72). Midline masses may be approached through a midline glossotomy. In all approaches, care must be taken to avoid damage to the lingual nerve, the submandibular duct, and the lingual artery on either side of midline. The prognosis is good for a fully excised lingual choristoma.

Oropharyngeal

Vallecular cysts, lingual thyroid tissue, and lingual thyroglossal duct cysts are fairly common congenital oropharyngeal lesions. Teratomas, vascular malformations, and hemangiomas have been described here as well (74). Because most congenital oropharyngeal lesions exert mass effect, all require some operative treatment with the exception of a small to moderate sized hemangioma, which might respond satisfactorily to propranolol or other systemic therapy (49). Prior to resecting lingual thyroid tissue, a careful investigation should be made for the presence of thyroid tissue in the neck (75,76). The management of vallecular cysts is detailed below.

Vallecular Cyst

Vallecular cysts are mucus retention (pseudo)cysts or, more commonly, respiratory epithelium-lined cysts that develop in the vallecular space in infancy (41). The most common presenting signs and symptoms are stridor or respiratory distress, or both, because the mass is forcing the epiglottis into the laryngeal inlet. The anterior–posterior dimension of the tongue base is functionally enlarged and less sensate, and dysphagia and aspiration are common findings. Respiratory distress also leads to feeding difficulties (41,77). Flexible nasopharyngoscopy is the simplest means to diagnose a vallecular cyst. From this vantage, a slightly eccentric, smooth, yellowish, bluish, or gray mucosalized mass is seen in the vallecular space (78). When the

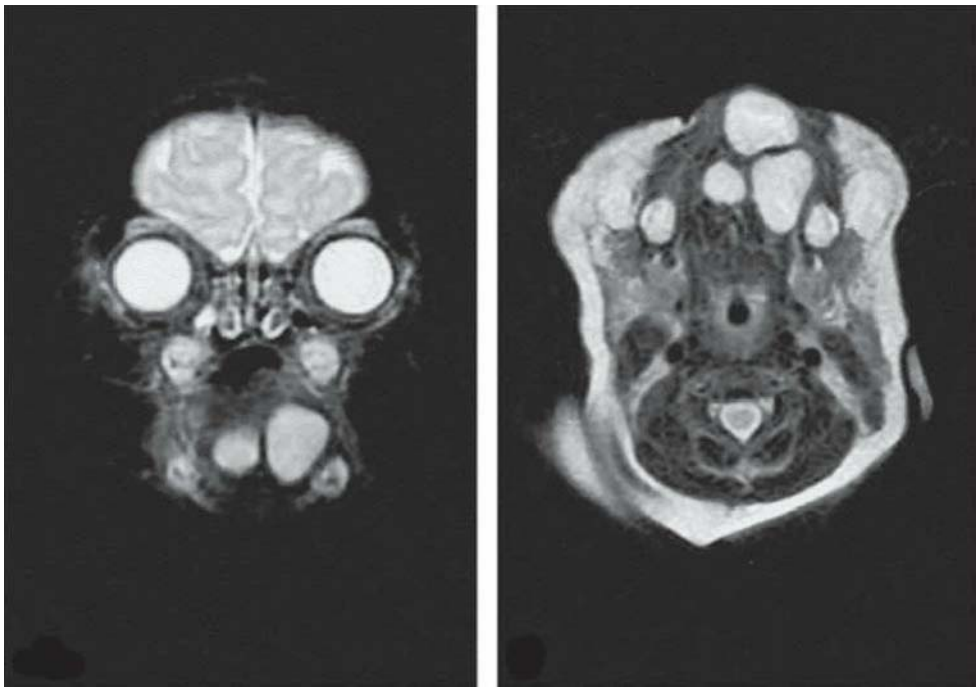


Figure 87.16 Coronal and axial T2-weighted MRI depicting a multicystic lingual choristoma involving the left portion of the tongue. From Burkart CM, Brinkman JA, Willging JP, Elluru RG. Lingual cyst lined by squamous epithelium. *Int J Pediatr Otorhinolaryngol* 2005;69(12):1649–1653, with permission.

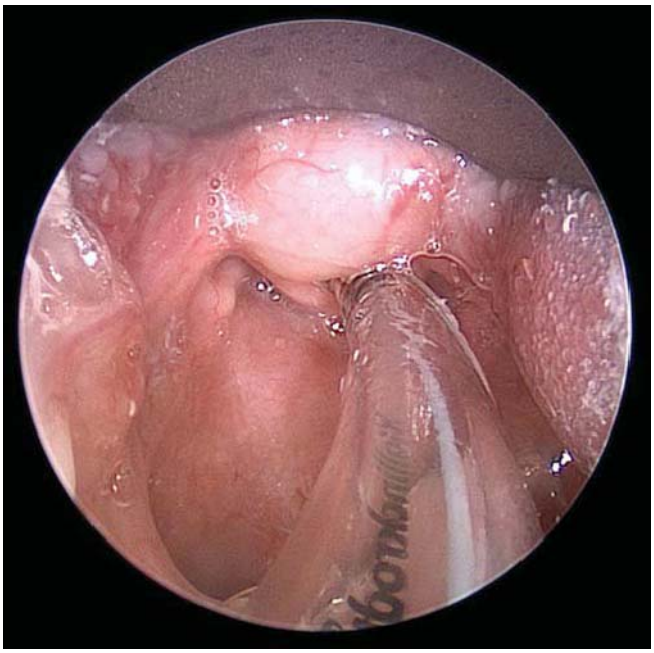


Figure 87.17 Endoscopic view of a vallecular cyst in an infant seen at intubation.

diagnosis is certain, radiologic exams are unnecessary. Sagittal CT or MRI is sensitive, specific, and useful to image recurrent lesions. Rigid endoscopy in the operating room is essential. It confirms the diagnosis and provides a safe means of securing the airway, which is often deranged by the cyst (Fig. 87.17). Because vallecular cysts drive the epiglottis posteriorly to occlude the endolarynx, intubation can be difficult. Definitive management requires surgical excision or marsupialization (41,77,78). Simple needle aspiration is associated with an unacceptably high risk of recurrence but may be necessary acutely if respiratory distress develops, especially during induction of anesthesia.

Hypopharyngeal and Laryngeal

The most common causes of stridor in the newborn are frequently listed as laryngomalacia, vocal fold immobility, and congenital subglottic stenosis. The onset of symptoms attributable to laryngomalacia usually begins a few weeks after birth. With appropriate gastroesophageal reflux disease (GERD) management and time, most patients do not require surgical treatment (26). When supraglottoplasty is indicated to resolve laryngomalacia, a variety of techniques exist including a laser, microlaryngeal instruments, or a microdebrider. Overall, results are good. Vocal fold immobility may be unilateral or bilateral. In the patient who fails expectant management (including GERD therapy), treatment depends on two factors (a) the type of immobility present—neurologic (including paralysis associated with Arnold-Chiari malformations) (79), cricoarytenoid joint fixation or restriction secondary to interarytenoid scarring, and (b) whether the immobility is unilateral or bilateral.

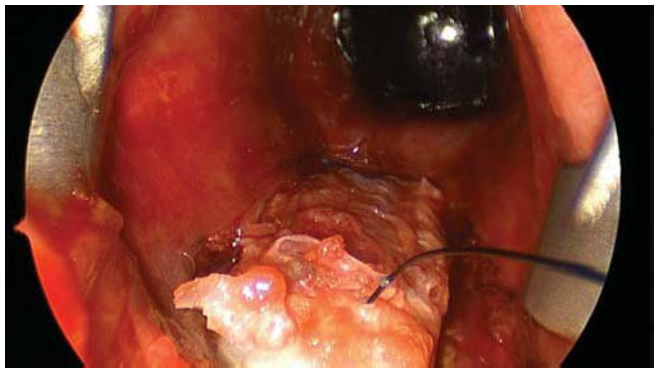


Figure 87.18 Endoscopic view of a posterior costal cartilage graft being placed endoscopically to relieve posterior glottic stenosis. The blue suture is a control suture that remains attached until the graft is placed and requires no additional manipulation.

Bilateral vocal fold immobility is the most symptomatic, and definitive management includes endoscopic cordotomy, arytenoidectomy or arytenoidopexy (endoscopic or open), vocal fold lateralization, or posterior glottic cartilage grafting (with endoscopic or open graft placement) (Fig. 87.18) (80–83). Congenital subglottic stenosis is one-tenth as common as acquired subglottic stenosis. In symptomatic patients, endoscopic incision and balloon dilation is usually attempted first (84), with anterior and/or posterior cartilage grafting or cricotracheal resection reserved for difficult or refractory stenoses (85). Subglottic hemangiomas can cause stridor in an infant, and frequently the subglottis is intrinsically narrow in these patients, even after resolution of hemangiomatous disease. Propranolol has emerged as an initial therapy for subglottic hemangiomas (12,86,87). Other therapies include submucosal injection of steroids, systemic steroids, laser ablation, and open excision with concomitant laryngotracheoplasty. Any congenital laryngeal anomaly that results in significant morbidity may be managed initially with a tracheotomy until other treatment options are appropriate. Additional consideration is given below to the management of laryngeal clefts and webs.

Laryngeal Cleft

Complex folding and inward movement of lateral mesodermal ridges from inferior to superior separates the trachea from the esophagus. Superior arrest leads to a laryngotracheoesophageal (laryngeal) cleft. This anomaly may occur in isolation or in association with other anomalies, such as Pallister-Hall syndrome (88), Opitz-G syndrome (88), and VATER/VACTERL association (12,89). Laryngeal clefts produce aspiration secondary to a persistent channel between the esophagus posteriorly and the airway anteriorly during swallowing. If the cleft margins are composed of floppy excess mucosa, some degree of airway obstruction results. Voicing may be impaired from turbulent airflow and from accumulation of secretions around the glottis. Flexible laryngoscopy usually demonstrates medialized

arytenoids with a suspicious trough between them, but rigid microlaryngoscopy and bronchoscopy are required to diagnose a laryngeal cleft. In this setting, the interarytenoid space can be spread and palpated. The distal extent of the cleft can be measured. Static radiographic examinations add nothing to the diagnosis of a laryngeal cleft, but a VFSS is indispensable. This examination diagnoses aspiration secondary to laryngeal incompetence as well as other levels of swallowing dysfunction and determines what consistencies may be taken safely by mouth. In a patient with chronic aspiration, a high-resolution chest CT may demonstrate bronchiectasis. Laryngeal clefts are categorized most commonly using the Benjamin-Inglis Classification (90), where a type I cleft constitutes a deep interarytenoid notch without posterior cricoid involvement; type II clefts extend into but not through the cricoid; type III clefts extend through the cricoid plate and into the cervical trachea, and type IV laryngeal clefts extend into the thoracic trachea or even into a bronchus. Management of type I and type II laryngeal clefts begins with GERD treatment and dietary modification to produce feedings of an appropriately thick consistency. When dietary modification fails or with type III (Fig. 87.19) or type IV clefts, operative management is required (91–93). Some authors report that good temporary disease control with type I laryngeal clefts can be achieved with gelfoam injection into the posterior interarytenoid space (94). Endoscopic suture closure of the cleft may be attempted if the patient does not have concomitant subglottic stenosis or other airway limitation. Other contraindications for endoscopic repair include low birthweight newborns, individuals with craniofacial anomalies, especially micrognathia, and clefts that extend beyond the second tracheal ring (93). Open surgical management through an anterior tracheal split and laryngofissure approach is appropriate for any cleft repair, but it is necessary for a cleft that is too difficult to expose endoscopically or one that is particularly deep. Type IV clefts are extremely rare, and repair is performed on extra-corporeal membrane oxygenation (ECMO) or cardiopulmonary bypass. In these circumstances, ECMO is superior because it can be maintained for 3 to 4 days postoperatively if tracheal swelling precludes intubation. Regardless of the type of cleft, a two-layered closure is desirable (91–93).

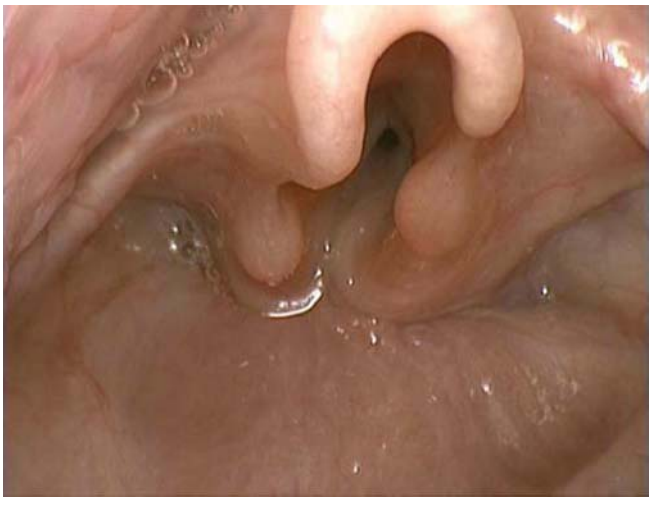


Figure 87.19 Endoscopic photograph of the supraglottic larynx in an infant with a type III laryngeal cleft.

Laryngeal Web

The epithelial lamina of the larynx recanalizes to open into the laryngeal cecum and allows the pharyngoglottic duct to unite with the cecum, thus forming the vestibule and the interarytenoid notch/posterior glottis. Failure of laryngeal recanalization leads to various degrees of laryngeal atresia. Complete atresia comprises the upper anatomical limit of the congenital high-airway obstruction syndrome (CHAOS), but milder versions result in a canalized posterior glottic airway with an anterior glottic web. Miyamoto et al. (95) established an association between velocardiofacial syndrome (22q11 deletion) and anterior glottic webs. Because the subglottic airway bounded by the cricoid cartilage is part of this obliteration/recanalization progression, a laryngeal web often is associated with an elliptical and congenitally stenotic cricoid. The patient presents with inspiratory or biphasic stridor, retractions, a high-pitched or breathy voice, and difficulty feeding due to respiratory limitation. Flexible laryngoscopy may detect a web if a good view of the anterior commissure is achieved. Conventional x-rays alert the physician to concomitant tracheal abnormalities, but for isolated laryngeal webs, imaging adds little. Rigid microlaryngoscopy and bronchoscopy allows for definitive diagnosis. Important considerations at laryngoscopy include the location and thickness of the web and any concomitant airway pathologies, such as congenital subglottic stenosis. When the patient has failed conservative measures, including feeding adjustments and GERD treatment, laryngeal webs merit operative management. A variety of endoscopic and open techniques have been described. Most authors agree that some sort of stent or keel is required after division of the web to keep opposing raw surfaces separated while healing takes place. This usually requires a double staged approach (i.e., the patient has a tracheostomy). However, several reports exist of endoscopic flap rotation with suture fixation and no stenting or endoscopic division with the use of a nonobstructive stent, such as silastic sheeting sutured anteriorly through the thyroid cartilage (96,97). Success is higher with thinner (gossameric) webs regardless of the technique. Thick webs that extend inferiorly into a stenotic cricoid may benefit from concomitant anterior and/or posterior cartilage graft laryngotracheoplasty, as glottic/subglottic webs or stenoses greater than 1 cm in length usually respond poorly to endoscopic incision and dilation alone. It should be noted that CHAOS syndrome in patients with complete laryngeal atresia increasingly is being diagnosed prenatally, and EXIT tracheotomy is lifesaving (22,98).

Tracheobronchial and Esophageal

Relatively common congenital tracheal conditions include tracheomalacia, a tracheal bronchus (pig bronchus) and TEF (99). Congenital tracheal stenosis secondary to complete tracheal rings is rare, but its management principles and techniques can be applied to a variety of tracheal lesions. Pfeiffer syndrome is associated with a cartilaginous "sleeve trachea," which represents a unique type of congenital tracheal stenosis (100). TEF and congenital tracheal stenosis are considered below.

Tracheoesophageal Fistula

Folding and inward movement of the lateral mesodermal ridges between the anterior foregut and the developing airway creates the posterior wall of the trachea that separates it from the esophagus (16). Errors in this mesodermal partitioning may result in a TEF or a laryngeal cleft, or both. In most circumstances, the development of a TEF coincides with failure of caudal development of the esophagus, and 95% of patients with a TEF have esophageal atresia (EA). Up to 60% of patients with TEF/EA have other anomalies (89), and these may be due to a genetic syndrome (such as CHARGE syndrome, Pallister-Hall syndrome, trisomy 18) or a nonsyndromic cause (such as the VACTERL association) (89). The symptoms of TEF/EA depend on the type of anomaly. Five anatomical configurations are commonly described: EA with distal TEF (84%), EA alone (8%), TEF alone (H-type TEF) (4%), EA with proximal and distal TEF (3%), and EA with proximal TEF (1%) (101) (Fig. 87.20). Infants present at birth with copious oral secretions, coughing, gagging, cyanosis, vomiting, and possibly respiratory distress. Only the H-type TEF may remain occult until recurrent episodes of aspiration pneumonia lead to diagnosis. Flexible laryngoscopy to the level of the vocal folds rules out most laryngeal etiologies of aerodigestive tract dysfunction. Today, TEF/EA may be suspected prenatally on ultrasound if a distended esophageal pouch is seen alongside polyhydramnios and the absence of a fluid filled stomach (102). Fetal MRI may be used to confirm the diagnosis (102). Postnatally, classic imaging findings on plain x-ray are a nasogastric tube coiled in the proximal esophageal pouch and a trachea that is compressed and deviated. The absence of a gastric bubble may suggest EA without TEF or EA with a proximal TEF. High-resolution CT scanning with 3-D reconstructions clarifies the anatomy (103). Rigid endoscopy greatly aids in the diagnosis of an H-type fistula, and both the trachea and the esophagus must be examined in the same setting to look for a tracheal mucosal mound, esophageal polyp, and other signs of distal airway inflammation. The initial management of TEF/EA includes placement of a suction catheter to prevent the collection of oral secretions, elevation of the head of the bed, and total parenteral nutrition. Most non-H-type TEFs are repaired along with the EA within the first few days of life. The mobilized atretic esophagus is anastomosed, and the TEF is closed, leaving a long pouch of mucosa on the trachea. Occasionally these tracheal pouches may become symptomatic, collecting secretions or trapping the tip of a tracheostomy tube. Symptomatic tracheal pouches may be endoscopically divided (104). Likewise, endoscopic techniques exist to close recurrent TEFs, possibly obviating the need for a repeat thoracotomy (Fig. 87.21). The tracheomalacia associated with TEF/EA usually resolves with time. If not, tracheomalacia may be managed with tracheotomy with or without pneumatic stenting (positive pressure ventilation). Aortopexy is reserved for specific mid-to-distal focal, pulsatile tracheomalacia that is caused by innominate artery or aortic compression (105).

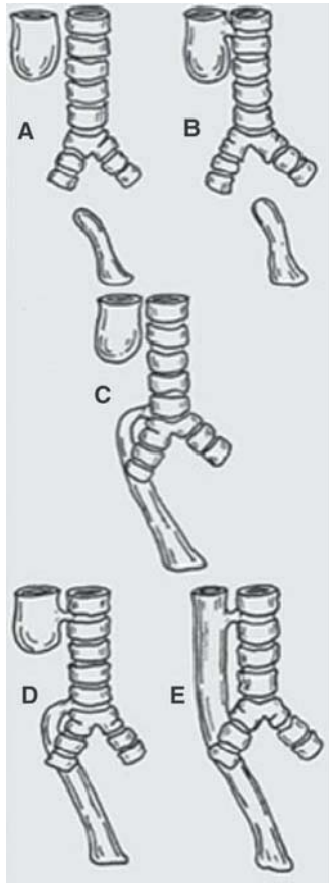


Figure 87.20 Gross classification of EA with and without TEF. The incidence of each type is: (**A**) EA alone (8%); (**B**) EA with proximal TEF (1%); (**C**) EA with distal TEF (84%); (**D**) EA with proximal and distal TEF (3%); (**E**) TEF alone (H-type TEF) (4%).

Congenital Tracheal Stenosis

In the carefully coordinated division of the trachea from the esophagus, contrasting molecular mechanisms are promoting tracheal cartilage development anteriorly and laterally and suppressing it posteriorly. Errors in these molecular mechanisms result in the formation of complete tracheal rings, also known as congenital tracheal stenosis. Infants demonstrate respiratory distress at birth. Breath sounds are characteristically wet in both inspiratory and expiratory phases. Feeding is difficult due to respiratory distress. On occasion, patients with congenital tracheal stenosis have an adequate tracheal airway despite the complete

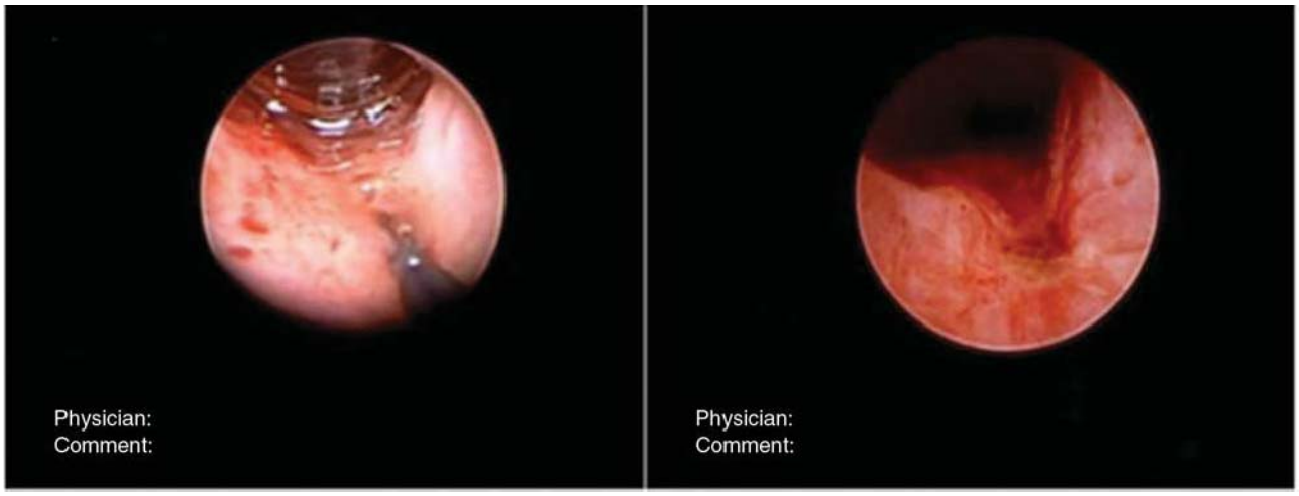


Figure 87.21 Endoscopic photo depicting repair of a recurrent TEF using fulguration, followed by the application of fibrin glue.

tracheal rings, and the ultimate diagnosis remains elusive for months or years (106). Flexible laryngoscopy rules out laryngeal causes of stridor and respiratory distress. If the endoscopist obtains an open glottic view, a stenotic trachea may be visualized. High-resolution scanning with CTA that includes 3-D reconstruction is a useful tool to diagnose the presence of congenital tracheal stenosis (Fig. 87.22), the length of the segment involved (including any bronchial involvement), and presence of concomitant mediastinal vascular anomalies, such as a left pulmonary artery sling. Rigid microlaryngoscopy and bronchoscopy provides a definitive diagnosis. Extreme care must be taken when performing rigid bronchoscopy on a congenitally stenotic trachea. The lumen is often extremely small, and any abrasion from the bronchoscope or telescope can lead to mucosal swelling, tracheal occlusion, and respiratory embarrassment (Fig. 87.23). An incomplete evaluation is preferable to a bad outcome. Goals of endoscopy are to identify the extent and location of the stenosis, the narrowest point in the airway, the diameter at this point and whether any other airway anomalies are present simultaneously, such as a right upper lobe tracheal (pig) bronchus. When the patient's condition demands repair, complete tracheal rings that involve the thoracic trachea require sternotomy. ECMO or cardiopulmonary bypass support gas exchange during repair. Various tracheal repair techniques have been described, including pericardial patch tracheoplasty, long-segment costal cartilage grafting, primary resection and anastomosis, tracheal autograft, and slide tracheoplasty (Fig. 87.24) (107). The latter technique has become the preferred method at experienced centers (48,107,108). Slide tracheoplasty results in a trachea that is half the length and twice the diameter of its



Figure 87.22 3-D coronal CT rendering of a trachea with complete tracheal rings leading to tracheal stenosis.



Figure 87.23 Endoscopic view of the same patient at the level of the glottis. The subglottis was spared, but the first tracheal ring is stenotic.

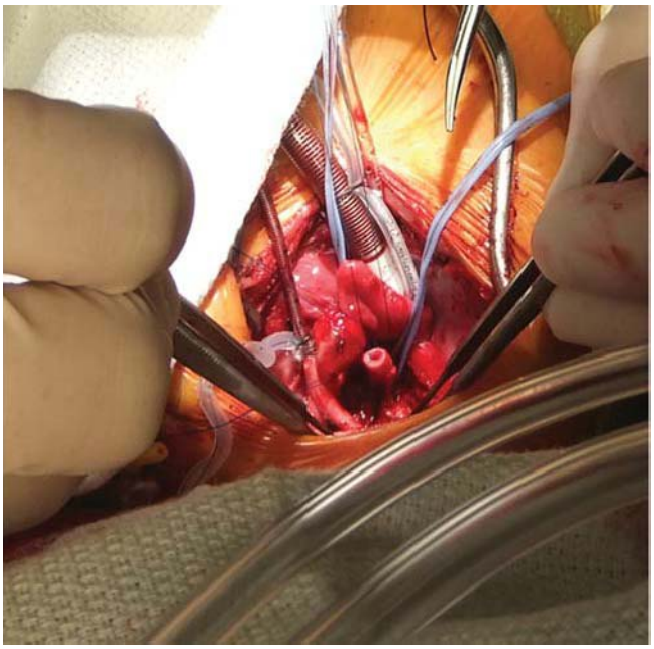


Figure 87.24 Intraoperative photos of the same patient's trachea at transection.

preoperative state (Fig. 87.25) (109,110). The anastomosis is distributed over most of the trachea. As a consequence, focal restenosis is rare, but a "figure of 8" deformity is common. Symptomatic deformities may be managed at surveillance endoscopy with some combination of balloon dilation or laser ablation of infolding tissue.

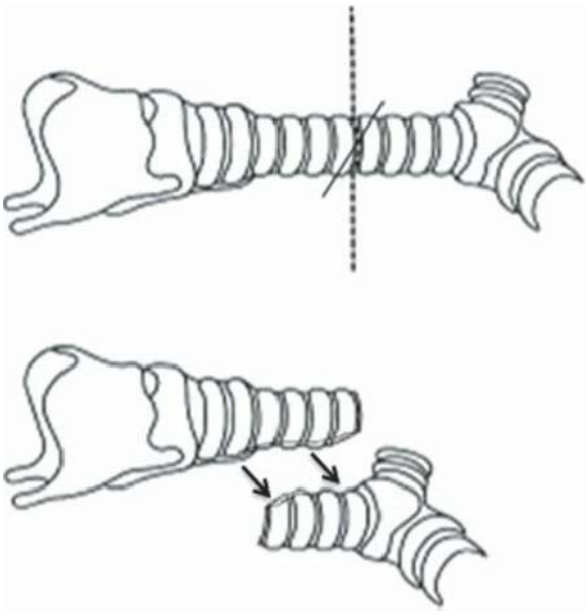


Figure 87.25 Illustration of the slide tracheoplasty technique. The trachea is transected (*dashed line*) at the midpoint of the stenotic segment. A bevel is applied to the upper and lower segments. In this illustration, the posterior wall of the upper segment is incised in the midline through the stenotic portion. The anterior wall of the lower segment is similarly incised, and the two segments are overlapped at anastomosis. Variations of the anterior and posterior tracheal incisions are possible. From Rutter MJ, Cotton RT, Azizkhan RG, et al. Slide tracheoplasty for the management of complete tracheal rings. *J Pediatr Surg* 2003;38(6):928–934, with permission.

SUMMARY

Taken in their broadest sense, congenital aerodigestive tract anomalies are relatively common. The aerodigestive tract is charged with feeding, breathing, and voicing, and seemingly isolated anatomical abnormalities produce significant morbidity in the affected individual. Because of this, history and physical examination alone constitute an incomplete workup. The treating physician must be familiar with the appropriate use of flexible endoscopy, imaging, and rigid endoscopy to arrive at the diagnosis as well as to stage dysfunction in other areas of the aerodigestive tract. Undiagnosed comorbidities remain untreated, and untreated comorbidities confound healing after a definitive repair of an aerodigestive tract anomaly. Many centers are increasingly adapting a multidisciplinary model of aerodigestive disease diagnosis and treatment, believing that in the management of these varied and interrelated conditions, many heads are better than one.

HIGHLIGHTS

- Taken as a whole, congenital aerodigestive tract anomalies are relatively common.
- The responsibilities of the aerodigestive tract include feeding, breathing, and voicing, and aerodigestive tract anomalies frequently produce symptoms that involve all three basic functions.
- Flexible and rigid endoscopy and selected radiographic examinations are frequently required to augment a careful history and physical examination in the diagnosis of congenital aerodigestive tract disease.
- The beneficial effects of treatment of an aerodigestive tract anomaly must be weighed against the impact that treatment will have on feeding, breathing, and voicing.
- Modern aerodigestive disease diagnosis and treatment frequently takes place within a multidisciplinary model, combining the expertise of the otolaryngologist with pulmonologists, gastroenterologists, speech pathologists, and other aerodigestive-related practitioners.

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88 Neonatal Respiratory Distress

Mark Boston

Respiratory distress occurs in up to 8% of newborn infants and may be manifested by tachypnea, increased work of breathing, nasal flaring, use of accessory muscles of respiration, inspiratory retractions, and cyanosis. Cardiopulmonary problems are the most frequent reasons for neonatal respiratory distress. Sepsis, hypoglycemia, hematologic and metabolic abnormalities, central hypoventilation, and airway obstruction may also cause respiratory distress in the neonate (1).

Congenital upper airway anomalies are rare but can cause significant respiratory distress during the neonatal period (2). Dynamic or fixed obstruction anywhere from the nose and mouth to the tracheobronchial tree may result in respiratory distress. The signs and symptoms of neonatal airway obstruction include noisy breathing (stridor or stertor), feeding difficulties, sternal and intercostal retractions, tachypnea, hypercarbia, hypoxia, cyanosis and, in severe cases, apnea, bradycardia, and cardiac arrest. While the signs and symptoms are often characteristic of the site of obstruction—nasal, oropharyngeal, laryngeal or tracheobronchial—significant overlap exists among the anatomic sites and their presenting symptoms. Therefore, a thorough evaluation of the distressed neonate is essential and includes a detailed history and physical and directed endoscopic, radiographic, and laboratory studies.

ANATOMY AND PHYSIOLOGY

The unique nature of the infant airway must be appreciated in order to appropriately evaluate and manage neonatal respiratory distress. The neonatal larynx is situated high in the neck between the second and fourth cervical vertebrae and forms an obtuse angle with the mandible. The high position of the larynx brings the tip of the epiglottis into contact with the soft palate, making the neonate an obligate nasal breather. The neonatal larynx is softer, collapses easily with higher negative airway pressures, is easily irritated, and is more prone to laryngospasm than is the adult larynx. Laryngeal spasm may result in bronchial constriction, apnea, and bradycardia with life-threatening consequences. Neonates also have small-caliber airways with high resistance, low lung compliance, high chest wall compliance, low oxygen reserve, and high oxygen consumption. As a result, neonates do not tolerate diminished ventilation or apnea for more than a few seconds without developing significant hypoxemia. Therefore, during endoscopic evaluation of the neonatal airway, diligence is required with respect to the appropriate depth of anesthesia, topical anesthesia of the larynx, gastric distention, and blood oxygen saturation monitoring.

EVALUATION

When presented with a neonate in respiratory distress, the physician must first decide if the airway needs to be emergently managed or if he or she can proceed with a detailed history and physical exam (Fig. 88.1). The physician should be able to determine if urgent airway intervention is required within a few seconds by carefully observing the child's level of consciousness, coloring, respiratory effort and listening for airway noise. With a stable or stabilized airway, the assessment may continue in order to determine the specific etiology of the airway obstruction. In all cases of neonatal airway distress, the history must include a detailed accounting of the pre- and perinatal histories, family history, onset and timing of airway noise, associated feeding difficulties, and the presence or absence of other associated signs and symptoms. Examination may follow the history or proceed simultaneously with active airway management in the severely distressed neonate.

The history, time of onset, and identification of initiating factors are helpful in the search for the cause of stridor in the neonate. The effects of positioning, feeding, or crying offer further diagnostic clues. A history of prematurity, difficult

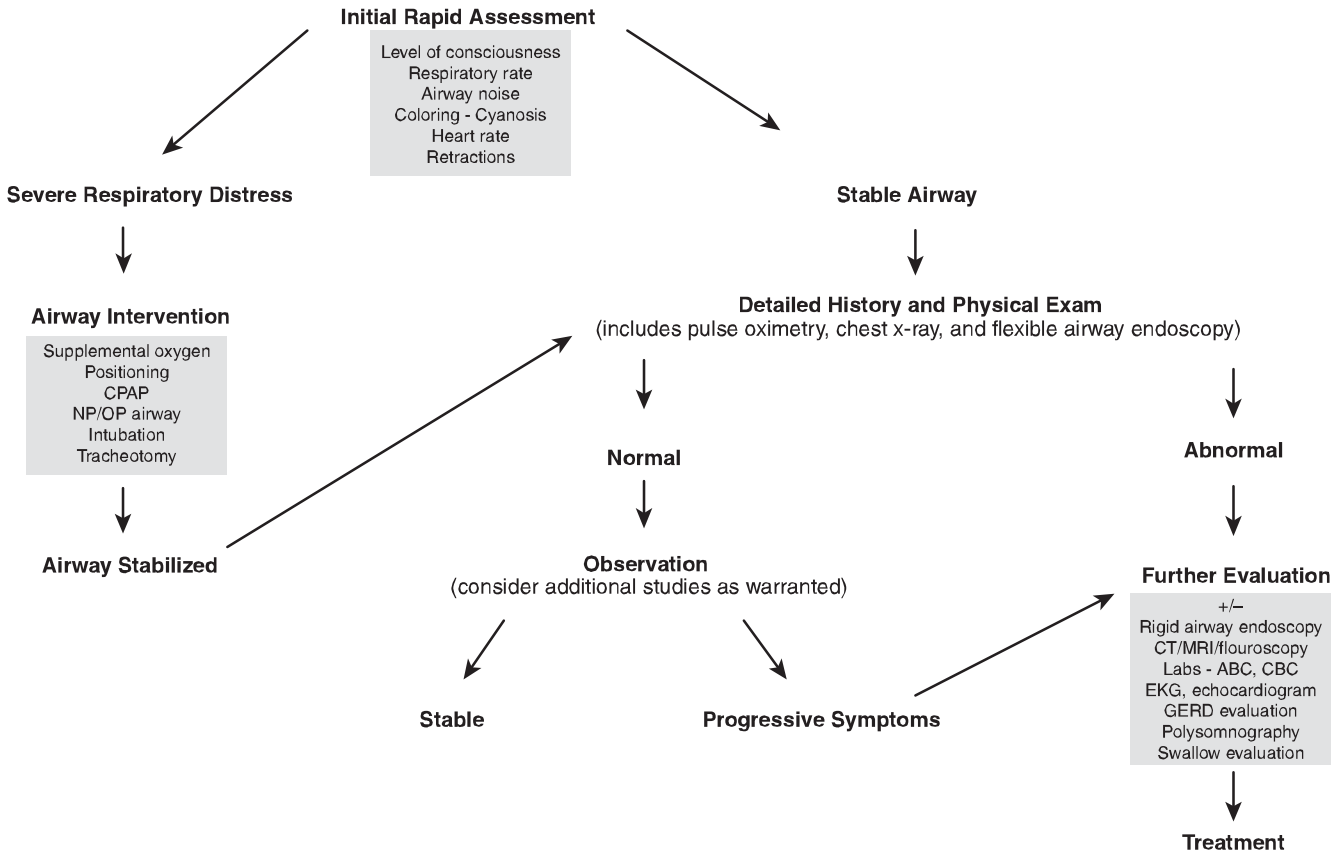


Figure 88.1 Algorithm for the evaluation and treatment of neonatal airway obstruction.

labor or delivery, or intubation may be contributory. The quality of stridor and its relationship to the respiratory cycle offer valuable diagnostic clues as does the character of the newborn's cry and the presence of dysphagia or a cough. The neck and lungs should be auscultated and, after completing the history and general physical examination, the airway should be examined endoscopically.

Flexible endoscopy using a pediatric flexible laryngoscope should be performed in all neonates with suspected airway obstruction. Care must taken, however, to ensure that the patient is stable for the exam and that the procedure will not exacerbate the airway problem. The pediatric flexible laryngoscope is used to assess the nose, nasopharynx, oropharynx, and larynx to the glottis and the upper hypopharynx. However, the pyriform sinuses, posterior cricoid region, and subglottis cannot be consistently examined with this technique. Whenever possible, the study should be performed with a camera attachment and recorded for documentation and review. Application of a topical nasal decongestant may be helpful, but the routine use of topical anesthesia is not necessary (3).

Not all neonates with suspected congenital airway obstruction need undergo rigid endoscopic examination under anesthesia if the diagnosis can be obtained confidently by a combination of flexible endoscopy and/or radiographic studies; however, if patients show a progression of symptoms marked by increasing respiratory distress or failure to thrive, microlaryngoscopy, bronchoscopy, and esophagoscopy are indicated for both diagnostic and therapeutic reasons.

Continuous pulse oximetry monitoring and a chest radiograph are standard for all neonates in respiratory distress (1). Additional studies are directed based on the history, general physical examination, endoscopic examination, and radiographic findings. In patients with suspected tracheomalacia, videofluoroscopy helps delineate the full extent of luminal collapse and diaphragmatic excursion (4). A contrast esophagogram can be useful in the diagnosis of tracheoesophageal fistulae, esophageal stenosis, and vascular anomalies or rings that cause extrinsic compression. Detailed information regarding airway stenosis, mass lesions, or thoracic vascular abnormalities may be provided by computed tomography (CT) or magnetic resonance imaging (MRI) (5). An echocardiogram and electrocardiogram are useful to assess for cardiac abnormalities and possible cardiac strain. An evaluation for gastroesophageal reflux disease (GERD) will be appropriate in selected patients and may include a pH probe study, esophagoscopy with biopsies, barium swallow, or esophageal scintiscan. When aspiration is suspected, a functional endoscopic evaluation of swallowing (FEES) may be useful.

After the diagnosis has been obtained, a treatment plan is instituted. In the patient with progressive respiratory distress but no identified airway obstruction, the physician should consider pulmonary, cardiac, central nervous, gastrointestinal, iatrogenic, or metabolic–nutritional causes of respiratory failure. If there is an upper airway abnormality, bypassing the obstruction should relieve the symptoms of respiratory distress. With coexisting pulmonary pathology, however, the patient may remain symptomatic with tachypnea, hypoxemia, and hypercarbia, and require ventilatory assistance. When upper airway pathology has been eliminated as a cause of the patient's respiratory distress, the neonatologist should assume primary management of the patient.

NOSE

Because infants are initially obligate nasal breathers, nasal obstruction frequently causes severe respiratory distress in neonates. Nasal obstruction typically results in stertor, a sonorous or snorting type of respiration, with nasal flaring. With complete nasal airway obstruction (e.g., bilateral choanal atresia) cyanotic episodes are frequent and may be alleviated during crying, a phenomenon known as cyclical cyanosis. Chest retractions are common and feeding is difficult because patients must breathe and feed through their mouths at the same time. Severe respiratory distress due to nasal obstruction should be managed with an oral airway or intubation prior to completing the history and examination.

Examination begins with an external assessment of the nose and surrounding facial structures. Small pits or dimples along the midline of the nose suggest a nasal dermoid (6). These may be found from the nasal dorsum to the columella. Similarly, a midline nasal mass may represent a cephalocele, glioma, teratoma, or extension of an intracranial vascular anomaly. Craniofacial anomalies, including Treacher Collins, Crouzon, and Apert syndromes, may present with nasal obstruction, and recognition of these anomalies should direct the examination to the nose and nasopharynx (7). Large intranasal hemangiomas or vascular malformations may also cause respiratory distress and may cause distortion of the external nose.

After the external assessment, a thorough intranasal examination should be undertaken. The most common cause of neonatal nasal airway obstruction is neonatal rhinitis. The patient with neonatal rhinitis typically presents with stertor and feeding difficulties. Examination reveals diffuse nasal mucosal edema and turbinate hypertrophy with a normal pyriform aperture and patent choanae. Treatment includes the use of nasal saline drops and or 0.1% dexamethasone ophthalmic drops into both nostrils for several days. GERD may also contribute to neonatal rhinitis and should be treated if suspected based on the history and physical examination.

Anterior nasal stenosis is uncommon, but obstruction at the level of the pyriform aperture secondary to medial overgrowth of the maxilla may cause distress. Airway distress may be especially prominent if there is associated turbinate hypertrophy. Examination of the intranasal structures with a flexible nasopharyngoscope or rigid telescope can identify the cause of obstruction. Inability to pass an endoscope through the anterior nose due to narrowing of the nasal fossa should alert the clinician to the possibility of pyriform aperture stenosis. Although rare, pyriform aperture stenosis can be associated with a single upper central incisor or other craniofacial dysmorphology (8,9). The inferior meatus should be examined carefully for nasolacrimal duct cysts (Fig. 88.2). Passing the nasopharyngoscope more posteriorly allows examination of the posterior choanae and nasopharynx. If choanal atresia is suspected because of the inability to pass either a nasopharyngoscope or a small feeding tube more than 5.5 cm from the alar rim, CT evaluation is appropriate (Fig. 88.3) (10,11). Children with either pyriform aperture stenosis or choanal atresia should be assessed by a geneticist because of a high incidence of concomitant craniofacial and developmental anomalies (e.g., CHARGE syndrome) (10). Adenoid hypertrophy or a nasopharyngeal tumor also may be identified as a cause of nasal airway obstruction.

Radiographic assessment of neonates with nasal obstruction is often necessary, and CT is the preferred study for most cases of neonatal nasal obstruction. In some conditions, however, including midline nasal masses with potential intracranial connections, MRI may also be indicated (6). Consultation with a pediatric neuroradiologist is recommended to optimize the radiographic evaluation of these patients.



Figure 88.2 A nasolacrimal duct cyst may be identified under the inferior turbinate and may cause nasal obstruction. Such children often present with concomitant dacryocystitis.

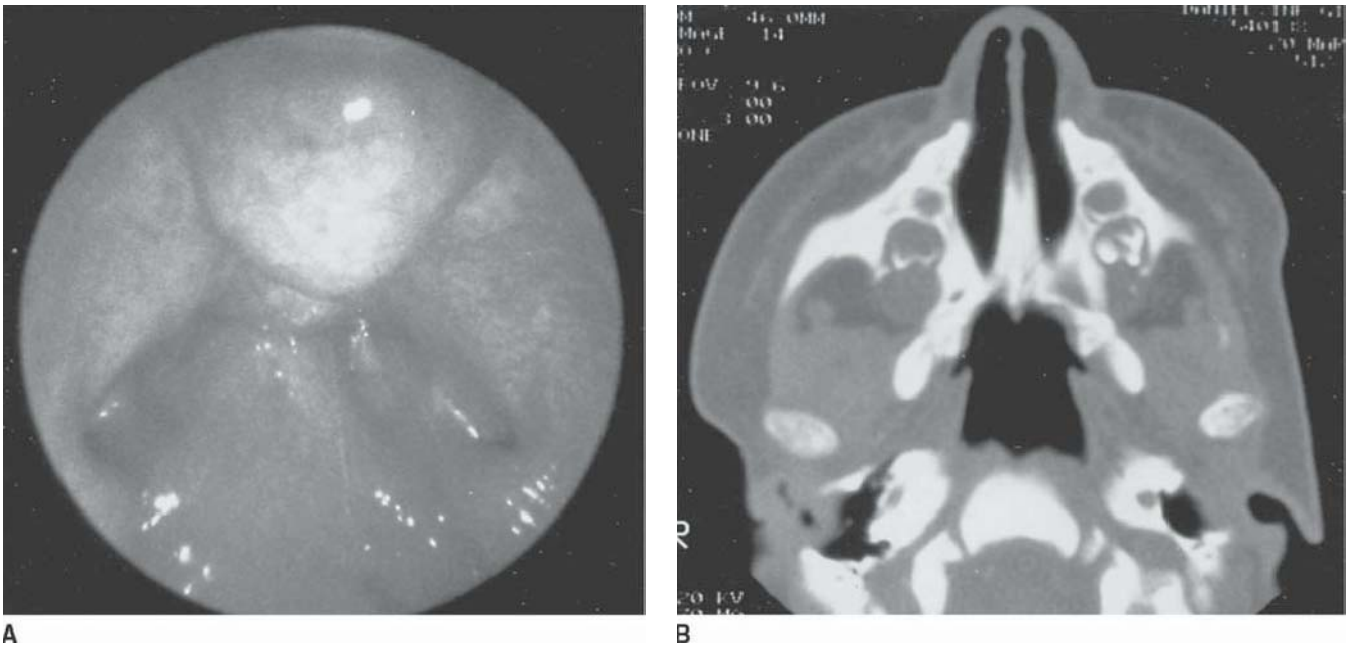


Figure 88.3 Choanal atresia may be identified endoscopically as seen in this view with a 120-degree telescope (**A**) and confirmed by CT scan (**B**).

Regardless of the cause of obstruction, establishing a secure airway is paramount. In many circumstances, this must be done prior to any investigative procedures. If the child has no underlying lung disease or laryngotracheal abnormalities, placement of an oral airway may be sufficient. An alternative to the conventional oral airway may be a feeding nipple cut at the end. Either of these should be secured by taping or with tracheotomy ties placed around the head. Oxygen saturation monitoring can determine the efficacy of this maneuver and, if the child does not maintain adequate oxygen saturation levels, supplemental oxygen may be required. Alternatively, orotracheal intubation with possible ventilatory support may be required. In any child with airway obstruction, failure to maintain adequate ventilation with an endotracheal tube in place may signify intrinsic pulmonary disease, and the active assistance of a neonatologist should be obtained (1).

ORAL CAVITY/OROPHARYNX/ HYPOPHARYNX

Examination of the mouth, oropharynx, and hypopharynx follows the nasal exam. Patients with obstruction in this area usually present with coarse inspiratory stertor that increases during sleep. The cry is usually normal, but may be muffled. Suprasternal and sternal retractions are common and may increase to total chest retractions with severe obstruction. Feeding may be difficult or impossible because of an anatomic obstruction. The airway noise is frequently worse with supine positioning, feeding, and agitation. If immediate intervention is needed, placement of an oral airway, nasopharyngeal airway, or endotracheal tube should be considered.

The presence of macroglossia, glossoptosis, or tumors should be ascertained during examination of the oral cavity and oropharynx. Congenital tumors may include teratomas (epignathus tumors), oral hairy polyps, or malignancies. A flexible endoscopic examination performed through the mouth or nose may demonstrate a mass in the vallecula, including a lingual thyroid, dermoid, or vallecular cyst. Hemangiomas, lymphatic malformations, or other vascular malformations may be identified. Children with craniofacial disorders and Down syndrome are at increased risk for oropharyngeal airway obstruction (7). The findings of micrognathia and glossoptosis in a neonate with airway obstruction are pathognomonic for Robin sequence (12).

If no obvious anatomic abnormality can be identified from the examination, but the child demonstrates evidence of airway obstruction at the oropharyngeal or hypopharyngeal level, a videofluoroscopic examination to observe dynamic changes of the airway may allow a diagnosis to be rendered. Glossoptosis, pharyngeal wall collapse, or laryngomalacia, a supraglottic cause of airway obstruction, may be identified by fluoroscopy. Cine MRI and multidetector CT evaluations are emerging as valuable tools in the assessment of dynamic airway collapse and can quantify the degree of obstruction at various sites in the airway (13,14). These studies, however, require cooperative or intubated patients and are not suitable for most neonates in respiratory distress. The routine use of pulse oximetry is important in the ongoing assessment of airway obstruction at any level of the airway.

Severe respiratory distress in patients with oropharyngeal or hypopharyngeal obstruction mandates immediate airway support. In some cases, the use of a nasopharyngeal or oropharyngeal airway may be all that is required. When

pharyngeal and/or hypopharyngeal collapse is present, the use of nasal continuous positive airway pressure may also relieve symptoms. In children with glossoptosis and retrognathia (e.g., Robin sequence), prone positioning may be beneficial. Pulse oximetry monitoring may be required during the first several months for an infant with Robin sequence because some of these children tend to develop progressive airway obstruction. Even if the child is relatively asymptomatic, intubation may be problematic because of the micrognathia and glossoptosis. Rigid bronchoscopy may be necessary for airway control and, in some circumstances, a tracheotomy with spontaneous mask ventilation may be needed (12).

Most infants with Robin sequence may be observed with monitoring and positioning to relieve their airway obstruction. Feeding is also often compromised and must be addressed through the use of special nipples or, in some cases, nasogastric or gastric tube feeding. A tracheotomy provides the most definitive airway for infants with Robin sequence and severe airway distress, although not without potential morbidity. If the child with Robin sequence has a cleft palate, the tracheotomy is not removed until the cleft palate is repaired. If there is no cleft palate, then the tracheotomy can be removed after the airway obstruction resolves, generally in a few months. Glossopexy (tongue–lip adhesion) or the use of a nasopharyngeal airway has been advocated as an alternative to tracheotomy in children with Robin sequence and airway obstruction that does not respond to positioning (12). Distraction osteogenesis of the mandible is a promising alternative to tracheotomy in selected infants with micrognathia and tongue base obstruction (15,16). Determining which children will benefit from distraction osteogenesis and which will require a tracheotomy, however, remains a clinical challenge.

LARYNX

The larynx is the most common site of stridor in infants. Children with supraglottic or glottic laryngeal abnormalities often present with a combination of problems involving respiration, phonation, and swallowing. In severe cases, suprasternal and intercostal retractions may be seen. Feeding is typically impaired and aspiration may occur if there is a mass lesion, cleft, or neurologic disorder. Infants with supraglottic laryngeal obstruction may present with a muffled cry and they frequently produce snorting respirations during sleep and coarse inspiratory stridor at rest (17).

Laryngomalacia is the most common laryngeal cause of respiratory distress and the most frequent cause of inspiratory stridor in infants. Laryngomalacia is thought to result from alteration of the laryngeal adductor reflex and may be exacerbated by GERD and neurologic disorders (18). Laryngomalacia is initially suspected in the neonate with inspiratory stridor that is worsened by supine positioning, feeding, and agitation. The stridor and airway distress of laryngomalacia are often not present at birth, but tend to worsen over the first few weeks of life. The presence and

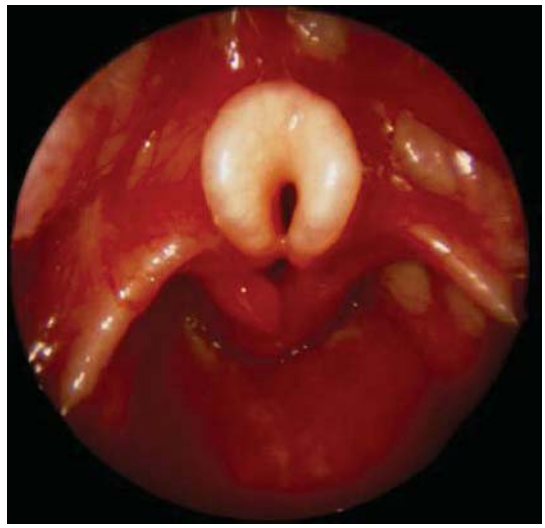


Figure 88.4 Laryngomalacia is demonstrated best by flexible laryngoscopy, but it may be demonstrated satisfactorily with rigid endoscopy.

severity of laryngomalacia is assessed with awake flexible laryngoscopy by observing the prolapse of the arytenoids and/or epiglottis into the laryngeal airway during inspiration (Fig. 88.4). The finding of an omega-shaped epiglottis by itself is not diagnostic of laryngomalacia. In rapidly breathing and crying infants, the examiner must take care in determining during which phase of respiration the supraglottic structures are observed to collapse or compress into the airway. While awake flexible laryngoscopy is the primary study needed to make the diagnosis of laryngomalacia, many children with laryngomalacia, especially those with severe airway distress requiring surgical intervention, have additional airway lesions, and consideration should be given to rigid endoscopic evaluation of these children (19). A FEES study is valuable for assessing the risk of aspiration, and videofluoroscopy may be used to look for concomitant tracheomalacia in children with laryngomalacia (4).

Flexible endoscopic evaluation of the larynx may also reveal the presence of supraglottic or glottic tumors, cysts, or webs. A CT or MRI scan is almost always needed for a thorough assessment of a mass lesion of the supraglottic larynx. In some patients, a diagnosis cannot be determined via these investigative means and then microlaryngoscopy, bronchoscopy, and esophagoscopy should be performed. Depending on the pathologic condition encountered, direct surgical intervention, including supraglottoplasty, or cyst aspiration, or marsupialization, may be appropriate. In other circumstances, endotracheal intubation or tracheotomy is necessary before performing definitive surgery at a later date.

Neonates with glottic airway obstruction may present with a combination of inspiratory or biphasic stridor, an abnormal cry, feeding difficulties, or aspiration. With severe obstruction, inspiratory and expiratory stridor, chest retractions, and nasal flaring are common. A flexible



Figure 88.5 In this autopsy specimen, the larynx has been sectioned in a superior to inferior manner (**right** to **left**) demonstrating laryngeal atresia (**right**) and a laryngotracheoesophageal cleft (**left**).

laryngoscopic examination is essential in the evaluation of the glottis because vocal fold paralysis is a dynamic process that cannot be readily determined when a patient is anesthetized. Because it may be difficult to assess vocal fold function in a crying neonate, it is helpful to record the flexible laryngoscopy study for later review. In neonates with a history of intubation, suspension laryngoscopy is necessary to assess for cricoarytenoid joint dislocation or fixation. Patients with vocal fold paralysis should also have MRI or CT scans performed to look for potential central nervous system lesions or cardiovascular abnormalities. Additionally, a video swallow study or FEES can be invaluable in helping to determine the presence and severity of aspiration in children with laryngeal abnormalities.

Neonates with unilateral vocal fold paralysis typically present with an abnormal cry, cough, or aspiration. Airway distress is more common with bilateral vocal fold paralysis, but can also occur in neonates with unilateral vocal fold paralysis. Children with bilateral vocal fold paralysis usually have a normal cry and biphasic stridor. The search for the cause of vocal fold paralysis includes CT and/or MRI scans of the head and chest to evaluate for neurologic (e.g., Arnold-Chiari malformation, hydrocephalus) or cardiovascular etiologies. Surgery to repair a patent ductus arteriosus or other cardiac abnormality may result in vocal fold paralysis. Other cases of unilateral vocal fold paralysis may be due to birth trauma or may be idiopathic (viral neuritis or delayed neural maturation) and often these patients regain normal vocal fold function over several weeks or months. While spontaneous recovery of bilateral vocal fold paralysis is possible, these children tend to have significant airway distress and many require a tracheotomy. Some children with bilateral vocal fold paralysis may avoid a tracheotomy, but they must have understanding and cooperative caregivers and be followed closely for years. Many of these children may require surgical procedures as they grow and their increased size and activity levels place greater demands on their airways. Because of the possibility of spontaneous recovery of vocal fold function, conservative and reversible laryngeal procedures are preferred during the first year of life (20).

Although other laryngeal abnormalities may be diagnosed with a flexible examination, including webs, atresia, neoplastic disorders, stenosis, and clefts, a rigid examination allows a more detailed and complete assessment to be made. Laryngeal atresia is rare and incompatible with life (Fig. 88.5). If it is identified, an emergent tracheotomy may be necessary; however, some of these patients may have an associated laryngotracheoesophageal cleft or a tracheoesophageal fistula that allows ventilation and oxygenation for a period of time. Patients with partial glottic obstruction can often be initially managed with endotracheal intubation.

Another potential cause of airway obstruction at the glottic level is laryngospasm. This may occur secondary to GERD and should be considered when the cause of obstruction is recurrent or obscure. In addition, GERD has been implicated as a causative or contributing factor in patients with apnea, apparent life-threatening episodes, chronic cough, laryngomalacia, recurrent croup, and subglottic stenosis (21). Gastroesophageal reflux is a common physiologic finding in most neonates and the relationship between neonatal extraesophageal reflux and airway obstruction is not certain (22). Consultation with a pediatric gastroenterologist may be appropriate before assessing the patient with a pH probe study, barium esophagogram, gastric scintiscan, or esophagoscopy with biopsy. A recent systematic review stratified laryngeal endoscopy findings and the presence of GERD and found the strongest correlation with vocal fold edema and posterior glottic edema and erythema (23). These findings, however, are not specific in neonates. Treatment for GERD in infants may include medications or surgery, depending on the severity of the problem.

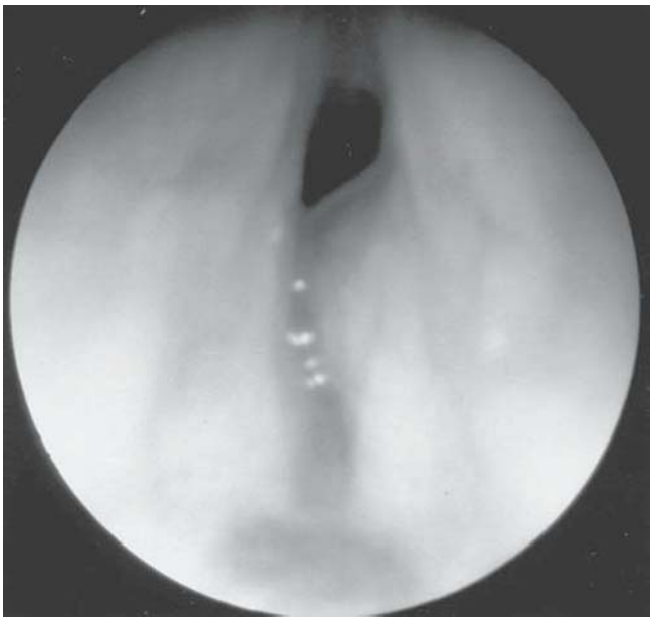


Figure 88.6 A subglottic hemangioma is characteristically located in the posterior and lateral portion of the larynx.

Neonates with subglottic airway obstruction may have a hoarse cry, but often the cry is normal. Similar to patients with glottic obstruction, infants with subglottic obstruction present with inspiratory stridor that can become biphasic as the obstruction increases. Xiphoid retractions are seen early in the course of subglottic obstruction and, as the obstruction increases, retractions may be seen in the intercostal, suprasternal, and supraclavicular regions. Infants with subglottic airway obstruction usually feed normally except when the airway obstruction is severe. Alar flaring may be seen and a barking cough is not uncommon with subglottic obstruction.

Flexible endoscopic examination of the airway alone is not sufficient for evaluating subglottic obstruction. The optics of the flexible laryngoscope do not allow for optimal examination of the subglottic airway and the common anatomic problems seen in this region, including stenosis, cysts, and hemangiomas, may be missed (Fig. 88.6). If the child's symptoms cannot be explained fully on the basis of the flexible endoscopic evaluation and radiographs, microlaryngoscopy, bronchoscopy, and esophagoscopy are necessary. When subglottic obstruction causes severe airway distress, intervention with an endotracheal tube or a tracheotomy may be necessary before definitive surgical repair is undertaken.

Congenital subglottic stenosis is uncommon but must be considered in the neonate with inspiratory or biphasic stridor. An elliptical-shaped cricoid ring may be seen on rigid endoscopy. Symptomatic neonatal subglottic stenosis may be surgically treated by tracheotomy, endoscopic dilation, laser procedures, anterior cricoid split, or laryngotracheoplasty (24,25). Subglottic webs and cysts may be treated by endoscopic division or marsupialization using cold steel, laser, or diathermy.

Although not typically symptomatic at birth, most subglottic hemangiomas become clinically apparent during the neonatal period. Infants with persistent "croup" symptoms should be suspected of having a subglottic hemangioma. Physical examination will reveal a cutaneous hemangioma of the head or neck in approximately 50% of infants with a subglottic hemangioma. Diagnosis is made by endoscopy, although MRI may be helpful to delineate the extent of the hemangioma. Recently, propranolol has been advocated as a primary treatment for subglottic hemangiomas and has shown promising results (26). Steroids, laser ablation, open surgical excision, and tracheotomy are other treatment options (27).

TRACHEA/BRONCHI

Patients with tracheobronchial obstruction usually present with a normal cry, expiratory stridor, and there may be a component of wheezing. With severe obstruction, the stridor may become biphasic. Nasal flaring is common and these patients may have a brassy cough. Retractions are uncommon unless there is severe obstruction. Feeding may be impaired with severe airway obstruction or with extrinsic compression of the esophagus.

The evaluation of patients with suspected tracheobronchial lesions includes anteroposterior and lateral chest radiographs, airway fluoroscopy, and a barium esophagogram. Many clinicians prefer to perform a rigid endoscopic examination before obtaining a contrast esophagogram. If fistulae are observed along the posterior tracheal wall, an attempt at catheterization can be made to demonstrate continuity with the esophagus. Airway fluoroscopy can aid in the differentiation of tracheomalacia and tracheal stenosis. Depending on the severity of the obstruction, immediate intubation may be necessary. After the airway is stabilized, the diagnosis of compressive lesions of the trachea and esophagus can be made with either MRI or CT angiography. Vascular rings, innominate artery compression of the trachea, and mediastinal cysts and neoplasms may all be identified by MRI and CT.

Intrinsic abnormalities of the tracheobronchial tree include primary tracheomalacia, complete tracheal rings, tracheoesophageal fistulae, and tracheobronchial tumors and cysts. Complete tracheal rings may involve a short segment or the entire trachea. Initial airway management may include intubation to the proximal end of the stenosis or the use of extracorporeal membrane oxygenation. Tracheotomy should be avoided in patients with complete tracheal rings because it may further compromise the airway. Slide tracheoplasty has emerged as the definitive treatment of choice for complete tracheal rings (28).

Primary tracheomalacia is thought to be due to a structural weakness of the tracheal cartilage that results in tracheal airway collapse during expiration. This condition generally improves over the first 2 years of life although

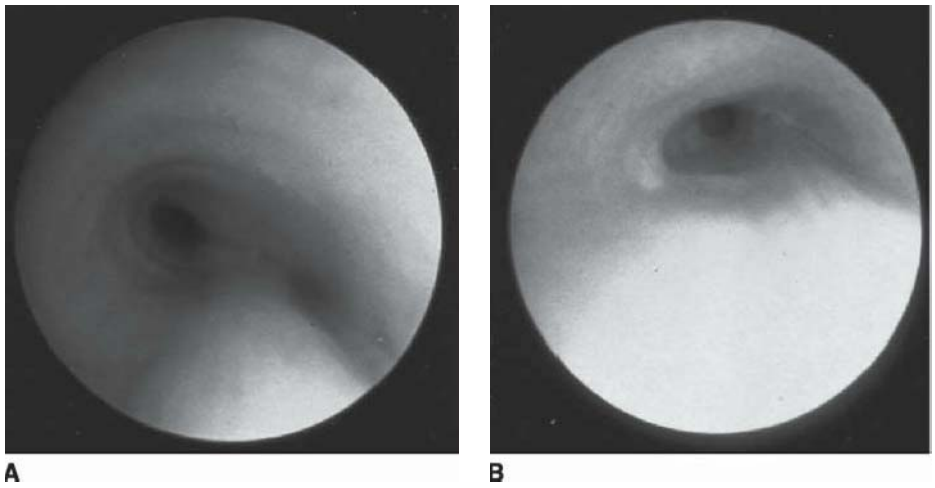


Figure 88.7 Vascular compression of the trachea as seen by tracheoscopy. These views demonstrate examples of innominate artery compression of the trachea (**A**) and a right aortic arch (**B**).

some children require a tracheotomy to bypass or stent open the collapsing area. Secondary tracheomalacia is more common and is the result of extrinsic tracheal compression, most often from vascular abnormalities (27). Neonates with significant tracheobronchomalacia may present with dying spells.

Extrinsic compressive abnormalities of the tracheobronchial tree are more common than intrinsic abnormalities and most cases of neonatal tracheobronchial obstruction are caused by thoracic vascular anomalies. Vascular anomalies causing tracheobronchial compression include an anomalous innominate artery, aberrant aortic arch, and a pulmonary artery sling (29). Endoscopic examination demonstrates the compressive nature of the anomaly and dictates further investigative and therapeutic maneuvers (Fig. 88.7). Esophagoscopy may confirm the compressive nature of the lesion or offer evidence of an alternative pathology, such as esophageal atresia.

PRENATAL FETAL ASSESSMENT

Advances in fetal assessment have allowed physicians to identify potentially life-threatening abnormalities of the developing fetus prior to birth. Fetal MRI provides detailed information regarding the fetal neck, larynx, and trachea, and this information can be used to stratify risk and plan for appropriate interventions. Teratomas and lymphatic malformations are the most common fetal cervical tumors; however, teratomas are much more likely to cause significant airway compromise in the developing fetus and these patients are the ones most likely to benefit from a multidisciplinary fetal center (Fig. 88.8) (30).

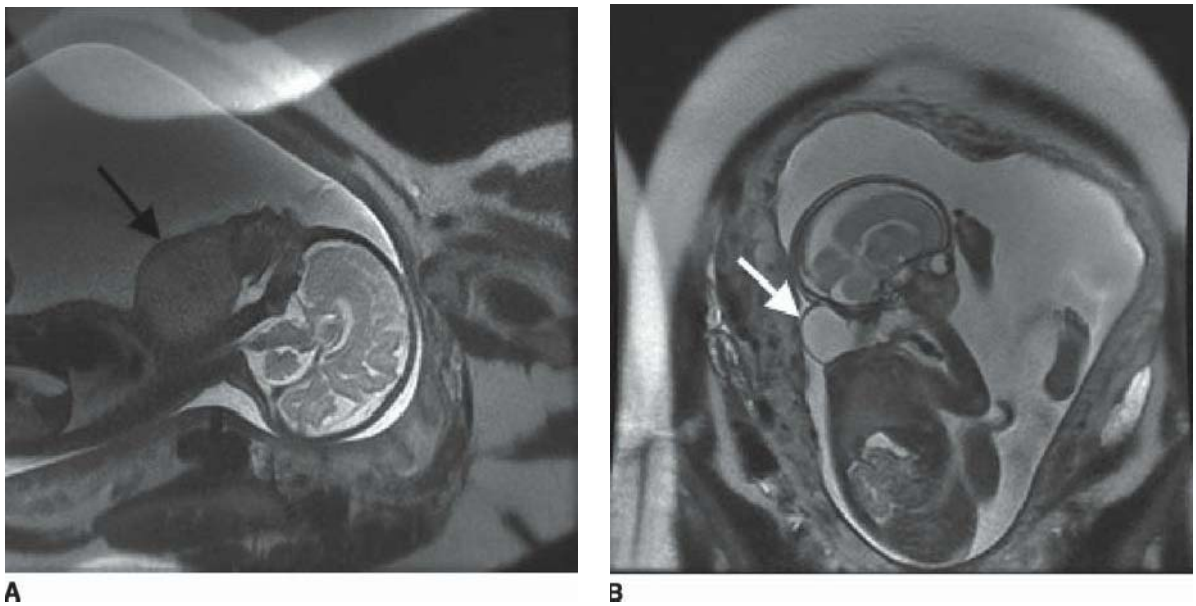


Figure 88.8 Fetal MRI provides detailed imaging of congenital cervical masses that may cause airway obstruction. These sagittal images demonstrate a cervical teratoma (*black arrow*) in (**A**) and a lymphatic malformation (*white arrow*) in (**B**). These studies allow for maternal counseling and planning for airway control at delivery.

The ex utero intrapartum treatment (EXIT) involves a planned Cesarean delivery under deep general anesthesia with delivery of only the fetal head and one or both shoulders. With the fetus maintained on placental circulation the surgeon has several minutes in which to secure the airway. The method of airway management during an EXIT procedure depends on the location of the mass and includes intubation, tracheotomy, distal tracheotomy with retrograde intubation, or mass excision. Proper planning by a skilled, multidisciplinary EXIT team can result in life-saving outcomes for newborns with large, obstructive tumors of the head and neck (31).

HIGHLIGHTS

- Rapid recognition of the severity of neonatal respiratory distress is essential to determining if airway intervention is needed before a complete history and physical exam are performed.
- Because neonates are obligate nasal breathers, nasal obstruction may precipitate life-threatening hypoventilation.
- Beyond the history and general physical examination, flexible airway endoscopy, a chest x-ray, and pulse oximetry are critical in the evaluation of neonatal airway obstruction.
- Airway obstruction at the oropharynx typically causes stertor and feeding problems.
- Most patients with Robin sequence can be managed with close observation, positioning, and monitoring.
- Laryngomalacia is often not clinically apparent at birth but progressively worsens over the first few weeks of life.
- All children with upper airway obstruction must be evaluated for their ability to feed and tube feedings instituted if they cannot maintain adequate caloric intake by mouth.
- Patients with glottic or subglottic airway obstruction typically present with inspiratory or biphasic stridor and an abnormal cry.
- Tracheomalacia is typically the result of compression by thoracic vascular abnormalities and MRI or CT is needed to properly define the problem.
- Differentiating between upper airway obstruction and primary pulmonary abnormalities is critical. Although the former may respond to intubation or tracheotomy, management of the later may require mechanical ventilation.
- The prenatally diagnosed fetus with a cervical mass suspicious for a teratoma should be considered for an EXIT procedure.

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89 Stridor, Aspiration, and Cough

Joseph E. Dohar *Samantha Anne*

INTRODUCTION

Love and a Cough Cannot be Hid

No truer words than these by George Hebert. Few signs and symptoms are perceived as being as distressing to parents as cough, aspiration, and stridor. At a glance, one may consider "stridor," "aspiration," and "cough" as each constituting chapters unto themselves. What unifies these three entities is their anatomic and functional interrelatedness that often results in the concomitant concurrence of all three. Although this chapter discusses each independently, the clinical reality is that any disruption of the complex structure and function of the upper aerodigestive tract often adversely alters the delicate coordination between swallowing and respiration. Hence, it is not uncommon for any combination of these three signs and symptoms to coexist. Even in clinical presentations where only one of these signs dominates, the astute clinician will always search for the other two. This is especially true for aspiration that is not uncommonly "silent" in children. Not only is such an assessment diagnostically imperative but also therapeutically significant as management is vastly altered by the relative proportionate degree to which each of these is playing a role. It is no wonder then that pediatric aerodigestive centers of excellence have emerged in tertiary children's hospitals as representative of the "gold standard" of such care. Such environments are predicated upon the dynamic overlap between stridor, aspiration, and cough. They integrate an interdisciplinary and systematic means by which to assess all three by combining traditional and fundamental tools with more recently developed diagnostic evaluations such as functional endoscopic evaluations of swallowing (i.e., FEES) and breathing.

STRIDOR

Stridor is an abnormal sound due to turbulent airflow through a partially obstructed airway. The level of obstruction can often be clinically localized to the supraglottis, the glottis, or the subglottis and trachea based on the characteristics of the stridor. Specifically, the type of stridor, whether inspiratory, expiratory, or biphasic, helps to localize the site of obstruction. Supraglottic obstruction generally presents with inspiratory stridor while intrathoracic obstruction presents with expiratory stridor. Fixed anatomic obstructive lesions tend to cause biphasic stridor. Finally, the quality of stridor may also provide clues to location and etiology. For example, high-pitched inspiratory stridor is nearly always seen in neonates with laryngomalacia.

Evaluation

The evaluation of a child with stridor begins with a thorough history and physical examination from which most often a differential diagnosis is derived. The most important step in evaluating a child with stridor is determining acuity of the respiratory distress. For an actively stridorous child with severe retractions and impending obstruction, urgent airway stabilization is necessary. Once stabilized, a full evaluation can follow.

History and Physical Exam

The perinatal history specifically determining whether or not endotracheal intubation or airway intervention was required is paramount. The onset, triggers, progression, and presence of exacerbating and/or alleviating factors must also be ascertained. Associated symptoms including presence of aspiration or difficulty with feedings, hoarseness, and signs of reflux must be identified. Positional

changes that worsen or lessen stridor should be noted as well as recurrent or persistent croup episodes. Noting cyanotic spells or apneas helps to quantify the severity of the obstruction. Lastly, comorbidities such as neurologic abnormalities and past surgeries such as those to correct congenital cardiac anomalies must be recorded.

The physical examination begins with an overall impression of the child without invoking excitement. Vital signs must be reviewed for the presence of fever suggestive of an acute infectious etiology, tachypnea, oxygen desaturations, and tachycardia. Dysmorphic features may suggest a syndrome. Observe the child for audible stridor at rest, signs of increased respiratory work including subcostal, intercostal, and suprasternal retractions. Some clinicians may confuse stertor with stridor, and this distinction must be ascertained as early as possible since the subsequent evaluation differs for each. Voice and/or cry quality should be perceptually assessed. Dysphagia may be immediately evident as drooling. A thorough head and neck examination must follow with careful attention to palpation and visualization of any masses within oropharynx and neck. Auscultation of the upper airway and chest qualifies the type of stridor and identifies its phase of occurrence as inspiratory, expiratory, or biphasic.

Radiology

Useful imaging may include chest and neck radiographs. Chest radiographs, in anterior–posterior, lateral upright, and lateral decubitus projections can aid in the diagnosis of several causes of stridor. Inspiratory/expiratory films can reveal foreign bodies in the central airway as well as in the bronchi. Biphasic radiographs may also reveal hyperinflation from obstructing lesions or lower airway disease such as infiltrates or pneumonias. Lateral neck films can reveal key findings such as the "thumbprint" sign of inflamed epiglottis in epiglottitis or thickened retropharyngeal soft tissue in phlegmon- and/or abscess-related airway obstruction.

Computed tomography (CT) and magnetic resonance imaging (MRI) can be used for airway evaluation but do not replace a thorough endoscopic evaluation of airway stenosis or malacia. CT with contrast identifies extrinsic masses or vascular lesions that compress the airway. Both CT and MRI can be used to evaluate vascular malformations in general.

Endoscopy

Following a careful selection of radiologic imaging and after a thorough examination of the child, endoscopy is crucial to complete the evaluation of a child with stridor.

Flexible nasopharyngolaryngoscopy (NPL) is an invaluable tool in evaluation of a stridorous child when possible. The presence of obstructive lesions, dynamic collapse of supraglottic structures, and dysfunction of vocal cord mobility are ascertained. Caution must be used when considering awake flexible endoscopy in a child with impending airway obstruction as the potential agitation may precipitate an emergent situation. Starting with evaluation of the nasal cavities and nasopharynx, systematic evaluation of the oropharynx, hypopharynx, and the larynx must follow. The true vocal cord function must be ascertained, and the presence of collapse of supraglottic structures must be documented. Signs of gastroesophageal reflux disease (GERD) should be noted including posterior glottic edema and edema/erythema of the arytenoids. Double pH probe studies, esophageal biopsy, and radionuclide studies can then further corroborate reflux findings on endoscopy.

Rigid laryngotracheobronchoscopy is the standard for evaluating a child with stridor. In anticipation of performing the procedure, it is crucial for the anesthesia team to coordinate with the endoscopist the plan for airway management during the procedure. Intravenous steroids, such as dexamethasone 0.5 to 1 mg/kg should be given in anticipation of airway edema after instrumentation. Prior to inserting the bronchoscope, topical lidocaine should be sprayed on the larynx and into the trachea to decrease airway reactivity and to prevent laryngospasm intraoperatively and on awakening.

The operative table must be carefully prepared with an age-appropriate bronchoscope and two sizes smaller in situations of anticipated airway stenosis. Additionally, appropriate pharyngeal, laryngeal, and bronchial rigid suctions, different size endotracheal tubes, and laryngoscopes—either Parsons type or anesthesia blades such as Miller or Phillips blade—must also be available. Decide whether the procedure is to be done under spontaneous ventilation, paralysis, or jet ventilation. Spontaneous respiration is ideal in that vocal cord function and dynamic compression can be evaluated. Maintaining spontaneous ventilation is also safer in the event that the airway is considered tenuous and/or there is risk of losing an airway. If possible severe stenosis is suspected, one can avoid injury from a rigid bronchoscope by substituting suspension micro-direct laryngoscopy and bronchoscopy with a Hopkins rod telescope under jet ventilation. The airway can be sized by intubating with a cuffless endotracheal tube and documenting the size at which an air leak is appreciated at less than 20 cm water pressure.

Differential Diagnosis

The differential diagnosis for a child with stridor is extensive, as seen in Table 89.1. Because an exhaustive review of all possible etiologies is impractical given the limitations of this chapter, the following discussion focuses on the five most common etiologies: laryngomalacia, vascular anomalies, laryngotracheitis, vocal cord immobility, and subglottic stenosis. The reader is referred to other chapters in this textbook that discuss most of the other etiologies.

Laryngomalacia

Laryngomalacia is the most common etiology for stridor in infancy. Laryngomalacia is posited to be due to immature cartilages and/or immature neuromuscular tone of the

TABLE 89.1 DIFFERENTIAL DIAGNOSIS: STRIDOR IN A CHILD

Congenital
Laryngomalacia, laryngocele, saccular cyst, laryngeal web/atresia, subglottic cyst, subglottic stenosis, tracheomalacia, tracheal web/stenosis, vascular anomalies, complete tracheal rings, thymic cysts

Infections
Retropharyngeal abscess, epiglottitis, angioedema, viral laryngotracheobronchitis, bacterial tracheitis

Neoplasms
Vascular tumors—hemangiomas, lymphatic/venous/arterial malformations, recurrent respiratory papillomas, thyroid tumors, mediastinal tumors

Other
Vocal cord immobility, foreign body, laryngeal fracture, intubation trauma-cricoarytenoid dislocation

larynx leading to obstruction of the supraglottis. Several classification systems exist for laryngomalacia based on severity or location (1,2). Based on an anatomic designation, the sites of obstruction can be due to inward collapse of the aryepiglottic folds, long tubular epiglottis that curls on itself, anteromedial collapse of the corniculate and cuneiform cartilages, posterior inspiratory displacement of the epiglottis against the posterior pharyngeal wall or inferior collapse toward the vocal folds, and/or short aryepiglottic folds (3).

Diagnosis of the condition is based primarily on history and physical examination findings. Patients usually present with onset of stridor that tends to worsen with crying, feeding, or in supine position within first few weeks of life. GERD has been shown to be frequently associated with laryngomalacia (4). Symptoms of GERD should be elicited including frequent spit-ups, recurrent emesis, and back arching after feeds. More severe laryngomalacia can cause weight loss and failure to thrive with or without cyanotic episodes, and this history must be attained.

On physical examination, high-pitched inspiratory stridor is the classic presentation. Suprasternal and/or substernal retractions suggest more severe obstruction. Flexible endoscopy in clinic on an awake child can confirm the diagnosis. Features of laryngomalacia including prolapse of the epiglottis, arytenoids, and supraglottic edema must be noted. Signs of reflux must also be documented (Figs. 89.1 and 89.2).

Fortunately, the natural history of laryngomalacia is spontaneous resolution over the first 1 to 2 years of life. Medical management with aggressive acid suppression therapy is often all that is necessary to control the symptoms and signs. However, increased severity of obstruction with failure to thrive, cor pulmonale, and/or cyanotic episodes prompts surgical intervention. Supraglottoplasty, done with either CO_2 laser or "cold" with microlaryngeal instruments, should address specific areas of collapse or in releasing areas of constriction such as tight aryepiglottic folds. Rarely is tracheotomy necessary.

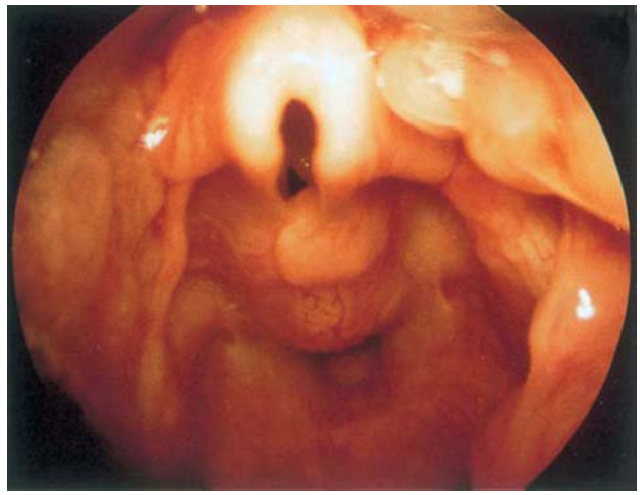


Figure 89.1 Endoscopic view of laryngomalacia during expiration.

Vascular Anomalies

Vascular anomalies that cause stridor in a child include aberrant right subclavian artery, high-riding innominate artery, pulmonary artery sling, and vascular rings and slings. An aberrant right subclavian artery is the most common congenital vascular anomaly. Although the majority of infants with this congenital vascular anomaly present with dysphagia lusoria due to the retroesophageal course of the artery, some may present with stridor. This diagnosis is often made with a barium esophagram that reveals a filling defect in the esophagus. It is confirmed with findings

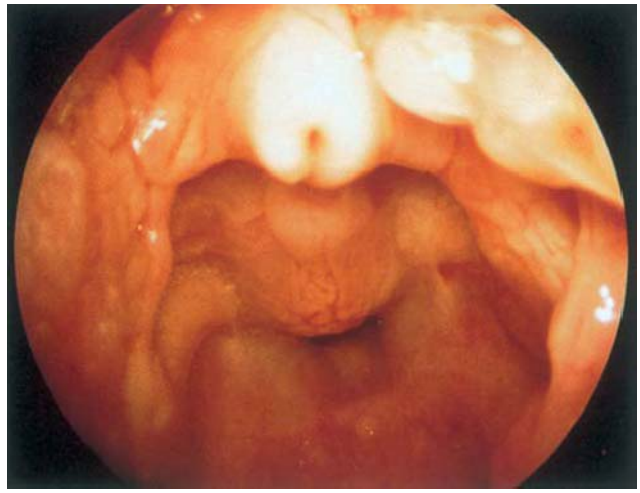


Figure 89.2 Endoscopic view of laryngomalacia during inspiration with folding inward of the epiglottis, shortened aryepiglottic folds, and collapse of the cuneiform cartilages completely obstructing the laryngeal introitus.

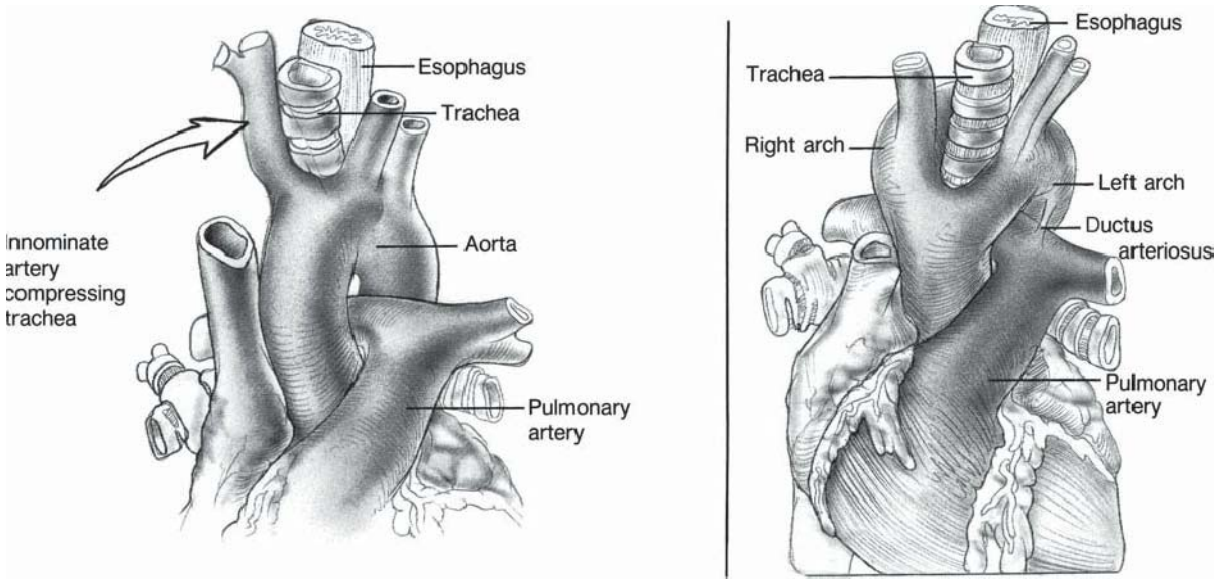


Figure 89.3 Vascular anomalies causing tracheal compression.

on CT angiography (CTA), MRI, or magnetic resonance angiography (MRA). Surgical correction via a right thoracotomy approach is recommended for symptomatic patients and has been to shown to be highly successful (5).

An aberrant course of the innominate artery commonly causes compression of anterior tracheal wall but rarely is symptomatic enough to warrant surgical intervention. In symptomatic children, expiratory, biphasic stridor, "recurrent croup," and/or recurrent pneumonia occur. Bronchoscopy demonstrates pulsatile compression of the anterior tracheal wall. Applying pressure on the anterior tracheal wall with the distal tip of the rigid bronchoscope may diminish the brachial pulse. Diagnosis can be confirmed with CTA, MRI, or MRA. Treatment is expectant in most cases. With severe symptoms, arteriopexy to the sternum is effective (6) (Fig. 89.3).

Lastly, a pulmonary artery sling or vascular ring can also present with stridor. The two most common types of complete vascular rings, double aortic arch and right aortic arch with left ligamentum arteriosum, make up nearly 85% to 95% of all vascular rings (7). Double aortic arches occur due to persistence of embryonic bilateral fourth branchial arch vessels and dorsal aortas. Pulmonary artery slings occur when the left main pulmonary artery arises as a branch of the right pulmonary artery, instead of from the main pulmonary artery due to an abnormality of the sixth branchial arch artery development. Pulmonary artery slings are often associated with complete tracheal rings (Fig. 89.4).

In general, both of these anomalies present with signs of tracheal compression such as biphasic stridor. In addition, chronic cough, recurrent pneumonias, and recurrent croup can occur. Symptoms of dysphagia with a double aortic arch tend to be a more frequent presentation of older children with milder tracheal compression who present later in life. Always suspect vascular anomalies in an infant with atypical "asthma" or in children with severe symptoms associated with respiratory tract infections out of proportion to what is expected; especially when a history of noisy breathing since birth is elicited.

Chest radiographs can reveal compression of the trachea, an abnormally positioned aortic arch, and/or hyperinflation of the right lung with anomalous left pulmonary artery. Since a right-sided aortic arch is almost always present in a vascular ring, identifying this on a chest radiograph is critical. A right-sided aortic arch courses over the right main stem bronchus instead of the usual left main stem bronchus as in a left-sided aortic arch. Thus, the arch

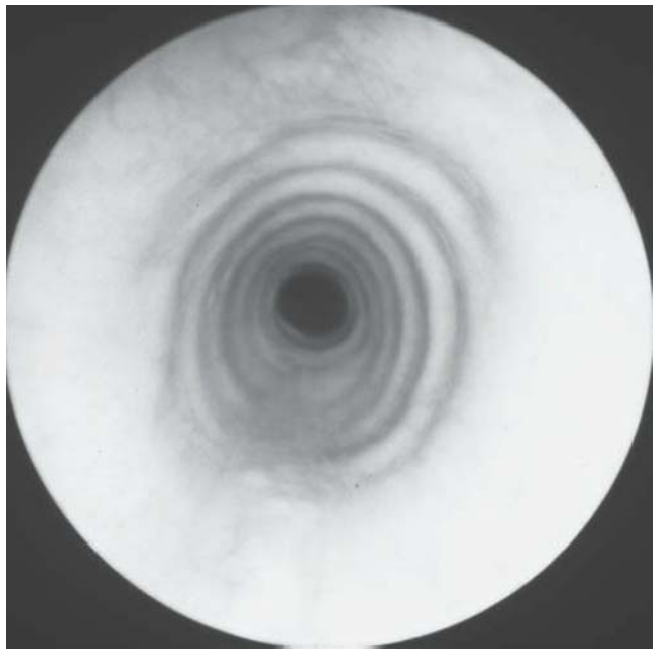


Figure 89.4 Endoscopic view of complete tracheal rings.

itself may not necessarily occupy the right hemithorax. The normal left-sided aortic arch displaces the carina to the right as it courses over the left main stem bronchus. This slight deviation in the normal tracheal air shadow can often be appreciated on the anteroposterior (AP) or posteroanterior view of the chest radiograph. In a right-sided aortic arch, the carina deviates to the left instead as the aorta courses over the right main stem bronchus.

A barium esophagram performed in patients with dysphagia may reveal a filling defect resulting from posterior vascular compression. Echocardiograms readily reveal anomalous vascular structures. CT/CTA or MRI/MRA generally confirms the diagnosis in cases of vascular rings or pulmonary artery sling. Lastly, bronchoscopy may be used to diagnose pulsatile vascular compression and cases of complete tracheal rings associated with a pulmonary artery sling.

While milder vascular anomalies may be observed closely, vascular rings and pulmonary artery slings generally require surgical repair. Prolonged intubation, reflex apnea, and failure of medical treatment are absolute indications for surgical repair. In addition, severe dysphagia and failure to thrive, recurrent bronchopulmonary infections, associated asthma/cystic fibrosis, or exercise intolerance are relative indications for surgical repair. Fortunately, patients without other significant comorbidities or associated anomalies have favorable surgical prognosis, and symptoms tend to resolve after repair.

Laryngotracheobronchitis

Viral laryngotracheobronchitis, or croup, is the most common infectious source of stridor in children. Although the most common cause is parainfluenza virus type 1, other viruses such as respiratory syncytial virus, influenza A, and parainfluenza types 2/3 can also cause viral croup. Most common age of occurrence is from age 6 months to 3 years, although it is rare in infants less than a year of age. When it occurs in a child less than 1 year of age, a possible underlying airway abnormality or stenosis should be suspected.

The diagnosis is largely based on history and physical examination findings. The usual course of illness begins with 2- to 3-day prodrome of upper respiratory illness–type symptoms progressing to barking cough and inspiratory stridor. If there is presence of high fever, rapid progression of symptoms, drooling, and odynophagia, epiglottitis should be considered, and rapid evaluation and treatment should be initiated. On examination, the child will exhibit a fairly prototypical barky cough, stridor, and varying degrees of increased work of breathing.

A high-kilo voltage soft tissue neck radiograph, AP view, may demonstrate the classic "steeple" sign, depicting the narrowing of the subglottis. Lateral soft tissue radiography may demonstrate an edematous epiglottis (thumbprint sign) seen in epiglottitis, which can sometimes present with early similar clinical symptoms as croup. Flexible NPL can be safely performed in a clinically stable child and sometimes reveals an edematous subglottis visualized through abducted vocal cords.

Laryngotracheobronchitis, is usually self-limited and is most often managed conservatively as an outpatient. However, with increased work of breathing, hospital admission and close observation may be necessary. Humidification, blow-by oxygen supplementation, and continuous pulse oximetry can be used in management. Corticosteroids, such as dexamethasone at dose of 0.5 to 1 mg/kg, are prescribed to decrease subglottic edema. Lastly, nebulized racemic epinephrine rapidly reduces subglottic inflammation while steroids are taking effect; however, the effects are transient and children often develop rebound edema. Rarely do the children develop worsening stridor and respiratory distress requiring intubation. Heliox, a mixture of helium and oxygen, may supplant endotracheal intubation by reducing the work of breathing. If necessary, nasotracheal intubation with an endotracheal tube one size smaller than expected for the child's age must be used. Failure to extubate despite observation and medical management should prompt direct laryngoscopy with bronchoscopy to evaluate for underlying subglottis stenosis or other airway anomalies.

Vocal Cord Immobility

Vocal cord immobility is the third most common congenital cause of stridor, occurring in nearly 10% of the cases. Causes of vocal cord immobility include neurologic causes such as Arnold-Chiari malformation or hydrocephalus, trauma from stretch injury to recurrent laryngeal nerve during birthing process, or trauma from injury to nerve during cardiac surgery.

Children with unilateral vocal cord immobility usually present with a weak voice and signs of aspiration. With bilateral vocal cord immobility, inspiratory stridor and an abnormal cry are also prominent. The diagnosis may be made with flexible NPL in an awake child although this assessment is often more challenging than is recognized. Vocal fold immobility is sometimes difficult to distinguish from movement resulting from a Bernoulli effect. Similarly, paresis may be over diagnosed in a sedated child. Children with significant laryngomalacia or supraglottic hyperfunction may simply obscure adequate visualization of their vocal cords. Finally, "pseudoparalysis" or cricoarytenoid joint ankylosis may be misdiagnosed as vocal fold immobility.

Such diagnostic challenges not withstanding, once diagnosed, further evaluation depends on suspected etiology. Imaging of the head down to the chest along the entire course of the recurrent laryngeal nerve might be necessary to identify neurologic or cardiovascular anomalies. Although more logistically challenging in children, laryngeal EMG may assist with the diagnosis in difficult cases and often provides information needed to make clinical management decisions. As more experience is gained with laryngeal EMG in children, it is likely that the role of this intervention will expand not only in cases with diagnostic uncertainty but as a means of providing objective data to assist in management decisions.

If an obvious cause of immobility is identified, treatment of that cause often leads to return of normal vocal fold movement such as decompression of a Chiari malformation. In idiopathic cases, observation is recommended since most cases resolve within first 2 years of life. Delayed resolution after several years has been reported in children and the precise timing beyond which spontaneous recovery of vocal fold movement in children cannot occur is unknown. If there is significant difficulty in maintaining an adequate airway in cases of bilateral vocal cord immobility, tracheostomy may be temporally needed. If the immobility is permanent, various surgical procedures are available to improve airway patency. In cases of bilateral immobility, vocal cord lateralization, excisional procedures such as laser arytenoidectomy, posterior cordotomy, and reinnervation procedures are all potential options pending the specific circumstances of the child.

Subglottic Stenosis

Subglottic stenosis is a congenital or acquired narrowing of the subglottis. The subglottis is the area extending from the lower surface of the true vocal cords to the inferior margin of the cricoid cartilage. The narrowest part of an infant's airway is the subglottis and it normally measures 4 to 7 mm. Less than 4 mm in size in a newborn or 3.5 mm in a premature infant is diagnostic of subglottic stenosis (Fig. 89.5).

Acquired subglottic stenosis is the most common type and requires treatment more often largely because of improved perinatal intensive care and survival of premature infants who required prolonged endotracheal intubation for premature lung disease. Nearly 90% of acquired cases are due to prolonged endotracheal intubation. Risk factors for development of subglottis stenosis include prolonged duration of intubation, overly large endotracheal tube, recurrent intubations, and presence of infection during course of intubation. Other causes of acquired subglottic stenosis include blunt, penetrating, or caustic laryngeal trauma. Iatrogenic damage to subglottis from previous cricothyroidotomy, high tracheostomy, or laser surgery can also be causative.

On the other hand, congenital subglottic stenosis is diagnosed when all other causes have been excluded. It is thought to occur due to failure of the laryngeal lumen to completely recanalize during embryogenesis. Congenital subglottic stenosis can be divided into a membranous type when there is mainly soft tissue occluding the lumen or a cartilaginous type when it is due to abnormalities of cricoid (elliptical cricoid), which narrow the lumen.

Presenting symptoms depend on the severity of the stenosis. If severe, audible biphasic stridor possibly with signs of respiratory distress and increased work of breathing are seen. In milder cases, the child may contract recurrent episodes of croup with or without feeding issues. A thorough birth history must be documented and includes prematurity, need for intubation, and any associated comorbidities. Any feeding difficulties and failure to thrive should be noted. Signs of reflux should be sought.

On physical examination, observation of the patient's overall body habitus and breathing patterns provides useful

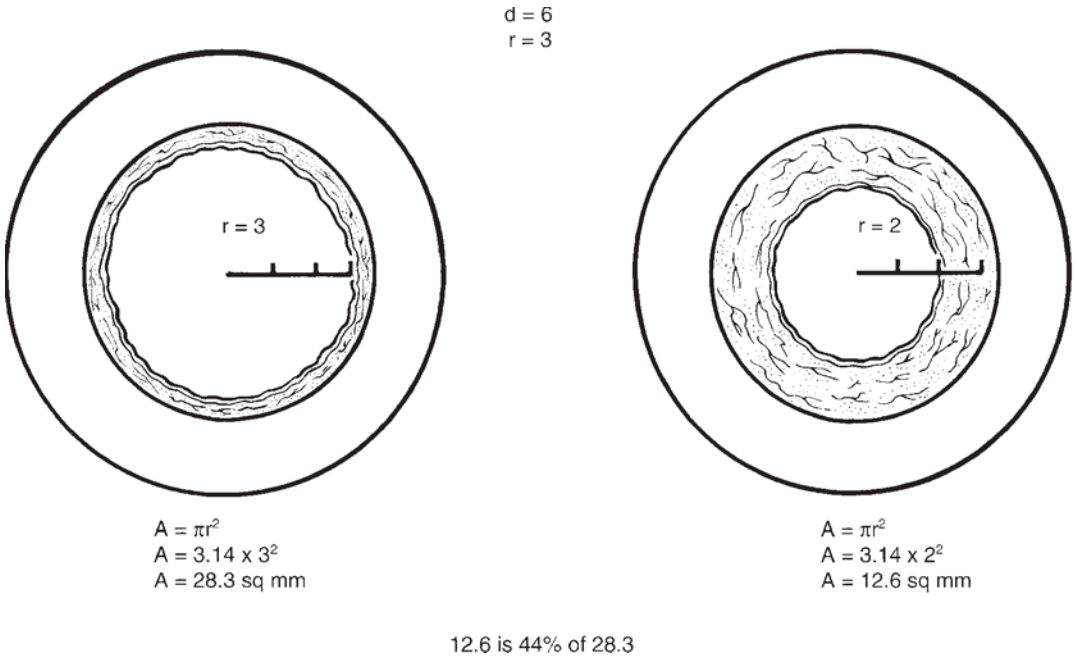


Figure 89.5 The normal newborn subglottic larynx has a diameter of 5 to 7 mm and a cross-sectional area of approximately 28.3 mm^2. Only 1 mm of edema reduces the area to 12.6 mm^2, 44% of normal. (From Holinger LD. Evaluation of stridor and wheezing. In: Holinger LD, Lusk RP, Green CG, eds. *Pediatric laryngology and bronchoesophagology.* Philadelphia, PA: Lippincott-Raven, 1997:41–48, with permission.)

diagnostic clues. Auscultation of chest and neck may reveal biphasic stridor and the voice may be hoarse or weak. Flexible NPL may allow for adequate visualization of the subglottis through abducted vocal cords. Diagnosis using a flexible fiberoptic laryngoscope in a nonsedated child may be challenging as a prominent anterior cricoid cartilage lamina may be confused with subglottic stenosis. In such cases, advancing the flexible endoscope through the vocal cords is not recommended due to the risk of inducing laryngospasm and life-threatening airway obstruction.

CT and MRI, although rarely necessary, may help to quantify the length of the stenosis and, hence, aid in surgical planning. The gold standard for evaluation of the subglottis is direct laryngoscopy and bronchoscopy, which also have the advantage of identifying secondary airway lesions. Sizing of the airway with endotracheal tubes according to the Myer-Cotton staging system is recommended. This staging system describes the percent narrowing of the subglottis as determined by various sized endotracheal tubes with one of four grades. Grade I is less than 50% obstruction, grade II is between 51% and 70% obstruction, grade III is 71% and 99% obstruction, and grade IV is no detectable lumen (8).

Management of stenosis is dependent on severity of stenosis and symptomatology of the child. In general milder stenosis, Cotton-Myer grade I/II can be managed medically and with close observation. GERD therapy is prescribed as it has been shown to reduce edema and decrease the number of croup episodes. More severe stenosis, grades III/IV usually necessitates surgical intervention. Surgical options depend on the type, length, and degree of stenosis in addition to patient characteristics such as overall general medical condition, swallowing ability, presence of aspiration, age, and weight of the child. Options include tracheostomy, endoscopic dilation, and open procedures. Open procedures can include expansion procedures such as anterior or posterior cricoid split or both with cartilage grafting or cricotracheal resection.

Management

Management of stridor in general depends on the severity and acuity of the airway distress. While preparations are underway for airway management, the patient must be evaluated expeditiously and vital signs must be assessed. Initial measures include determining the patient's oxygen saturation and initiating humidified supplemental oxygen keeping in mind the potential for CO_2 retention as a possibility even if the patient exhibits normal oxygen saturation. Appropriate medical therapy must be initiated including steroids, intravenous antibiotics, and nebulized racemic epinephrine depending on the working diagnosis. Once clinically stable, the patient should be transferred to an appropriate monitored unit.

When there is impending obstruction, preparations must be made for intubation. If possible, intubation should proceed in a controlled environment with an anesthesia team present in the operating room and with the operative plan clearly discussed with all members of the team. The size of an endotracheal tube for intubation should be age appropriate and is determined by the formula: (age + 4)/4 except situations of airway stenosis where the smallest size adequate for oxygenation and ventilation should be used. Rarely is emergency tracheostomy necessary. Cricothyroidotomy is not recommended in pediatric patients due to the small size of the cricothyroid membrane and the increased incidence of laryngeal injury.

ASPIRATION

Aspiration is the penetration of oral and nasal secretions, food particles, or refluxate through the vocal cords. A small amount of aspiration occurs normally and is not considered pathologic provided effective clearance mechanisms are intact. However, when the amount aspirated overwhelms clearance and defense mechanisms, bronchopulmonary complications result.

A normal swallowing mechanism includes three phases—oral, pharyngeal, and esophageal. The oral phase includes the oral preparatory phase and the oral transport phase. The oral preparatory phase involves formation of a bolus and the transport phase involves propulsion of the bolus from the mouth into the oropharynx. The pharyngeal phase is a complicated process of movement of the bolus from the oropharynx into the esophagus that includes soft palate elevation to close the nasopharynx, laryngeal elevation, glottic closure, contraction of the pharyngeal constrictors, and relaxation of the cricopharyngeus to allow passage of bolus. Lastly, the esophageal phase is the transport of the bolus from the esophagus into the stomach. Normal swallow function is essential to prevent aspiration. In addition, protection is also provided by glottic closure that depends on normal function of the epiglottis, vocal cords, and aryepiglottic folds.

Diagnosis

Diagnosis of a child with aspiration begins with an accurate history. Aspiration often presents with cough and choking with feeding. With silent aspiration, a protective cough reflex is absent. Depending on the etiology of aspiration, the child may also present with hoarseness, stridor, or dysphagia. There may be a history of recurrent pneumonia or chronic respiratory illness. The medical history should include recent surgeries, traumas, comorbidities, and a complete birth history. Risk factors for aspiration include prematurity, central nervous system anomalies, and anatomic abnormalities of the aerodigestive tract.

A thorough head and neck examination is performed with attention to cranial nerve function. Examination of the oral cavity should focus on both form and function of the tongue and palate. Note any masses or lesions that are present. Facial dysmorphisms and any neurologic deficits must be identified.

Endoscopy

Once a thorough history and physical examination is completed, an endoscopic evaluation can diagnose aspiration and, in addition, may reveal the etiology in many cases. Simple flexible NPL can evaluate vocal cord mobility and identify obvious structural abnormalities such as a laryngeal cleft. The nasopharyngolaryngoscope, in addition, can be used to perform a functional endoscopic evaluation of swallowing, or FEES, to directly evaluate swallow mechanism. The scope is positioned at the level of the soft palate and used to visualize the hypopharynx and the larynx while the patient is fed various consistencies of colored food. Several parameters are recorded including laryngeal penetration, aspiration, pharyngeal pooling, and premature spilling. While this technique is advantageous in that it avoids radiation and is relatively inexpensive, the success of the procedure depends largely on the skill of the physician and speech language pathologist and most importantly depends on the patient's cooperation. FEES is also considered more sensitive in detecting microaspiration. The most distinct limitation of FEES is the "white out" that precludes visualization of the swallow itself. The interpretation of the study relies on what is visualized immediately before and after the swallow. FEES is not physiologic, which is another limitation of the technique. When sensory testing to assess the laryngeal adductor reflex (LAR) is included, the study is referred to by the acronym FEEST.

Operative endoscopy is often necessary for further diagnosis. Direct laryngoscopy, bronchoscopy, and esophagoscopy can be performed to evaluate for structural abnormalities of the aerodigestive tract such as laryngeal clefts, tracheoesophageal fistulas (TEFs), or strictures. Bronchial alveolar lavage can be performed to assess for lipid-laden macrophages suggestive of aspiration and esophageal biopsy can reveal signs of reflux esophagitis.

Radiology

Radiographic studies can aid in the diagnosis of aspiration and include videofluoroscopic swallow study, scintigraphy, and upper gastrointestinal (UGI) series. Videofluoroscopic swallow study is performed in a fluoroscopic unit. The patient is in an upright position and is fed different consistencies of food with small amounts of barium while the phases of swallowing are evaluated under fluoroscopy by a speech language pathologist. This study is considered the "gold standard" physiologic means by which cervical swallowing function is assessed in children suspected of aspiration. All phases of swallowing are assessed. Esophageal abnormalities such as cricopharyngeal opening disorders, esophageal wall pouches, or even regurgitation can be documented and the study can be extended to assess for gastric outlet obstruction. UGI series nicely defines the esophageal anatomy and may identify anomalies that predispose to aspiration. Lastly, radionuclide scintigraphy is performed by having the patient swallow a small amount of water with ^{99m}Tc and the radioactive tracer that enters the lungs is quantified as a percentage of the total radioactive count. It is also quite useful in assessing rate of gastric emptying.

Other studies that may be useful in specific situations include CT or MRI to evaluate the brain and brainstem. Manometry may be indicated to evaluate for aspiration when esophageal motility disorders and manometric abnormalities of the upper esophageal sphincter tone are suspected. Lastly, dual pH probe testing is the "gold standard" by which to diagnose GERD when aspiration "from below" is suspected.

TABLE 89.2 DIFFERENTIAL DIAGNOSIS: ASPIRATION IN A CHILD

Congenital	Neurologic	Other
Laryngeal cleft	Hypotonia	Vocal cord immobility
Tracheoesophageal fistula	Encephalopathy	Cleft palate
Esophageal atresia/webs/duplications, vascular rings, achalasia	Anoxic brain injury Arnold-Chiari malformation Muscular dystrophies Cerebral palsy	Neoplasm GERD Foreign body Postsurgical

Differential Diagnosis

The differential diagnosis of a child with aspiration is listed in Table 89.2. Neurologic dysfunction and various aerodigestive anomalies account for a significant number of cases of aspiration in children. Neurologic dysfunction may result from diffuse injury to the brain during delivery, trauma, or perinatal infections. Degenerative diseases such as amyotrophic lateral sclerosis, myasthenia gravis, or spinal muscular atrophy and peripheral nerve disorders, especially involving cranial nerves can also cause aspiration. Lastly, pharyngeal hypotonia, whether from muscular dystrophies, cerebral palsy, or other muscular disorders can lead to poor pharyngeal tone and poor control of swallowing mechanics.

Laryngeal Clefts

Laryngeal clefts are congenital anomalies that result from failure of the airway to separate from the esophagus during embryogenesis. Laryngeal clefts are graded as grade I involving only the interarytenoid muscle, grade II involving part of the cricoid, grade III involving the entire cricoid, and grade IV extending the cleft into the trachea (9). Laryngeal clefts are often associated with various syndromes such as Pallister-Hall or Smith-Lemli-Opitz, which must be considered during evaluation. The typical presentation of a child with a laryngeal cleft is aspiration in milder cases. Cyanotic episodes with feeding and recurrent pneumonias

are seen in more severe cases of higher grade. Diagnosis is confirmed with direct laryngoscopy and bronchoscopy by palpating the interarytenoid musculature in type I clefts when there is no obvious cleft visible. Confusion in the literature exists regarding the precise means by which to distinguish a type I laryngeal cleft from a deep interarytenoid notch. Further adding to the diagnostic uncertainty is the reported increased incidence of reflux aspiration in both. Fortunately, the treatment approach is similar in both and depends largely on the consequences of either anomaly. This relegates much of the discussion to academic interest alone. The major dilemma arises due to a natural spontaneous resolution of symptoms with growth and development in both conditions. When this fact is coupled with the reality that surgically converting a high-grade type III or IV cleft into a type I cleft is often reported as a "surgical success," it is sometimes difficult to accept aggressive surgical recommendations for mildly symptomatic infants. Judicious assessment and conservative algorithms are prudent. Milder clefts can be observed and treated conservatively. If needed, endoscopic repair is often successful. With advanced clefts, open surgical repair is often necessary either via a laryngofissure or posterolateral approach with extension into trachea.

Tracheoesophageal Fistula

Tracheoesophageal fistula, TEF, is another congenital anomaly that results in aspiration due to an abnormal connection between the trachea to the esophagus. By far, the most common type of deformity is esophageal atresia with a concomitant distal TEF in nearly 90% of the cases. Less common types include isolated esophageal atresia without TEF, isolated TEF, and esophageal atresia with proximal or proximal and distal TEF. Most cases are diagnosed immediately after birth due to severe aspiration and life-threatening perinatal complications. TEFs are often associated with syndromes such as VACTERL and Down syndrome, the latter of which includes other developmental anomalies such as congenital cardiac disease. As such, presence of a TEF must prompt a thorough examination of the child for comorbidities. Postnatal diagnosis can occur with chest radiography revealing the absence of a gastric bubble due to esophageal atresia. In addition, insertion of nasogastric tube may be complicated by coiling in the mediastinum. CT and MRI can also be used for diagnosis. Surgical repair is required with TEF and may have to be deferred until concomitant comorbidities such as prematurity, pneumonia, and low birth weight are stabilized.

Management

Medical Management

Upon diagnosis of aspiration, multidisciplinary care must be instituted including the following pediatric specialists; pulmonologists, speech–swallow therapists, otolaryngologists, and depending on etiology, neurologists, geneticists, intensivists, and pediatric surgeons. Initial management involves treating underlying pneumonia and respiratory complications. Appropriate antibiotics are given and aggressive pulmonary toilet is instituted as directed by pulmonologists and respiratory therapists. Control of aspiration is necessary and all oral feeding must be discontinued while evaluation and treatment is in progress. Nasogastric tube and enteral feeding are both options but do not completely eliminate aspiration. Gastrostomy or jejunostomy tube feeding is necessary when a protracted course is anticipated. Control of sialorrhea with anticholinergics and/or antihistamines may be useful. The side effects of these medications must be discussed with the family prior to institution. Recently, ultrasound-guided botox injections into the submandibular and parotid glands have successfully decreased salivary production and subsequent salivary aspiration. This results in temporary relief for 3 or more months and should be considered as a minimally invasive alternative to surgery, especially in younger children under the age of 7 years whose swallowing function is expected to improve.

Surgical Management

Surgical procedures for aspiration can be divided into two main subsets: control of sialorrhea and laryngeal control of aspiration. Surgery to control sialorrhea either reduces salivary production or changes the location where saliva enters and includes a myriad of procedures such as salivary duct rerouting, excision of salivary glands, or any combination of the above procedures. See Table 89.3. Laryngeal control of aspiration can be achieved with vocal cord medialization, tracheostomy, laryngeal closure, and laryngotracheal separation (10).

Control of Sialorrhea

A complete review of all procedures that can be used for control of sialorrhea is not feasible within the context of this chapter. However, some commonly performed procedures that are highly successful are described below.

Submandibular gland duct rerouting is achieved by rerouting the Wharton ducts to the tonsillar fossae. Initially, a tonsillectomy is performed. Next, the Wharton ducts are identified, dissected, and then sutured to the tonsillar fossae. The advantages of this procedure include avoidance of external incisions and prevention of xerostomia. However, since the secretions are not decreased but just rerouted posteriorly, this procedure may increase aspiration in a child that is neurologically incompetent and/or is already at risk of aspiration for other reasons. Excision of sublingual glands in conjunction with submandibular duct rerouting is effective in controlling sialorrhea and prevents the complication of ranula formation (11).

Excision of bilateral submandibular glands with or without parotid duct ligation has also been shown to be highly successful in decreasing sialorrhea (12). Advantages

TABLE 89.3 SURGICAL MANAGEMENT OF SIALORRHEA

Surgery	Advantages	Disadvantages
Submandibular gland duct rerouting/ Parotid duct rerouting	Avoidance of external incisions Unlikely xerostomia	May increase aspiration Without sublingual gland excision, risk of ranula
Excision of sublingual glands	Internal approach possible	Insufficient control unless combined with other procedures
Excision of submandibular glands	Decreased resting flow Good control of sialorrhea Internal approach possible	External scar
Excision of parotid glands	Decreased stimulated flow Good control of sialorrhea	External scar
Parotid duct ligation	Decreased stimulated flow Avoidance of external incisions	Risk for dental caries Risk of xerostomia when combined with other procedures Risk for sialocele, parotitis
Transtympanic neurectomy	Technically easy, fast	Predictable return of salivary function; usually requires revision

include decreased resting salivary output. If the parotid ducts are also ligated, stimulated flow from the parotid glands is decreased. As the amount of saliva is decreased, however, the risk of dental caries and xerostomia increase. In addition, sialoceles, parotitis, and external scars can complicate this surgery (13).

Laryngeal Control of Aspiration

Vocal cord medialization can be achieved either by vocal cord injection or by medialization procedures. Vocal cord injections with temporary fillers such as resorbable synthetic polymers (sodium carboxymethylcellulose) combined with water and glycerin, a bovine gelatin agent (gelfoam), hyaluronic acid, freeze-dried micronized acellular human cadaveric dermis, cross-linked bovine collagen, or semipermanent injection with fat, fascia, synthetic calcium hydroxylapatite, or polytetrafluoroethylene can be used to medialize vocal cords to decrease aspiration. The procedures are highly effective especially in cases of vocal cord immobility. Alteration of the laryngeal framework by using implants externally remains the criterion standard for long-term medialization of the vocal cords. A recent study, however, failed to demonstrate improved outcomes with aspiration following framework surgery as compared to vocal cord injections. Advantages of endoscopic vocal cord injections include avoidance of external scars and reversibility in cases of expected vocal cord function recovery (14).

Tracheotomy is an option for patients with aspiration; however, inherent to the procedure is possible worsening of aspiration. Tracheotomy is primarily useful in providing access to suction and for airway management in cases that otherwise would require prolonged endotracheal intubation. In addition, cuffed tubes may decrease the volume of secretions that enter the lower airway. An inflated cuff decreases the phonatory capacity of the child and along with the tracheostomy tube impairs laryngeal elevation due to tethering. Together these factors may worsen aspiration. Cough may also be impaired, which compromises the primary pulmonary clearance mechanism that prevents pneumonia. For these reasons, tracheostomy should be viewed as a temporizing measure until more definitive control of aspiration can be achieved and should be recommended judiciously.

Definitive approaches to aspiration include laryngeal closure and laryngotracheal separation. Laryngeal closure may be achieved by suturing the glottis or supraglottis temporarily until swallowing function improves and aspiration decreases. Procedures described in the literature include closure of the false vocal folds (15) while preserving separation of the true vocal cords and arytenoids. Alternatively, closure of the glottis and supraglottis using hinged flaps from true and false vocal folds has also been described (16). Laryngotracheal separation completely isolates the airway from the digestive tract and, hence, eliminates aspiration. It has been shown to be 90% to 100% successful in eliminating aspiration (17). The procedure divides the trachea into two segments; the proximal trachea with the larynx is oversewn into a blind pouch and the distal trachea is converted into tracheostomy. Although vocalization is no longer an option, the patient is able to continue oral feeding and maintain an airway without aspiration. The procedure is also potentially reversible although the underlying neurologic condition of the child that required the procedure may preclude reversal. When considering these later interventions, the clinician must be sensitive to the family's perception of the utility of the child's voice. Although to a clinician, the child may be deemed nonverbal and, hence, in no need of vocal capacity, many of these families consider the child's voice critical in alerting them to pain and discomfort. Anecdotally, it is rare that the families of these children are comfortable eliminating the capacity for phonation.

COUGH

For the Otolaryngologist, it Cannot Just be About Sinusitis

There are many ways that the symptom of cough can be conceptually approached. Much of the conceptualized approach is predicated upon the specialized orientation and training of the health care provider. Emergency room physicians focus on ruling out conditions that require urgent diagnosis and treatment. At the top of their lists are diagnoses such as pneumonia and pulmonary embolus. Gastroenterologists search for extrapulmonary causes of cough such as GERD and primary digestive abnormalities such as esophageal diverticula. Conversely, pulmonologists tend to focus on lower airway causes of cough such as asthma and tracheobronchomalacia. Although allergists have evolved into specialists that overlap considerably with pulmonologists with respect to reactive airway disease, they also explore otolaryngologic diagnoses such as sinonasal etiologies albeit with a greater focus on allergic drivers of inflammation rather than infectious or anatomic drivers. Primary care physicians screen all of the organ systems and often base suspected diagnoses on history alone while attempting to confirm their suspicions by prescribing "shot-gun" empiric medications directed at the most likely causes.

So where does this position the niche of the otolaryngologist? At the very least, an otolaryngologist is expected to identify or eliminate upper aerodigestive sources of cough. Having spent a career in a pediatric tertiary care center, patients are often referred following a general otolaryngology evaluation. After review of many such consultation reports, it has not been uncommon to find the following sole conclusion; "This is a patient with chronic cough who does not have rhinosinusitis as the underlying etiology. Alternative causes should be investigated." Although this may help the referring physician and patient to some degree, it is certainly not the model consultation to be emulated.

The deft otolaryngology consultant understands two objectives. First, what patients and referring physicians really seek is the etiologic identification and treatment of cough. To the extent possible, these should be the consultant's goals as well. Second, developing at least a working knowledge of nonotolaryngologic causes of cough is critical. This is especially true in cases where the cough is recurrent, as opposed to chronic, and not necessarily present on the day of the otolaryngology consultation.

A common chief complaint that exemplifies this scenario is "recurrent croup." Often such patients never had croup at all but had recurrent cough of a nonproductive and barky nature. A second reason the otolaryngology consultant must be mindful of other causes of cough is that it is not uncommon for chronic cough to result from more than one cause. The literature reports that chronic cough has more than 20 causes, and in up to 62% of cases more than one cause is identified (18). Finally, one often cannot definitely rule in or rule out certain head and neck causes of cough without also considering nonotolaryngologic etiologies. Because separate chapters are included in this book on nearly all of the etiologies to be identified, this chapter's focus is on the diagnostic approach needed to identify the underlying cause(s) of cough. Discussions of individual etiologies are limited to particular mechanisms and aspects specific to cough. Similarly, treatment recommendations for the underlying causes of cough (asthma, GERD, allergic rhinitis, infectious rhinosinusitis, etc.) are mentioned but not comprehensively outlined as more detail is included in other chapters. The only detailed therapeutic treatment discussion in this chapter focuses on the treatment of cough primarily. This discussion includes a review of the most recently published evidence-based best practice guidelines by the American College of Chest Physicians (ACCP) in January 2006 (19). With these tenets in mind, this section emphasizes a multidisciplinary approach to cough. In other words, "it's just not all about sinusitis!"

Step One: Commit to Memory an Anatomic Image of Where All the Cough Receptors are Located and Use it as a Systematic Map to Direct the Evaluation

Understanding that each specialty-specific approach to cough has its own set of advantages and disadvantages, and accepting the logistical limitations of being unable to exhaust all of them, a reasonable algorithmic framework is needed. Having experience with most of these, the approach that best systematizes the evaluation is one which identifies the locations within the body of each set of cough receptors. By committing this framework to memory, the clinician can algorithmically obtain a history, focus a physical examination, and optimally select the most effective diagnostic studies.

Such structure is particularly critical for the evaluation of cough for several reasons. First, cough is one of the most common complaints for which patients seek medical attention. There are nearly 30 million physician visits for cough in the United States each year positioning cough amongst the top five for number of doctor visits (19). Second, cough may result from pathology in more than a half dozen distinct anatomic locations. Third, the empiric treatment of cough has resulted in several public health issues such as the over use of antibiotics leading to bacterial resistance. About 3.5 billion dollars are spent each year on over-the-counter (OTC) cough medications alone such as expectorants and cough suppressants (19).

Although the focus of this chapter is on clinically relevant information, it is important to review certain fundamental basic science concepts that lay the conceptual foundation for this algorithmic approach.

Step Two—Determine if Cough is Physiologic or Pathologic

Before delving into the "pathology" of cough, it is important to emphasize that, in and of itself, cough does not represent a sign of disease. To the contrary, cough is an important normal protective reflex activity. The most widely recognized neural response involved in airway protection is cough. Cough is generally characterized by a reflex-evoked modification of the breathing pattern in response to airway irritation (20). Reflex cough occurs when subsets of airway afferent (sensory) nerves are activated by inhaled, aspirated, or locally produced substances. Although an occasional cough is normal, excessive coughing or coughing that produces blood or thick, discolored mucus is abnormal.

The cough reflex has five components: (a) cough receptors, (b) afferent nerves, (c) a poorly defined cough center, (d) efferent nerves, and (e) effector muscles.

Key to cough particularly in pathology is the cough receptors. In summary, cough receptors are throughout all the airways and UGI tract as well as the pericardium and diaphragm. Specifically, receptors that activate the cough reflex are situated mainly in the proximal airways within the soft tissues and smooth muscle. It is important to bear in mind that receptors are concentrated in the larynx and carina and at other airway bifurcations. No receptors lie beyond the terminal bronchioles. Receptors are found in the nose, nasopharynx, posterior oropharynx, external auditory canals, tympanic membranes, stomach, esophagus, pleura, pericardium, and diaphragm.

Step Three—Apply the Basic Science

So what is the practical clinical significance of a basic science review of the anatomic cough receptors? From an otolaryngologist's perspective, a systematic, thorough, and sequential assessment of the nose, paranasal sinuses, nasopharynx, oropharynx, hypopharynx, larynx, external auditory canal, tympanic membrane, esophagus, trachea, carina, and main-stem bronchi must be performed. Clearly, the fact that there are primary cough receptors in every anatomic subregion considered within the primary domains of otolaryngology emphasizes two important points. First, this chief complaint encompasses arguably the broadest range of potential otolaryngology differential diagnoses. Second, the majority of the etiologies of cough are within our specialty. Referring physicians are well aware of this fact which is why otolaryngologists are consulted early, often and frequently before any other specialists.

If a head and neck assessment fails to identify a cause for cough, a screen for nonotolaryngologic etiologies should focus on cardiac, pulmonary, and gastrointestinal alternatives. In many such instances, the otolaryngologist's skill sets are ideally suited for making the diagnosis even in cases where there is no head and neck pathology. In other cases, prudent referral to specialists in cardiology, pulmonology, gastroenterology, infectious disease, or allergy is needed. Neurologic and orthopedic causes must also be considered as cough can occur with vagus neurilemomas and cranial nerve stimulation from cervical osteophytes. Although many of these causes are beyond the scope of this chapter, it is critical to never lose site of the wide range of organ systems potentially involved.

Step Four—Don't Forget Functional Etiologies—Tic Cough, Habit Cough, and More…

The last basic science reality that is important to mention is that cough can also be voluntarily initiated without stimulation from other afferent pathways. The efferent fibers of the cough reflex carry their signals from the cough center to the diaphragm and intercostal muscles through the phrenic and spinal motor nerves, respectively. The abdominal and pelvic muscles also participate in the efferent limb. This reality highlights the need to consider tic, psychogenic, or habit cough when no other organic etiology is identified. Unfortunately, this is a diagnosis of exclusion and cannot be confirmed until several different specialists have ordered costly, invasive, and extensive diagnostic tests. At times, because so many tests are obtained, several "red herrings" are found that further complicate the evaluation as they must all be pursued as well. With this conceptual framework in hand, how should the otolaryngologist proceed?

Step Five—The History…

Precisely quantifying the duration of cough is crucial. Pediatric chronic cough (i.e., cough in children aged less than 15 years) is defined as a daily cough lasting for more than 4 weeks (21). This time frame was chosen based on the natural history of upper respiratory tract infections (i.e., URTIs) in children and differs from the definition of chronic cough in adults. Cough quality may suggest an etiology, yet, surprisingly there are no published studies that rigorously compare etiologies of "dry cough" versus "wet cough." Chronic cough is subdivided into specific cough (i.e., cough associated with other symptoms and signs suggestive of an associated or underlying problem) and nonspecific cough (i.e., dry cough in the absence of an identifiable respiratory disease of known etiology). Most cough characteristics recognized as classical have not been systematically studied. Such traditional recognized cough characteristics and the etiologies they suggest are as follows:

Cough Characteristics	Etiologies Suggested
Barking/Brassy cough	Tracheomalacia (22–24) Croup (25) Habit cough (26,27)
Cough productive of casts	Plastic bronchitis (28)
Honking cough	Psychogenic (29)
Paroxysmal cough +/− whoop	Pertussis (30) Parapertussis (31) Psychogenic
Staccato cough	*Chlamydia* in infants (32)

A history of neurodevelopmental abnormalities strongly implicates aspiration as the cause of cough. Aspiration as a cause of cough was discussed in detail above (21). Finally, although cough as a side effect of medication is less common in children, review medication lists for those which may have cough as a side effect. This etiology is far more prevalent in adults who are on medications such as angiotensin-converting enzyme (i.e., ACE) inhibitors.

Step Six—The Physical Examination...

Specific causes of cough are suggested by several physical findings. Pulmonary etiologies are suggested by auscultatory findings such as wheezing and crepitations. Physical signs of viral URTIs are significant in three ways. First, nasopharyngeal cough receptors are stimulated by copious viscous secretions in the nasopharynx. Second, endobronchitis is not uncommonly seen in the latter stages of a viral respiratory tract infection. Finally, 80% of childhood asthma exacerbations are due to viral URTIs. Similarly, cardiac anomalies and chest wall deformity clearly suggest specific etiologies of cough. Digital clubbing and failure to thrive markedly raise the index of suspicion for cystic fibrosis.

Step Seven—Which Diagnostic Tests Should be Obtained...

Children with chronic cough should undergo, at a minimum, a chest radiograph and, if age appropriate, spirometry with or without methacholine challenge. Chest radiographs are readily available and quickly obtained and interpreted. In general, spirometry is reliably performed in children over 6 years of age and can be obtained with appropriate resources down to 3 years of age. In extraordinarily challenging cases, anesthesia protocols exist for younger children. There is no reason for otolaryngologists to defer spirometry to other specialists.

Much attention has been paid not only in the medical literature but also in the lay press to radiation risks associated with medical imaging. Parents often ask for clarification of these very real and historically underappreciated risks. Suffice is to say that the lifetime radiation-induced cancer risk is age and dose dependent. A single chest CT scan delivers about 5.8 mSv, which is the equivalent of that delivered with 300 plain chest radiographs that only deliver approximately 0.02 mSv. Depending on the algorithm, CT scans of the paranasal sinuses deliver less than that associated with chest CT scans. Although the initial driver to abbreviate sinus CT algorithms was cost effectiveness in comparison to the previous gold standard of four-view plain sinus series, the more meaningful advantage in retrospect relates to the lower radiation-related cancer risk.

High-resolution chest and sinus CT are the current gold standards for evaluating airway anatomy. Although much discussion has ensued over the relative value of alternative surrogates such as four-view plain sinus x-rays, ultrasound, and transillumination, such a discussion here would only speak to historical significance.

A purified protein derivative (i.e., PPD) may be valuable to rule out tuberculosis (TB) in immunocompetent patients. Remember that a PPD may not convert in immunocompromised patients who are most likely to contract the illness. Hemoptysis may suggest either malignancy or TB. Indirect laryngoscopy will often reveal blood-tinged secretions in the posterior commissure and on the mucosa of the true vocal cords in active TB. Induced sputum for gram stain, acid-fast stain, and culture may be useful.

Step Eight—If the Diagnosis Remains Elusive...

Airway endoscopy must be considered. For the otolaryngologist, an endoscopic survey begins in the nose. Although not included in the traditional "panendoscopy" sequence, nasal endoscopy has become a very important diagnostic tool in several clinical pediatric scenarios with none more compelling than chronic cough. By carefully evaluating the nose and nasopharynx, congenital anomalies such as pyriform aperture stenosis, choanal atresia, and septal deviations can be identified. The status of the nasal mucosa and secretions can be established. In cases of suspected infection due to resistant pathogens, directed middle meatal and nasopharyngeal cultures can serve the same role as tympanocentesis in middle ear disease. Lastly, the adenoid can be carefully assessed, which is particularly important since adenoidectomy is often the first and most common surgical procedure recommended for children with medically refractory sinonasal disease.

Bronchoscopy must be considered when there is a suspicion of a foreign body, an airway abnormality, focal and localized radiographic changes, and aspiration lung disease.

Similarly, esophagoscopy may assist in the diagnosis of esophageal anatomic anomalies, reflux or eosinophilic esophagitis, and food impaction. It is important to note that esophageal foreign bodies serve as an important and often overlooked cause of chronic cough. This factor underscores the importance of panendoscopy, which includes a careful survey of the esophagus in such cases.

Step Nine—Remember Once Again that Children with Cough are Not Simply Small Adults...

Hence, the adult literature cannot be blindly extrapolated to children. Although there are several reasons for this, the most important are as follows. First, viruses that only cause "common colds" in adults can cause serious respiratory illness in children. Second, there are distinct maturational differences in airway anatomy, respiratory musculature, and chest wall structure. Third, there are vastly different responses to medications. Fourth, medical history in very young children is limited by parental perception and availability. The conclusion, therefore, is obvious. Children should be managed according to pediatric studies and guidelines when available.

Step Ten—Remember this Important Pearl…

Children with chronic productive purulent cough should always be investigated for possible bronchiectasis and underlying treatable causes such as cystic fibrosis, primary ciliary dyskinesia, and immunodeficiency. It is the rule and not the exception that over the course of a career, a pediatric otolaryngologist will be the first to make one of these diagnoses.

Final Step—Don't Ignore the Absence of a Cough When there Should be One

It has often been said that crimes of commission are readily apparent. Crimes of omission are more challenging to identify. The practice of medicine is no different. Health care providers are more inclined to suspect pathology based on the *presence* of signs and symptoms. The astute clinician must also know when to be concerned by symptoms that are absent. There are several reasons why cough may be absent despite pathology normally associated with this symptom. The most common reason is loss of the cough receptor or the afferent limb of the reflex arc. It is for this reason that testing for an LAR has become a standard part of every swallowing assessment. The second reason that may either weaken or eliminate cough pertains to the mechanics of cough production. Specifically, the mechanics of a cough involve first developing and then sustaining a high velocity column of air. To do this, the cough begins with an initial inspiratory phase during which the vocal cords are maximally abducted and the chest dimensions increase; the lungs are filled with air to a high volume. Abnormalities that would compromise cough during this initial mechanical phase include restrictive or obstructive lung disease that prevents forceful inspiration, diaphragmatic weakness, or conditions that prevent vocal fold abduction such as paralysis and cricoarytenoid joint fixation. It is important to be mindful that a single flexible fiberoptic laryngoscopy may not be sufficient to rule out abnormal vocal fold mobility as certain etiologies such as Chiari malformation may present with intermittent paresis. The central pathology underlying the vocal fold immobility may not be diagnosed prior to the consultation. The otolaryngologist must consider brain, neck, and chest imaging in such cases where there is a reasonable index of suspicion. Generally, this index of suspicion arises during endoscopy where the inflammatory findings are out of proportion to what is generally a paucity of symptoms.

The second phase follows with rapid closure of the larynx at the supraglottic and glottic levels. Expiratory muscle contraction forces a rise in airway pressure during this compressive phase of coughing. It is the closure of the ventricular bands (false focal folds) that contributes the greatest sphincteric effect in preventing the flow of air during the compressive phase.

The third (expiratory) phase occurs as the glottis suddenly opens and rapid airflow expectorates mucus and foreign material. Maintenance of airflow velocity is assisted during expiration by continued narrowing of the opened supraglottic larynx. Vibrations of the laryngeal mucosa also assist in secretion clearance during the expiratory phase. Disorders affecting these latter two phases include those which weaken or prevent sphincteric laryngeal function (i.e., paralysis) and neuromuscular disorders that cause paresis. Finally, loss of sensitivity of the cough reflex is most commonly seen as a function of age. In children, it almost always suggests the presence of a very chronic pathologic process. This is most commonly seen in children with severe long-standing oromotor dysmotility who have aspirated for many years. Eventually, these patients only cough in response to extreme stimulation. If the clinical picture does not render the etiology of such a process obvious, an exhaustive search for such an explanation is imperative.

Etiologies of Cough

It is beyond the scope of this chapter to comprehensively detail the various etiologies of cough. What follows is a brief listing of diagnostic considerations with the exception of GERD, which is more completely discussed.

Sinonasal Causes of Cough

All such entities are covered elsewhere in this text in detail. A few points specific to cough, however, are warranted. First, although it is well documented that upper airway cough syndrome (i.e., "postnasal drip") is a common cause of cough in adults, no such data exist in children. In fact, to the contrary, a relationship between nasal secretions and cough is far more likely in children to be linked by a common infectious or inflammatory etiology. Second, abnormal sinus radiographs are found in between 18% and 82% of asymptomatic children. One of the biggest frustrations for otolaryngologists arises in children referred with abnormal sinus radiographs and cough whose parents have been prematurely and often erroneously set up to expect sinonasal disease as the definitive cause. It requires substantially more effort for the consultant to prove to parents that sinonasal disease is not the cause of cough than it does to prove that it is. Third, to date, there are no published prospective randomized controlled trials that assess the efficacy of medical therapies for upper respiratory tract disorders using nonspecific cough as the primary outcome measure.

Airway Lesions and Cough

Interestingly, the prevalence of airway lesions found in asymptomatic children is unknown, hence, their identification in children with chronic cough fails to definitively establish a cause-and-effect relationship. A relationship between an airway lesion and chronic cough can only be postulated. Tracheomalacia may impede airway secretion

clearance and also increases the risk of pneumonia distal to the malacia (33). Laryngomalacia is highly associated with reflux laryngopharyngitis.

Environmental Toxicants

A very sensitive issue to discuss with parents is the impact of passive smoke inhalation on their children. The data are irrefutable that passive smoke inhalation increases susceptibility to respiratory infections (34,35) and cough illnesses (36,37). Such relationships are especially true in children with asthma. In all children with chronic cough, exacerbating factors such as environmental toxicant exposure must be identified and interventional options for the cessation of the exposure be advised and initiated.

Chronic Nocturnal Cough

Traditionally, this pattern was said to immediately suggest two things. First, a chronic cough present only at night was thought to essentially eliminate rhinosinusitis as an etiology. Second, chronic nocturnal cough was said to be a direct indicator of asthma. In reality, neither of these precepts are absolute truisms. It is common that children with rhinosinusitis will experience a marked worsening of cough at night. The contrast is so striking that parents often only notice nighttime cough. Because parents are trying to sleep at night and the household is generally quiet, parental perception is often focused on nighttime cough even when rhinosinusitis is the cause. Regarding asthma, community-based studies reveal that only one-third of children with isolated chronic nocturnal cough have asthma. Surprisingly, no studies have objectively proven that nocturnal cough is worse than daytime cough in controlled asthmatics. In the end, these features are worth noting but in and of themselves do not constitute a basis for diagnosis.

Post-Infectious Cough

A cough that follows a viral URTI is referred to as a post-viral cough. The natural history has not been rigorously studied beyond 25 days. What further complicates the study of this etiology is the development of a new viral infection prior to complete recovery from the initial one. This is especially prevalent in younger children enrolled in daycare. At times simply identifying this etiology and presenting the self-perpetuating scenario to parents provides impetus to explore alternative child care that in and of itself may lead to resolution of the cough. It is also instructive to point out to parents that children under the age of 4 years average 5 to 8 distinct infections per year. Children 10 to 14 years of age average 2.5 to 5 infections per year (38). It is important to keep in mind that classic infections with cough as a primary symptom such as pertussis or "walking pneumonia" (i.e., *Mycoplasma*) generally present with symptoms in addition to cough. Confounding this basic tenant, however, is that antibiotics and vaccination must be considered as potential modifiers of the classical presentation and natural history.

Foreign Body

It is rare that acute onset of cough in the setting of a witnessed foreign body aspiration or choking episode is not evaluated endoscopically for the presence of an airway foreign body. Far more pernicious are cases of chronic cough, especially in younger children under 5 years of age, with onset not preceded by any such witnessed event. The otolaryngologist must always consider the possibility of an airway foreign body when presented with a child with chronic cough. Unfortunately, a normal plain radiograph of the chest does not exclude the diagnosis. Inspiratory and expiratory plain chest radiographs may increase the diagnostic yield as may an auscultatory examination with a double-headed stethoscope. In this author's opinion, facility with a double-headed stethoscope is the single most important part of the physical examination in such cases.

Gastroesophageal Reflux Disease—It's ok to Put the Cart Before the Horse

As stated earlier, chronic cough has more than 20 causes, and in up to 62% of cases, more than one cause is identified (18). Of these potential etiologies, reflux-related cough is the second most common cause of cough identified in 40% of this patient population. Interestingly, gastroesophageal reflux (GER)-related chronic cough is *defined as a cough that improves or is eliminated with GER-specific therapy*. It is rare in medicine to include in the diagnostic definition of an entity a mandatory concomitant response to treatment. As is true of most entities described in this section, not only can an entire chapter be easily dedicated to GER but as readily an entire book. Virtually every respiratory tract disorder including otitis media, sinusitis, laryngitis, laryngotracheal stenosis, recurrent pneumonia, and apnea has implicated some role for GERD.

So, specific to cough and in addition to the epidemiology just described, what are the salient issues? Unlike most diagnoses that are suggested over 80% of the time based on history and symptoms, GER is clinically silent in up to 75% of patients with GER-related chronic cough. This sets the stage for a very mixed blessing. On the one hand, it serves as a justification to not only consider but to also empirically diagnose and treat patients with chronic cough for GER. This often creates a vicious diagnostic web from which it is often very difficult to escape when GER does not apply. On the other hand, if one attempts to lessen the emphasis on GER, one risks overlooking a very obvious, common, and straightforward cause. In the ACCP published evidence-based guidelines for the diagnosis and management of chronic cough, initiating empiric GER therapy using lifestyle modification therapy and proton

pump inhibition in order to identify and treat GER-related chronic cough was recommended.

How long should empiric GER treatment be prescribed? The answer is not straightforward as cough often resolves within 2 weeks of proton pump inhibitor therapy though may take more than 50 days to respond in some patients. Most clinicians consider a 2-month empiric trial reasonable before pursuing more aggressive interventions. Clearly, the keys are to communicate to patients and their families that the diagnosis and treatment are empiric, meaning that GER may not play a role. One must also emphasize the variable timing of response. Finally, it is absolutely critical to have explored other serious causes of cough requiring more immediate treatment. Delaying treatment of a malignant tumor for 60 days is medicolegally unacceptable.

So, if one adheres to this guideline, in what instances should one consider diagnostic testing? At the most basic level, nonresponders should be considered for endoscopy, impedance monitoring, and/or dual esophageal pH-probe testing. From a treatment standpoint, medical nonresponders will have to be considered for fundoplication. Consider early consultation for fundoplication in patients suspected of having nonacid GER. Gastric outlet obstruction should be considered. Much of the confusion pertains to lack of a readily available diagnostic gold standard to make this diagnosis. Further complicating the diagnostic approach is confirming that, even if evidence for GER exists, it is also directly causing the symptom. Although many assume that one naturally leads to the other, such is not the case. In the end, proof that GERD causes chronic cough in children is rare. Infants often regurgitate, yet few well infants cough with these episodes. The prospective data available suggest that GERD is infrequently the sole cause of cough in children.

Etiology Specific Cough Treatment

In real estate, the hackneyed mantra is "location, location, location!" The authors suggest that for cough it should be "inflammation, inflammation, inflammation!" When considering etiology and most definitely when recommending treatment, invariably the final common denominator is most often inflammation. At times, the inflammation will spontaneously resolve upon identification, elimination, and treatment of the underlying cause of the inflammation. Such is the case for airway foreign body, GER, and atopy to some degree. At other times, the inflammatory mediators and mechanisms have become self-perpetuating and autoregulating. Various immune-mediated conditions serve as the prototype for this category of patients. In the latter instance, "breaking the inflammatory" cycle may restore physiologic homeostasis and "cure" the patient. In other such instances, the very best that can be achieved is "control" of the chronic inflammatory process. Still other conditions represent an amalgamation of the two. Reactive airway disease serves as such a condition as potentiators can be identified and treated. Many other patients, however, have no such clearly identifiable triggers. There is still much to be investigated and understood about the inflammatory pathways that define cough. This is arguably the most intense focus of contemporary research and defines the next major breakthrough and advance for these patients.

Nonspecific Cough Treatment

One of the most notable and controversial implications of the ACCP guidelines is that OTC expectorants and cough suppressants (i.e., cough syrups and drops) are usually a waste of money. Surprisingly, the new ACCP cough guidelines were the first to provide comprehensive, evidence-based recommendations for the diagnosis and management of cough in children. They included a particularly strong warning against the use of OTC cough and cold medications in children 14 years old and younger.

The effectiveness of these remedies is unproven in the pediatric age group and thus may place younger children unnecessarily at risk for medication side effects such as liver damage due to accidental overdose. Particularly concerning are reports that accidental ingestion in children younger than 5 years is common. The American Academy of pediatrics also recommends against the use of codeine or dextromethorphan for treating cough resulting from any cause. Fundamental to all of these recommendations is that in most cases, a cough that is unrelated to chronic lung conditions, environmental influences, or other specific factors will resolve spontaneously. If the reader is to permanently commit but one principal from this section to memory it should be this. *Cough in children should be treated based on etiology, and there is no evidence for using medications for the symptomatic relief of cough.*

If antitussives and other related medications are used, children must be evaluated after all medication had been discontinued if cough persists beyond a reasonable time frame. An evaluation of the time to response is important. As far as asthma treatments, there is no evidence to support use of β_2 agonists or anticholinergic agents in children with acute cough and no evidence of airway obstruction. Similarly, there are no randomized controlled trials evaluating the use of systemic steroids in children with acute cough. Low-dose inhaled corticosteroids have been proven effective in most cases of childhood asthma (39–41), hence, a trial of budesonide at a dose of 400 μg/d equivalent dose with another evaluation in 2 to 3 weeks is recommended.

Antibiotics, Antihistamines, Decongestants

Antibiotics are often empirically prescribed for children with chronic cough. Two randomized controlled trials examined the treatment of chronic cough with antibiotics. The first trial comprised a cohort wherein 23% of the children had cough for more than 30 days while the second with a mean duration of cough for 21 to 28 days. Significant improvement was noted in the antibiotic treatment arm

in both studies with nasopharyngeal colonization predominantly consisting of *Moraxella catarrhalis*. A Cochrane review concluded that a 10-day course of antibiotics reduces the duration of short- to medium-term cough. Conversely, for acute cough, antihistamine in combination with decongestant were no more effective than placebo. Neither diphenhydramine nor dextromethorphan were more effective than placebo in treating nocturnal cough in children. A meta-analysis concluded that neither antihistamines alone nor in combination effectively reduced symptoms of the common cold in children. No level-one evidence has been published evaluating the treatment of cough persisting for greater than 4 weeks in children.

Irrespective of diagnosis, environmental influences and parental expectations should be discussed and managed accordingly. The astute clinician understands that cough often impacts the quality of both the child's and the parents' lives. Explicitly defining parental expectations and fears will enhance the efficacy of the management of cough in children. This final point is where the science of medicine ends and the art of medicine begins. If a clinician does not purposefully explore parental fears, the clinician may miss that the parent is actually seeking consultation to alleviate a fear of the child choking and dying, Sudden Infant Death Syndrome (SIDS), progression into life-threatening status asthmaticus, and possible resultant permanent chest wall injury. By these parents' criteria, a successful consultation concludes no more than the exclusion of these fears. Not unlike most conditions, a lower likelihood to administer OTC medications and fewer doctor visits occur with more highly educated mothers (42).

CONCLUSION

Indeed, the quote by George Hebert which began this chapter affirmed that "…cough cannot be hid." So fortuitous is that fact since cough along with stridor and aspiration serve as important warnings of potentially life-threatening pathology. It is most fitting to end with Chevalier Jackson's description of aspiration in children that he termed "self-drownage." He explained that, "The accumulation may literally drown the patient in his own secretions. Infants cannot expectorate, and their cough reflex is exceedingly ineffective in raising secretion to the larynx. The cough reflex may be entirely absent in children. Age may be cited as one of the most frequent etiologic factors in the condition of self-drownage. Bronchoscopic aspiration is quite efficient, and can save any patient not affected with conditions that are fatal by other pathologic processes" (43). As this chapter has described, modern medicine has advanced a long way from the methods of Chevalier Jackson. Yet, at the same time, the fundamental principals of diagnosis and management have remained constant. Perhaps this is yet another example of the time-honored precept that "the more things change, the more they stay the same."

HIGHLIGHTS

- Cough, aspiration, and stridor, although clinically distinct entities, often coexist due to the anatomic and functional interrelatedness of the structural etiologies of each.
- The complex structure and function of the upper aerodigestive tract often adversely alter the delicate coordination between swallowing and respiration.
- Always suspect vascular anomalies in a child with "atypical asthma" or in children with severe symptoms associated with respiratory tract infections out of proportion to what is expected, especially when a history of noisy breathing since birth is elicited.
- Cricothyroidotomy is not recommended in pediatric patients due to the small size of the cricothyroid membrane and the increased incidence of laryngeal injury.
- Tracheostomy should be viewed as a temporizing measure until more definitive control of aspiration can be achieved and should be recommended judiciously.
- Chronic cough has more than 20 causes, and in up to 62% of cases more than one cause is identified from more than a half dozen distinct anatomic locations with receptors found in the nose, nasopharynx, posterior oropharynx, external auditory canals, tympanic membranes, stomach, esophagus, pleura, pericardium, and diaphragm.
- There are nearly 30 million physician visits for cough in the United States each year, positioning cough amongst the top five for number of doctor visits with nearly 3.5 billion dollars spent on OTC cough medications.
- In and of itself, cough does not represent a sign of disease. To the contrary, cough is an important normal protective reflex activity. The most widely recognized neural response involved in airway protection is cough.
- Cough in children should be treated based on etiology, and there is no evidence for using medications for the symptomatic relief of cough.

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90 Laryngeal Stenosis

Michael J. Rutter *Aliza P. Cohen* *Alessandro de Alarcón*

Airway management of the infant, child, or adolescent may transform from the stable and routine to abrupt and life-threatening loss of the airway. This may occur either as a result of the underlying pathology or from the management of the pathology. Given the importance of a potentially emergent situation, the clinician must have a sound understanding of the causes, clinical presentations, and management of laryngotracheal stenosis. Our chapter therefore focuses on this content.

AGE-RELATED ANATOMIC DIFFERENCES IN THE LARYNX

Although the three portions of the larynx (supraglottis, glottis, and subglottis) are the same in children and adults, there are a number of age-related differences that play a role in the development of laryngotracheal stenosis.

Laryngeal Size

The infant larynx is approximately one-third the size of the adult larynx; however, it is proportionally larger than the adult larynx relative to the rest of the tracheobronchial tree. The infant vocal fold also differs in length from the adult vocal fold; it is approximately 7 to 8 mm long, whereas the adult vocal fold is 14 to 23 mm long. In the infant, half of the length of the true vocal fold is composed of the vocal process of the arytenoid. In the adult, the vocal process occupies only one-fourth to one-third of the total length of the true vocal fold. The subglottis is the narrowest part of the airway because of the complete ring structure of the cricoid cartilage. In the infant, the subglottis is approximately 4.5 to 7 mm in diameter. A child with a subglottic diameter of 4.0 mm or less has subglottic stenosis (1).

Laryngeal Location

The position of the larynx in relation to other structures of the neck is different in infants and adults. In the infant, the superior border of the larynx is located as high as the first cervical vertebra, with the cricoid cartilage positioned at approximately the level of the fourth cervical vertebra. This results in the hyoid overriding the superior larynx in an infant, with the thyroid notch usually being impalpable as a consequence. Because of the superior positioning of the larynx, the epiglottis approximates the dorsal surface of the soft palate. This contributes to the obligate nasal breathing seen in the first months of life. As the child grows into adulthood, the larynx gradually descends, and the cricoid cartilage eventually rests at the level of the sixth cervical vertebra. The infant epiglottis is the structure that demonstrates the most dramatic change in configuration. At birth, the epiglottis, which is shaped like the Greek letter omega (Ω), is narrower and softer than the epiglottis in older children and adults. It has a less stable base, and there is a more acute angle between the epiglottis and glottis, allowing the epiglottis to fall into the laryngeal inlet. As the child grows, cartilaginous support of the epiglottis becomes more rigid, and the angle of the thyroid cartilage changes from 110 to 120 degrees to an angle of 90 degrees in the adolescent male. In the adult female, this angulation remains more obtuse, as in childhood. Because cartilage, muscle, and submucosal tissues are more pliable and less fibrous in the infant than in the adult and because the airway is so narrow at the subglottis, any process that produces edema can cause significant airway obstruction. Circumferential mucosal edema of 1 mm within the larynx of an infant narrows the subglottic space by more than 60% (2). Within the fixed ring of the cricoid cartilage, edema will cause a marked diminution in potential

airflow. This diminution is best explained by Poiseuille's Law, which relates resistance to airflow (Q) across an area of narrowing to the inverse of the radius of the lumen to the fourth power ($Q \approx 1/r^4$). Thus, 1 mm of edema in an infant results in a 75% decrease in luminal diameter and a 16-fold increase in resistance through the airway. This same degree of narrowing in the adult reduces the diameter of the airway by only 30% and doubles airway resistance.

LARYNGEAL STENOSIS

Laryngeal stenosis may occur in the supraglottis, glottis, or subglottis. Clinically, subglottic stenosis is by far the most common problem requiring intervention, followed by glottic stenosis. Supraglottic stenosis is rare in children and is usually a consequence of thermal or chemical injury or iatrogenic injury following previous airway reconstructive surgery. Evaluation of congenital stenosis of the larynx can often be determined by the signs and symptoms of obstruction, which differ depending on the specific anatomic level of laryngeal narrowing. These signs and symptoms help the clinician in the initial assessment of the patient (Table 90.1).

Subglottic laryngeal obstruction produces a hoarse and husky voice with pathognomonic biphasic stridor. Patients may also have a barking cough. Feeding is normal unless there is a severe airway obstruction.

Signs and symptoms of glottic obstruction include a hoarse, aphonic voice with inspiratory stridor that may become biphasic as the severity of the obstruction increases. As in patients with subglottic obstruction, feeding is normal unless the airway obstruction is severe. Patients usually have no cough. Patients with posterior glottic stenosis usually present with a normal voice, and may mimic bilateral vocal fold paralysis in this regard.

Supraglottic laryngeal obstruction produces a muffled or throaty voice with an inspiratory fluttering stridor. Patients may present with significant feeding problems but no cough. The airways of children with supraglottic stenosis are among the most challenging airways to manage, as the stenosis is often further complicated by dynamic supraglottic collapse. An individualized approach is essential in these patients.

TABLE 90.1 SIGNS AND SYMPTOMS OF LARYNGEAL STENOSIS

Laryngeal Region	Signs and Symptoms
Subglottis	Hoarse or normal voice, biphasic stridor, normal feeding (except with severe obstruction), barking cough
Glottis	Hoarse voice or aphonia, inspiratory (early) or biphasic (late) stridor, normal feeding (with or without severe obstruction), no cough
Supraglottis	Muffled voice, fluttering inspiratory stridor, severe feeding problems, no cough

Adapted from Reichert TJ. *Diseases of the Larynx in Infants and Children*. Washington, DC: American Academy of Otolaryngology-Head and Neck Surgery, 1987.

Congenital Laryngeal Stenosis

Subglottic Stenosis

Subglottic stenosis in the neonate is defined as a lumen 4.0 mm in diameter or less at the level of the cricoid. A relevant reference point is the outer diameter of an endotracheal tube. For example, a 2.5 endotracheal tube has an outer diameter of 3.6 mm, and a 3.0 endotracheal tube has an outer diameter of 4.2 mm.

It is important to differentiate congenital from acquired subglottic stenosis. Acquired subglottic stenosis is caused by intubation or other forms of laryngeal trauma; this is often an iatrogenic injury caused by a complication of medical therapy. Acquired subglottic stenosis is generally more severe, requiring aggressive, long-term management (discussed later in this chapter). In the absence of trauma, an abnormality of the cartilage or subglottic tissues is usually considered to be congenital. The cause of congenital subglottic stenosis is thought to be a failure of the laryngeal lumen to recanalize (3). This abnormality lies on a continuum of embryologic failures that includes laryngeal atresia, stenosis, and webs. In its mildest form, congenital subglottic stenosis manifests with a normal-appearing cricoid with a smaller-than-average diameter, usually with an elliptical shape.

A mild case of subglottic stenosis may produce a clinical picture of recurrent upper respiratory infections, often diagnosed as croup, in which minimal subglottic swelling precipitates airway obstruction. The greatest obstruction is usually 2 to 3 mm below the true vocal folds in a young child.

More severe cases of congenital subglottic stenosis may present with acute compromise of the airway at delivery. If endotracheal intubation is successful, the patient may require intervention before extubation. In more severe cases, when intubation cannot be achieved, a tracheotomy may be lifesaving at the time of delivery. Interestingly, however, infants with congenital subglottic stenosis may have surprisingly few symptoms, and even children with grade III subglottic stenosis may not present for weeks or months.

Congenital subglottic stenosis is often associated with other congenital head and neck lesions and syndromes (e.g., a small larynx in Down syndrome). After the initial management of congenital subglottic stenosis, the larynx will grow with the patient and may not require further surgical intervention.

Congenital subglottic stenosis can be divided histopathologically into membranous and cartilaginous types (1,2) (Table 90.2). The membranous type is usually

TABLE 90.2 HISTOPATHOLOGIC CLASSIFICATION OF SUBGLOTTIC STENOSIS

Membranous stenosis
- Granulation tissue
- Submucosal gland hyperplasia
- Submucosal fibrosis

Cartilaginous stenosis
- Cricoid cartilage deformity
  - Normal shape that is small for infant's size
  - Abnormal shape
    - Large anterior lamina
    - Large posterior lamina
    - Generalized thickening
    - Elliptical shape
    - Submucosal cleft
    - Other congenital cricoid stenosis
- Trapped first tracheal ring

Combined stenosis

From Bluestone CD, Stool SE, eds. *Pediatric Otolaryngology*, 2nd ed. Philadelphia, PA: WB Saunders, 1990:1098, with permission.

TABLE 90.3 GRADING SCALE FOR LARYNGEAL STENOSIS

Grade	Laryngeal Lumen Obstruction
I	<50%
II	51%–70%
III	71%–99%
IV	Complete obstruction

circumferential and presents as a fibrous soft tissue thickening in the subglottis caused by increased fibrous connective tissue or hyperplastic mucous glands. It usually includes the area 2 to 3 mm below the true vocal folds, but it may extend upward to include the true cords. The cartilaginous type commonly presents as a thickening or deformity of the cricoid cartilage that creates a shelf-like plate of cartilage on the inner surface of the cricoid ring, extending posteriorly as a solid sheet and leaving only a small posterior opening (1). Stenosis may also be caused by a trapped first tracheal ring.

Although the histopathologic picture may vary, the diagnosis of subglottic stenosis is based on endoscopic assessment. The stenosis due to a scar, granulation tissue, submucosal thickening, or a congenitally abnormal cricoid can be differentiated from subglottic stenosis with a normal cricoid, but endoscopic measurement with endotracheal tubes or bronchoscopes is required for an accurate evaluation. Many laryngeal stenoses represent a combination of a congenitally small larynx further traumatized by endolaryngeal intubation or instrumentation.

Radiographic evaluation of a patient's unintubated airway may give the clinician clues about the site and length of the stenosis. Useful imaging modalities include inspiratory and expiratory lateral soft tissue neck films; fluoroscopy to demonstrate the dynamics of the trachea and larynx; and a chest radiograph. The single most important investigation, however, remains high-kilovoltage airway films. These films are helpful in identifying the classic steepling seen with subglottic stenosis and also in providing a warning of tracheal stenosis; this is usually caused by complete tracheal rings, which may place the child in a life-threatening situation during rigid endoscopy.

Endoscopy is necessary for the diagnosis of laryngeal stenosis. Flexible fiberoptic endoscopy provides information on dynamic vocal fold function. Rigid endoscopy with Hopkins rod lens telescopes provides the best possible examination. Precise measurement of the endolarynx and staging of the laryngeal stenosis can be carried out. The most commonly used system for staging subglottic stenosis is the Myer-Cotton grading scale (Table 90.3). Most grade I and many grade II lesions do not require surgical intervention; however, grade III and grade IV lesions generally necessitate a surgical approach.

Laryngeal Webs

Supraglottic webs represent fewer than 2% of congenital laryngeal webs (Fig. 90.1). These webs are diaphragmatic outgrowths that usually arise anteriorly. If partial, they provide air passage posteriorly. The web is typically thickened anteriorly and thins out toward the posterior edge. Symptoms, including dyspnea and voice change, depend on the size and position of the web. Ten percent of children with supraglottic webs have associated congenital anomalies.

More than 90% of laryngeal webs are anterior glottic webs, representing a failure to completely recanalize the larynx. Patients usually present with an abnormal cry or respiratory distress at birth. Virtually all glottic webs are anterior, with varying degrees of compromise of the glottic airway. Although some webs are gossamer thin, most anterior glottic webs are thick and usually associated with a subglottic "sail" compromising the subglottic lumen. As such, they may be considered a form of partial laryngeal atresia. Thin webs may escape detection because neonatal intubation for airway distress may lyse the web. Thick webs require open reconstruction with either reconstruction of the anterior commissure or placement of a laryngeal keel. Approximately 40% of patients with thick membranous webs require tracheotomy placement. There is a strong association between anterior glottic webs and velocardiofacial syndrome (4).

A web can also form in the subglottic region, mimicking cricoid cartilage deformities or subglottic stenosis. Subglottic webs account for approximately 7% of laryngeal webs and are anteriorly based, with a small posterior

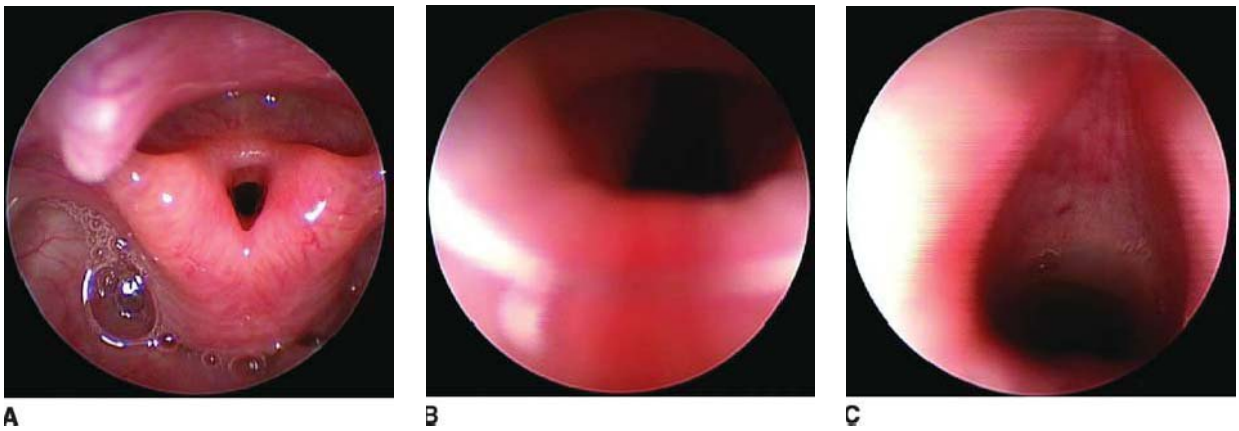


Figure 90.1 Endoscopic view of a patient with a congenital supraglottic web **A**: 0-degree telescope. **B**: 30-degree telescopic view. **C**: 30-degree telescopic view showing normal vocal folds beyond the web.

opening that may be only the size of a pinpoint. The superior surface is covered with squamous epithelium, and the inferior surface is mucous membrane. A slight female predominance has been reported. Symptoms include aphonia, respiratory distress, and biphasic stridor. The diagnosis must be made by flexible fiberoptic or rigid endoscopy.

Atresia

Laryngeal atresia (supraglottic, glottic, subglottic) represents complete failure of the lumen of the larynx to recanalize, and is therefore the most severe form of laryngeal stenosis. This condition is associated with a high frequency of other congenital anomalies, including esophageal atresia, tracheoesophageal fistula (TEF), urinary tract anomalies, and limb defects, particularly those that involve the radius. If a TEF exists, ventilation may occur through this communication. Tracheotomy is essential if the patient is to survive. Many children are not properly diagnosed in time for the appropriate intervention, and the diagnosis may be made postmortem. In the absence of a TEF, the lungs and major airways expand due to the pressure of fluid secreted by the lungs, leading to eversion of the diaphragms, development of a prune belly, and fetal hydrops; this constellation is known as congenital high airway obstructive syndrome.

Complete laryngeal atresia is challenging to repair due to the associated small cricoid. Reconstruction involves anterior cricoid resection, posterior cricoid expansion, web division, and prolonged stenting. This is usually best left until the child is older than 4 years of age. It is unlikely that a single operation will achieve decannulation.

Acquired Laryngeal Stenosis

Postintubation Stenosis

In 1965, McDonald and Stocks (5) advocated long-term nasotracheal intubation in the management of the unstable neonatal airway. Although this revolutionized neonatal care, especially for the premature infant, there was a corresponding increase in the incidence of acquired subglottic stenosis in neonates with prolonged stays in neonatal intensive care units. The incidence of combined congenital and acquired subglottic stenosis also rose as infants with congenital subglottic stenosis were intubated for airway compromise, often with inappropriately large endotracheal tubes. Acquired subglottic stenosis resulting from prolonged neonatal intubation is now more common than congenital stenosis in the pediatric age group.

The pathogenesis of acquired subglottic stenosis is still not understood, although several theories have been proposed. Autopsy studies demonstrate that there is a period of ulceration and necrosis of cricoid mucosa in the first hours and days of intubation (5). Quiney and Gould (6) reported healing and reepithelialization in the cricoid region, even while the endotracheal tube remained in place. However, 1% to 8% of neonates develop stenosis after prolonged intubation (7). The incidence has steadily dropped over the last three decades despite the longer periods of intubation that have become commonplace in increasingly smaller infants. Although several factors are involved, the two most significant factors have been the abandoning of red rubber endotracheal tubes and the realization that the ideal endotracheal tube size is not the largest that will fit but rather the smallest that can permit adequate ventilation. Ideally, an endotracheal tube should leak air around it with subglottic pressures below 20 to 25 cm of water.

Flexible fiberoptic laryngoscopy should be a routine part of the initial evaluation of the larynx. Vocal fold paralysis may prohibit decannulation, even after successful surgical reconstruction of a compromised airway. Rigid endoscopy using Hopkins telescopes is necessary for diagnosis and photo documentation. Correct sizing of the airway should be accomplished with appropriate-sized endotracheal tubes or rigid bronchoscopes. Radiographic assessment can provide information about the site and length of the stenosis that will assist in management decisions. In patients

with acquired stenosis, a prolonged period of observation after tracheotomy is inappropriate because of the high risk of death should the tracheotomy tube become obstructed. Therefore, surgical reconstruction is often undertaken to create a safer airway.

Post-Tracheotomy Stenosis

During a tracheotomy, additional injury may result in laryngotracheal stenosis or suprastomal collapse. Secondary infection, chondritis, or pressure exerted by the curvature of the tracheotomy may result in stenosis or suprastomal collapse above the tracheotomy site. Stenosis may occur because of a high tracheotomy, which is performed through the thyroid, cricoid, or first tracheal cartilage; a high tracheotomy also includes cricothyroidotomy. Although this procedure is well known to otolaryngologists and emergency room physicians as a lifesaving intervention, it may result in a complication rate as high as 32% (8).

Post-Reconstruction Restenosis

Subglottic stenosis may also result after failed laryngotracheoplasty. This is more likely to occur if the original procedure was not aggressive enough or there is concomitant bacterial infection, development of granulation tissue, malalignment or improper stent sizing, or histopathologic changes. Indeed, any form of airway surgery, endoscopic or open, has an attendant risk of resultant airway restenosis. There is greater risk of restenosis following airway reconstruction if the larynx is actively inflamed. This is most commonly seen in patients with gastroesophageal reflux disease (GERD), but may also be seen in patients with eosinophilic esophagitis (EE). Optimally, both of these conditions should be treated before reconstructive surgery is performed. Occasionally, an active larynx is seen in a patient who does not have either GERD or EE. In this setting, spontaneous resolution with time is expected, and patience prior to airway surgery is recommended.

Infectious or Inflammatory Stenosis

Laryngeal stenosis caused by infectious or inflammatory disorders is usually the result of end-stage processes of untreated disorders.

Granulomatous Disease

Tuberculosis of the larynx is the most common granulomatous disease of the larynx, and it is usually associated with pulmonary disease. The most common sites for laryngeal tuberculosis are the interarytenoid space, arytenoid cartilages, posterior surface of the true vocal folds, and laryngeal surface of the epiglottis. The patient may present in the early stages of disease with diffuse edema and erythema of the cords, which may mimic an early-stage glottic carcinoma. However, disease progression manifests with nodular lesions and ulceration of the epithelium, which can lead to perichondritis and chondritis. Due to interarytenoid muscular involvement or cricoarytenoid joint fixation, patients may also present with symptoms that mimic vocal fold paralysis. Diagnosis is made by demonstration of *Mycobacterium tuberculosis*. Successful treatment usually leads to complete healing of the larynx. If the disease is not treated, chondritis and necrosis will destroy the larynx with extensive scarring and stenosis.

Sarcoidosis, rhinoscleroma, and Wegener granulomatosis are all rare disorders in children. Wegener granulomatosis may respond well to steroids, cyclophosphamide, and possibly, co-trimoxazole. It has a predilection for the subglottis and, once quiescent, may require airway reconstruction with cricotracheal resection being more efficacious than standard laryngotracheal reconstruction utilizing expansion cartilage grafting techniques.

Trauma

Because laryngeal trauma is discussed in Chapter 77, our comments here are brief. If trauma is mismanaged or unrecognized, it may lead to laryngeal stenosis. Sources of internal trauma include foreign bodies and instrumentation during endoscopic procedures. These forms of trauma usually lead to glottic and subglottic scarring and resultant stenosis. External forms of laryngeal trauma, such as motor vehicle accidents, sports-related injuries, and assaults, including blunt and penetrating trauma, can also produce laryngotracheal stenosis.

Anterior blunt trauma, as sustained in motor vehicle accidents or sports-related injuries, usually leads to posterior supraglottic and glottic stenosis. An external force at the hypopharyngeal level may cause scar formation between the epiglottis and posterior pharyngeal wall. Fracture of the hyoid bone displaces soft tissues posteriorly, narrowing the laryngeal inlet. These injuries may also cause web formation on the posterior hypopharyngeal wall and stenosis in the postcricoid area. Blunt and penetrating trauma may lead to laceration or hematoma formation in the glottis, which will produce laryngeal stenosis if not treated appropriately.

Systemic Diseases

Laryngeal stenosis due to fixation of the cricoarytenoid joint may be caused by rheumatoid arthritis or juvenile rheumatoid arthritis (Still disease). About 25% of patients with rheumatoid arthritis present with limitation of the motion of the cricoarytenoid joint. Systemic lupus erythematosus and gout may also cause arthritis of this joint, leading to narrowing of the laryngeal inlet. Hoarseness, stridor, dyspnea, and pain are the signs and symptoms of arthritic involvement. Erythematous edema of the arytenoid with the vocal fold fixed in the paramedian or intermediate position may be found during examination. Diagnosis must include direct laryngoscopy with palpation of the arytenoid to differentiate this from vocal fold paralysis. Appropriate laboratory studies

include erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, and rheumatoid factor.

Thermal Injuries

Thermal injuries of the glottis and subglottis may occur without thermal injury to the trachea and lung due to the cooling of air by the upper airway and reflex closure of the cords. Thermal injuries from steam, possessing 4,000 times the heat-carrying capacity of heated air or gas, may cause significant laryngeal burns. Laser airway fires may be particularly damaging. The pathophysiology of stenosis in laryngeal thermal injuries is thought to be governed by three factors: direct thermal injury, toxic effects of combustion products, and prolonged intubation. Once the scar tissue has matured, airway reconstruction may be successfully undertaken (9).

Caustic Ingestions

The results of caustic ingestions on oropharyngeal and esophageal mucosa are extensively reviewed in the literature, and indicate that laryngeal stenosis is rare. Both acidic and alkaline ingestions may cause supraglottic edema and airway obstruction, thus necessitating tracheotomy placement (10). Severe caustic ingestions may lead to fibrosis of the posterior cricoarytenoid muscle. Hypopharyngeal and supraglottic mucosal injury may cause supraglottic scarring and stenosis.

GERD and EE

GERD has long been thought to be an exacerbating factor in subglottic stenosis. GERD is common in children and disproportionately prevalent in children with subglottic stenosis. Although the appearance of the larynx and subglottis may strongly suggest GERD, there is no single definitive test to establish the presence of reflux that reaches the larynx. Gross reflux may occur with no obvious clinical signs on endoscopy. The clinician should therefore weigh the results of rigid laryngoscopy, esophagogastroduodenoscopy, esophageal biopsy, and dual pH probe or impedance probe tests in determining the role of GERD in each patient. In severe cases, GERD should be treated with H_2 blockers and proton pump inhibitors or fundoplication prior to reconstructive surgery.

EE is an uncommon disorder that, if untreated, may have a significant effect on the aerodigestive tract. Although many children with EE also have esophageal, laryngotracheal, and sinonasal complaints, many are asymptomatic (11). The diagnosis is made by histologic examination of biopsies taken from the esophagus at the time of esophageal endoscopy. In patients with active EE, the laryngotracheal complex is often inflamed. In this setting, surgery frequently elicits a brisk inflammatory response that can lead to graft failure or restenosis. If EE is present, our experience indicates that medical management followed by repeat endoscopy with biopsies is prudent. Once biopsies reveal that there is no active EE, surgery may be performed.

Radiation Effects

The effects of radiation on the adult pharynx and larynx are well established, particularly in the context of management of laryngeal malignancy (12). Although radiation therapy in curative doses in children is rarely required, the consequences may be similar to or worse than those seen in adults. Pharyngeal or laryngeal edema and stenosis may result, often with associated aspiration. Reconstructive surgery in these children is fraught with problems.

TRACHEAL STENOSIS

As with laryngeal stenosis, tracheal stenosis may be either congenital or acquired. Acquired stenosis is often secondary to trauma caused by intubation. The most commonly encountered congenital condition is complete tracheal rings. Although rare, this anomaly is life threatening. It presents with progressive worsening of respiratory function over the first few months of life, stridor, retractions, and marked exacerbation of symptoms during intercurrent upper respiratory tract infections. Children with tracheal stenosis generally exhibit a biphasic wet-sounding breathing pattern referred to as "washing machine breathing." This pattern transiently clears with coughing. The risk of respiratory failure increases with age in congenital tracheal stenosis, as the infant typically grows faster than the stenosis. Decompensation may occur around 4 months of age and is often incited by an upper respiratory tract infection.

An initial high-kilovolt airway radiograph may reveal tracheal narrowing; however, the diagnosis is established with rigid bronchoscopy. This must be performed with utmost caution, using the smallest possible telescopes, as any airway edema in the region of the stenosis may transform a narrow airway into an extremely critical airway. If the stenosis is severe, the stenotic airway should not be instrumented, even with the smallest telescope. The initial bronchoscopic view is often sufficient to establish the diagnosis, thereby avoiding the risk of airway edema. Because 50% of children have a tracheal inner diameter of approximately 2 mm at the time of diagnosis, the standard interventions for managing a compromised airway are not applicable. The smallest endotracheal tube has an outer diameter of 2.9 mm, and the smallest tracheotomy tube has an outer diameter of 3.9 mm. The stenotic segment can therefore not be intubated. This may leave extracorporeal membrane oxygenation (ECMO) as the only viable alternative for stabilizing the child. This circumstance is best avoided by performing bronchoscopy with the highest level of care. Over 80% of children with complete tracheal rings have other congenital anomalies, which are usually cardiovascular in origin. In view of this, investigations should include a contrast-enhanced chest high-resolution CT scan and an echocardiogram. Given that a pulmonary artery sling is a common association, it should be ruled out. If present, it should be repaired at the time of the tracheal repair. Most children with complete tracheal rings require tracheal reconstruction (13).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of laryngeal stenosis in children and adults must include all conditions that may cause stridor, dyspnea, and respiratory distress. For patients who do not present with acute respiratory distress, careful history taking can help the clinician localize the site of pathology. Because the presentation of laryngeal stenosis may vary from asymptomatic congenital subglottic stenosis in the infant to acute airway obstruction with supraglottic injury in the adult, the differential diagnosis is quite extensive. Table 90.4 outlines the major causes of stridor and respiratory distress that should be considered in the differential diagnosis of laryngeal stenosis in children and adults. Endoscopic examination with or without a biopsy provides the best chance for definitive diagnosis.

MANAGEMENT

Natural History

Severe congenital laryngeal stenosis requires immediate airway intervention, but fewer than half of patients with congenital laryngeal stenosis require tracheotomy. These patients may present only after repeated episodes of childhood laryngotracheal infections or later with exercise intolerance. Patients with acquired laryngeal stenosis produced by internal or external trauma, infectious processes, or iatrogenic causes are more likely to require surgical reconstruction or a tracheotomy because of more severe stenosis.

TABLE 90.4 COMMON CONDITIONS THAT MIMIC LARYNGEAL STENOSIS

Neonate
- Laryngomalacia
- Vascular compression (e.g., innominate artery, aberrant subclavian artery, vascular ring)
- Vocal fold paralysis
  - Bilateral (e.g., Chiari deformity)
  - Unilateral (e.g., traumatic post ductus ligation)
- Hemangioma, subglottic
- Complete tracheal rings
- Laryngeal cleft
- Cri du chat syndrome
- Laryngeal saccules, laryngoceles

Child
- Dermoid, saccular, epiglottic cysts
- Lingual thyroid
- Infections (e.g., epiglottitis, croup, bacterial, laryngotracheitis)
- Foreign body
- Papillomatosis

Adult
- Vocal fold paralysis (status post thyroid surgery, laryngeal carcinoma)
- Viral, granulomatous, fungal laryngitis
- Reinke edema
- Laryngeal trauma (blunt or penetrating)
- Postintubation
- Hemangioma, supraglottic
- Idiopathic (e.g., spastic dysphonia)
- Neurologic (e.g., amyotrophic lateral sclerosis, multiple sclerosis)
- Caustic ingestion
- Systemic disease (e.g., rheumatoid arthritis, polychondritis)
- Tracheal tumors or obstruction

Medical Therapy

Treatment of laryngeal stenosis must include prevention. In children, this consists of precise airway management, particularly of patients who require prolonged intubation. In children requiring prolonged intubation, management of sedation or paralysis by experienced personnel, and selection of an appropriate size of endotracheal tube, may all influence the laryngeal outcome. In adults, careful management of mucosal injuries after trauma or surgical resection reduces the chance of acquired laryngeal stenosis. Efficient and appropriate management of infectious or inflammatory disorders, thermal or chemical injury, and gastroesophageal reflux can diminish the chance of iatrogenic stenosis. Medical treatment often consists of supportive therapy, including humidification, antibiotics, or steroid therapy in a monitored and closely supervised setting if temporary airway compromise is anticipated. Management of GERD or EE may occasionally lessen the degree of subglottic stenosis without having to resort to surgery. Similarly, treatment of the underlying disorder in autoimmune subglottic stenosis may allow nonsurgical resolution of the disease.

Preoperative Assessment

If laryngeal stenosis is of a magnitude to warrant surgical reconstruction, the potential outcome of surgery should be optimized. GERD should be treated with proton pump inhibitors and H_2 blockers. Antireflux medication should be continued for 3 months postoperatively. Treatment of EE with either an elimination diet or with swallowed fluticasone will improve the surgical outcome.

An adequate pulmonology workup is required in many children, especially those with a history of bronchopulmonary dysplasia and an oxygen requirement. Removal of a tracheotomy tube in a patient requiring over 1 L/min of oxygen is not recommended.

If there is a suspicion of ongoing aspiration, if surgery will involve the glottis, or if surgery will repair a stenosis that may be preventing aspiration, it is prudent to have the patient undergo a swallowing assessment comprising both a videofluoroscopic swallow study and a fiberoptic endoscopic evaluation of swallowing (FEES). These complementary studies can evaluate the ongoing aspiration with swallowing as well as the likelihood of future aspiration (14,15). FEES offers the advantages of allowing visualization of laryngeal protective mechanisms, documentation of vocal fold motion, and assessment of the potential risk of aspiration prior to reconstructive surgery. Information

obtained from these assessments is crucial in planning the operative procedure and in counseling the family about the potential risk of aspiration.

For children who have a tracheotomy, aspiration in general as well as specific causes of aspiration can be assessed by conducting a dye test with green food coloring. Aspiration is suspected if stained secretions or feeds are noted from the tracheotomy during feeding or at any time after feeding. This test has no value in the evaluation of aspiration in children with a grade IV stenosis.

Because many airway reconstructive procedures involve a compromise between voice quality and airway improvement, preoperative voice evaluation has become increasingly important (16–18). For further discussion of this evaluation, refer to Chapter 91.

In light of the prevalence (30%) of colonization by methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* in our patients with complex aerodigestive problems, we routinely screen for these bacteria by culturing of the nares and tracheal aspirate, both of which have a propensity for infecting cartilage and can lead to operative failure. Patients who test positive are treated with perioperative and postoperative antimicrobial therapy (19).

Endoscopic Evaluation

Endoscopic and surgical management are based upon two key principles: safely securing the airway and establishing a diagnosis based on endoscopic findings. Performing microlaryngoscopy and rigid bronchoscopy allows clinicians to identify anatomic levels of airway obstruction from the larynx to the carina. The supraglottis and glottis are assessed for stenosis, and the glottis is then evaluated for posterior glottic stenosis, anterior glottic web, and laryngeal cleft. If vocal fold immobility is suspected or seen on the FEES or voice evaluation, the cricoarytenoid joints should be palpated to determine if there is any fixation of the joint.

Rigid bronchoscopy is performed using Hopkins rod telescopes and rigid bronchoscopes. The subglottis is first evaluated. If subglottic stenosis is present, it is classified by the Myer-Cotton scale and sized using appropriate endotracheal tubes. The length of stenosis as well as its proximity to the vocal folds is also assessed and documented. If a tracheotomy is in place, attention is paid to the evaluation of the suprastomal area, considering the possibility of suprastomal collapse, granuloma, intratracheal skin tract, and high tracheotomy. The trachea is evaluated to the level of the carina, looking for additional pathology, including tracheal stenosis, complete tracheal rings, TEF, TEF pouches, vascular compression, and tracheomalacia.

Endoscopic and Surgical Management

Endoscopic management of laryngeal stenosis is successful in most cases involving grade I or II stenosis when there are no factors that predispose to failure (Table 90.5), whereas grade III and grade IV stenoses are more likely to require an open surgical approach. Endoscopic techniques include dilatation and scar division.

TABLE 90.5 FACTORS PREDISPOSING TO FAILURE IN TREATING SUBGLOTTIC STENOSIS WITH A CO_2 LASER

Failure of previous endoscopic procedures
Significant loss of cartilaginous framework
Combined laryngotracheal stenosis
Circumferential cicatricial scarring
Fibrotic scar tissue in the interarytenoid area of the posterior commissure
Abundant scar tissue >1 cm in vertical dimension
Severe bacterial infection of trachea after tracheotomy
Exposure of perichondrium or cartilage during CO_2 laser excision predisposing to perichondritis and chondritis
Concomitant tracheal disease

Endoscopic laser management of laryngeal stenosis has yielded success rates ranging from 66% to 80% (20). Careful patient selection is necessary for successful treatment. The advantages of successful endoscopic management include precise surgical excision, low surgical morbidity, minimal damage to underlying or surrounding tissues, and the ability to vary the amount of energy delivered. Endoscopic management of laryngeal stenosis potentially allows a successful outcome without a tracheotomy. Endoscopic laser techniques that use high energy over prolonged periods and damage underlying cartilage may create or worsen stenosis. Because of bacterial colonization of the aerodigestive tract, prophylactic antibiotic therapy is recommended.

Balloon dilatation of the airway using high-pressure noncompliant balloons has become a valuable addition to the tools used to manage airway stenosis. The best candidates for balloon dilatation are stenoses involving either thin or web-like scars, or relatively fresh stenoses. Repeated dilatation, at 1 to 3 week intervals, on up to four occasions may provide the optimal outcome. Adjunctive interventions, such as scar division (whether with a sickle knife or a laser) and steroid injection may further enhance the outcome of balloon dilation. Selection of balloon size is based upon the expected size of the normal airway—for example, a 4 year old should be intubated with a 5.0-mm endotracheal tube, with an outer diameter of nearly 7 mm. Therefore, the balloon size selected would be 7 to 8 mm for the larynx and 8 to 9 mm for the trachea.

If endoscopic management is unsuccessful or there are factors predisposing to endoscopic failure, a wide variety of open surgical techniques are available for managing laryngeal stenosis. This is generally the case in the setting of severe advanced acquired stenoses. Endoscopic diagnosis is imperative in selecting the appropriate surgical technique. The status of vocal fold mobility, the involvement of the posterior commissure, and a complete evaluation of the upper and lower airway are essential to the assessment.

The goal of open surgery for correcting laryngotracheal stenosis is to optimize voice function and permit early decannulation. Relative contraindications to open reconstructive surgery include (a) a significant risk in administering a general anesthetic, (b) the continued need for tracheotomy, and (c) significant laryngeal inflammation (GERD,EE) (21).

Open surgical management of the stenotic airway has evolved from Rethi's (22) original description of cricoid expansion in adults, which required a vertical cricoid split with prolonged stenting. Much of the subsequent work on laryngeal stenosis was performed in children because a growing patient population was created by the prolonged intubation of neonates. In 1971, Grahne (23) published a modification of the Rethi procedure. In 1972, Fearon and Cotton (24) introduced a new procedure developed in primates that successfully corrected subglottic stenosis in pediatric patients using grafts to increase the airway lumen.

Open surgical techniques for reconstruction of the airway compromised by laryngotracheal stenosis are usually considered in patients who are tracheotomy dependent and in patients who do not have a tracheotomy but who have significant exercise intolerance or sleep disturbance.

Otolaryngologists should have several open surgical techniques in their armamentarium to enable successful management of a variety of pathologic conditions (Table 90.6). Airway surgery should be tailored to the specific pathology of each patient, as no single procedure can adequately deal with all manifestations of laryngotracheal stenosis.

Anterior Cricoid Split

The anterior cricoid split procedure can be used instead of tracheotomy in the neonate who has failed extubation (Fig. 90.2). Table 90.7 outlines suggested criteria for this procedure. It is important to eliminate other causes of airway obstruction, such as laryngomalacia, tracheomalacia, choanal atresia, and retrognathia. Management in this age group requires careful endoscopic examination and management of reversible conditions (e.g., subglottic edema, laryngeal granulation) by intubation, steroid therapy, or laser excision. More severe laryngeal injury, especially with extensive mucosal injury, may be treated with an anterior cricoid split, allowing extubation without tracheotomy (25). Because the level of the anterior commissure in the infant lies at the junction of the upper two-thirds and lower one-third of the thyroid cartilage, the anterior laryngofissure should only extend to the lower one-third of the thyroid cartilage. The infant requires intubation for 7 to 10 days following the split, although this time period may be reduced if a thyroid alar cartilage cap is placed over the split site. In our experience, the addition of a thyroid alar graft offers the potential advantage of higher success rates while adding little operative morbidity (26).

TABLE 90.6 TREATMENT LARYNGEAL STENOSIS

Medical
- Prevention
  - Experienced intubation personnel
  - Correctly sized endotracheal tube
- Infectious diseases
  - Diagnostic biopsy
  - Prompt treatment
- Supportive therapy
  - Pulmonary toilet
  - Humidification
  - Antibiotics, steroids

Surgical
- Preoperative workup
  - Secure airway, endoscopic evaluation of airway sizing
  - Cardiac and pulmonary function
  - Gastroesophageal reflux assessment
  - Functional endoscopic evaluation of swallowing
  - Radiographic studies
- Grade I or II stenosis, unilateral lesions (e.g., hemangioma, cysts, or thin webs)
  - Dilatation
  - Division
  - Micro-trapdoor flaps
  - Endoscopic resection
  - Laser surgery
- Failed extubation stenosis
  - Anterior cricoid split (e.g., newborn, infant)
  - Tracheotomy (e.g., O_2 requirement, severe lung disease)
- Grades II, III, and IV stenoses, circumferential lesions, thick webs, failed endoscopic therapy, loss of cartilaginous framework
  - Anterior cartilage graft (e.g., moderate stenosis, stomal collapse)
  - Anterior graft/posterior split with stent (e.g., severe stenosis)
  - Anterior/posterior split with lumen augmentation (i.e., cartilage, myoperiosteal flaps)
  - Cricotracheal resection

Laryngotracheal Reconstruction–Anterior Cartilage Graft

For grade I or grade II subglottic stenosis, an anterior autogenous costal cartilage graft is a highly effective method for reconstruction of the airway when endoscopic management is either not possible or unsuccessful (27,28) (Fig. 90.3). This approach may also be effective in selected grade III lesions. A boat-shaped flanged graft is placed between the divided anterior lamina of the cricoid cartilage and, if required, may extend inferiorly across two or three tracheal rings. It should not transgress the anterior commissure. Other options for graft material include thyroid alar and auricular cartilage, although neither has the same structural integrity as costal cartilage.

Laryngotracheal Reconstruction–Posterior Cartilage Graft

Posterior glottic stenosis is a common sequela of prolonged intubation and is often misdiagnosed as bilateral cord paralysis. There may be associated fibrosis or ankylosis of the cricoarytenoid joints. A posterior costal cartilage

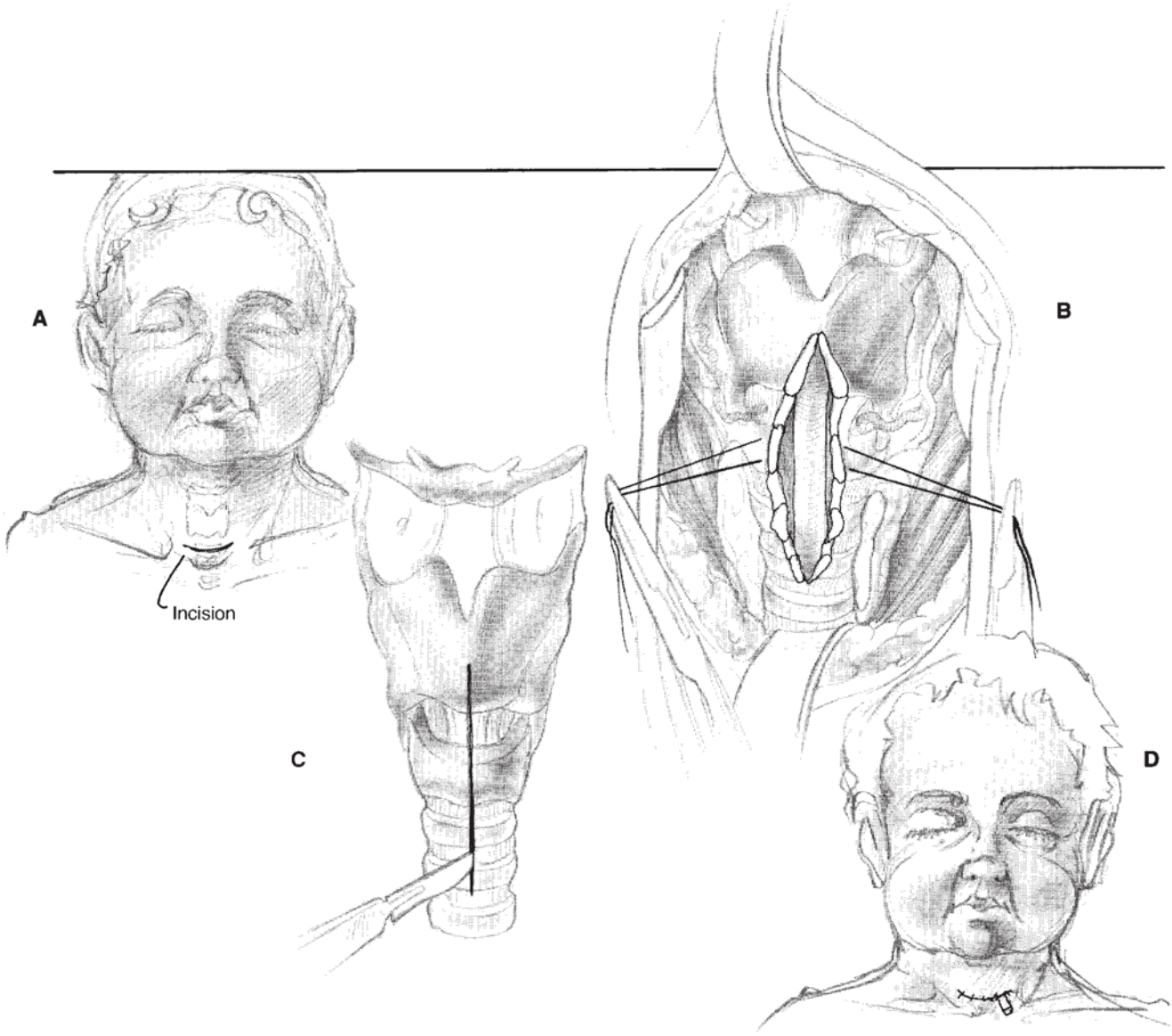


Figure 90.2 Anterior cricoid split. **A**: Skin incision (cricoid level). **B**: Vertical incision through the upper two tracheal rings, cricoid, and lower thyroid cartilage. **C**: Stay sutures. **D**: Loose skin closure with drain.

TABLE 90.7 CRITERIA FOR PERFORMING AN ANTERIOR CRICOID SPLIT PROCEDURE

Two or more extubation failures secondary to laryngeal pathologic conditions
Child weighs more than 1,500 g
No assisted ventilation for 10 d before evaluation
Supplemental O_2 requirement <30%
No congestive heart failure for 1 mo before evaluation
No acute upper or lower respiratory tract infection at the time of evaluation
No antihypertensive medication for 10 d before evaluation

Adapted from Cotton RT, Seid AB. Management of the extubation problem in the premature child: anterior cricoid split as an alternative to tracheotomy. *Ann Otol Rhinol Laryngol* 1980;89:508.

graft placed after division of the posterior cricoid lamina may be performed as a single- or two-stage procedure (29). A narrow graft (less than 6 mm) is usually adequate and excessive augmentation risks aspiration. The same technique is employed for grade II or III subglottic stenosis with primarily posterior cricoid scarring. Although a complete laryngofissure allows excellent access to the posterior cricoid, particular care should be taken to both accurately divide and reconstruct the anterior commissure to ensure perfect cord alignment and to minimize the risk of long-term vocal dysfunction. It is possible to split the posterior cricoid without a laryngofissure, even in a neonate, but placing sutures to stabilize a cartilage graft in the posterior cricoid is very challenging in a younger child if a laryngofissure is not performed. An alternative is the placement of a

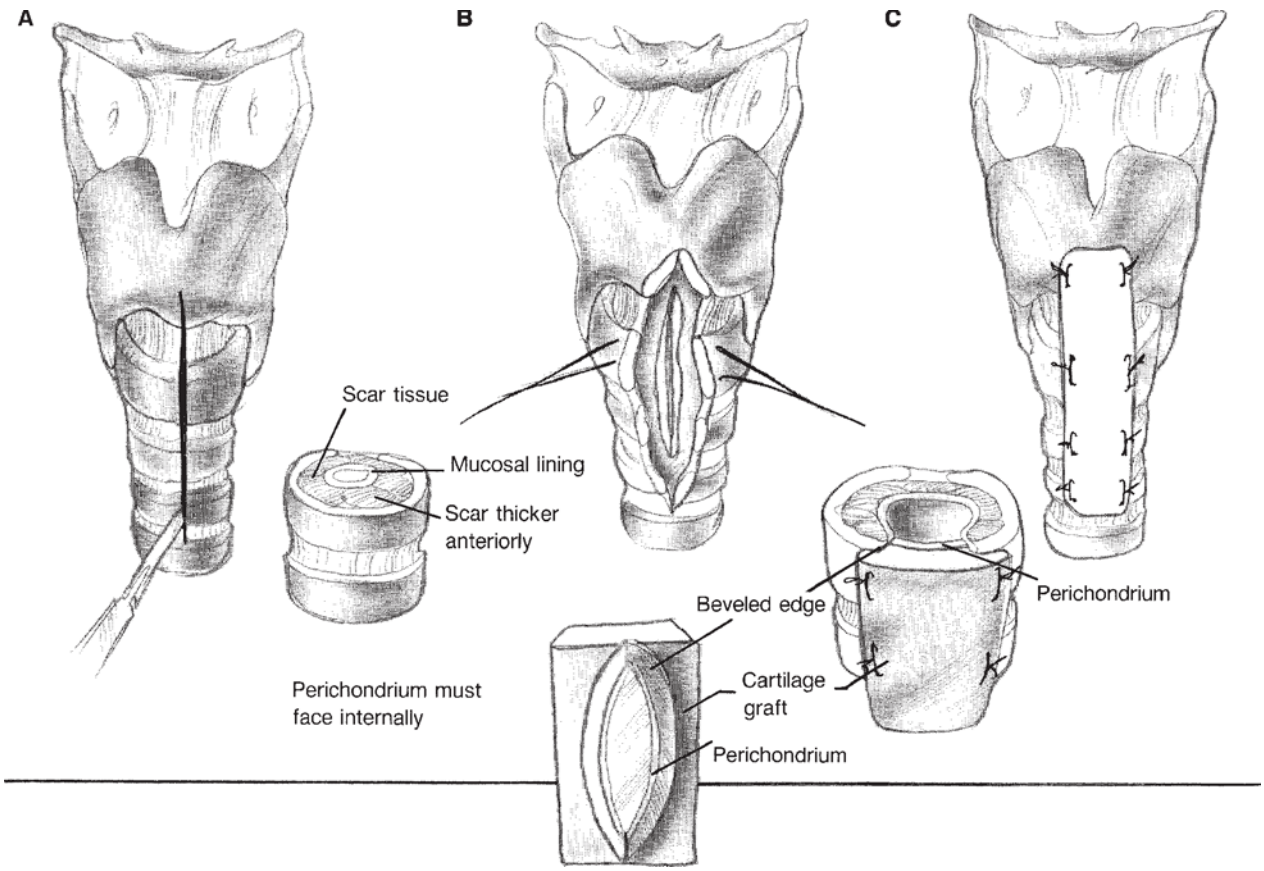


Figure 90.3 Anterior laryngofissure with anterior augmentation. **A**: Vertical incision (inferior to the cords) through the thyroid cartilage, cricoid, and upper tracheal rings. **B**: Beveled and elliptical cartilage graft. **C**: Cartilage graft in place with Vicryl sutures.

flanged posterior cartilage graft, where stability is such as to not require sutures. This procedure may also be performed using an endoscopic approach. The posterior cricoid plate is divided endoscopically with cold instrumentation or lasers. The graft is then placed endoscopically. This may be performed with or without a tracheotomy (30)

Laryngotracheal Reconstruction–Anterior and Posterior Cartilage Grafts

Grade III and grade IV subglottic stenoses usually require anterior and posterior costal cartilage grafting. After placement of the posterior cartilage graft, the anterior airway can then be closed over an appropriately sized endotracheal tube to estimate the size of the anterior graft required. If the anterior cricoid can be closed without tension, then an anterior graft may not be required. A variation of this procedure is an anterior graft with a posterior split of the cricoid lamina—an option usually limited to younger children. Grade IV subglottic stenosis usually requires more than one procedure to achieve decannulation using cartilage expansion techniques (31)

Cricotracheal Resection

An alternative to anterior/posterior cartilage grafting is cricotracheal resection (32,33) (Fig. 90.4). The concept is the removal of the diseased portion of the airway with the introduction of healthy tissue into the subglottis. This is a more technically challenging procedure than anterior/posterior cartilage grafting and is therefore usually reserved for patients with severe (grade III or IV) subglottic stenosis. It also has particular application in the reconstruction of the airway that has failed previous laryngotracheal reconstruction. There is a higher chance of achieving decannulation after a single procedure with cricotracheal resection than with standard cartilage augmentation laryngotracheal reconstruction. The advantages of the procedure include glottic sparing, avoidance of donor site morbidity, and a near normal appearing and mucosalized airway. The disadvantages include a risk to the recurrent laryngeal nerves and anastomotic dehiscence. Patient selection is important, and subglottic scarring within 3 mm of the vocal folds is a relative contraindication.

Slide Tracheoplasty and Cervical Slide Tracheoplasty

For children with complete tracheal rings, slide tracheoplasty is the recommended surgical intervention (34). This approach yields significantly better results than other tracheal reconstruction techniques and is applicable to all anatomic variants of complete tracheal rings. Slide tracheoplasty is generally performed on cardiopulmonary bypass

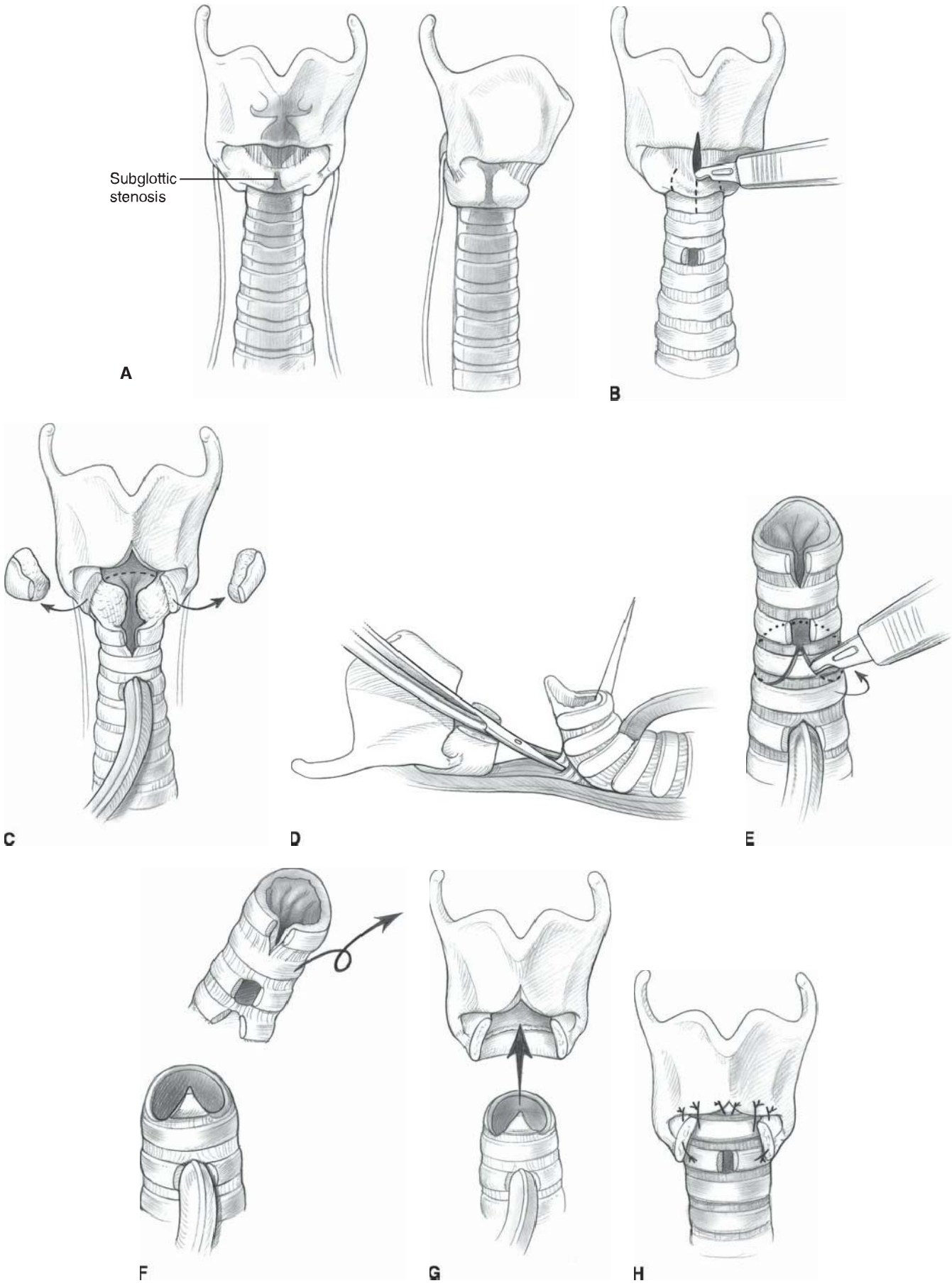


Figure 90.4 Cricotracheal resection. **A**: Stenotic segment for resection. **B**: Anterior cricoid split. **C**: Excision anterior cricoid lamina. **D**: Elevation of trachea off esophagus. **E**: Stenotic upper trachea for sacrifice. **F**: Removal stenotic upper trachea. **G**: Telescoping trachea into posterior cricoid lamina. **H**: Thyrotracheal anastomosis.

or ECMO through a midline sternotomy. Cardiopulmonary bypass offers a number of advantages: (a) the heart and lungs can be decompressed, allowing better access to the trachea during the procedure; (b) possible cardiac anomalies can be addressed at the time of surgery; and (c) during bypass, ventilation is not a concern while working in the exposed airway.

As originally described by Tsang et al. (35) and popularized by Grillo et al. (36), the slide tracheoplasty overlaps stenotic segments of the trachea, shortening the trachea, but doubling the circumference and diameter of the stenotic area. After the patient is placed on cardiopulmonary bypass and the airway is exposed, intraoperative bronchoscopy is performed to establish the upper and lower limits of the segment of complete rings, with a 30-gauge needle placed through the anterior tracheal wall and visualized bronchoscopically. The length of the stenosis is measured and the trachea is transected at the midpoint of the stenosis. The trachea is mobilized, taking care to preserve the lateral vascular attachments to the trachea. The posterior wall of the distal segment is divided until the trachealis muscle is encountered or the carina is reached. The anterior wall of the proximal segment is divided until beyond the most proximal complete ring. The segments are then slid over each other using a running double-armed 5.0 or 6.0 PDS suture (34). Most patients are left intubated for 24 to 48 hours postoperatively. Because secretions are often collected at the anastomosis, the airway requires humidification for several weeks. Possible postoperative complications include dehiscence and lateral anastomotic prominence (referred to as "figure-of-8" deformity).

Cervical slide tracheoplasty is a modification of the classic slide tracheoplasty. This operation offers an alternative to the classic technique for addressing problems in the upper two-thirds of the trachea (i.e., long-segment stenosis). Unlike the classic slide tracheoplasty, the cervical slide procedure is usually performed without the need for cardiopulmonary bypass, and is performed through a cervical neck incision.

Stenting Options

The primary decision that needs to be made in terms of stenting is the required duration of stent placement. The more unstable the airway reconstruction (e.g., following an anterior/posterior graft), or if there is a history of previous failed reconstruction, the longer the period of stenting required. Long-term stenting may be achieved with a T-Tube (Montgomery or Hood) or a wired-in metal tracheotomy tube within a Teflon stent (Aboulker or Cotton-Lorenz) (Fig. 90.5). Although once the mainstay of laryngotracheal reconstruction, the wired-in stent has become an increasingly rare method of postoperative airway stabilization. Generally, in children younger than 4 years, a T-Tube is best avoided because T-Tubes with less than an 8-mm outer diameter carry a higher risk of mucus occluding the lumen of the tube. Shorter-term stenting may be adequately achieved with a suprastomal Teflon stent, but this should ideally be removed after several weeks to prevent stenosis occurring between the distal end of the stent and the tracheotomy tube. Newer generation silicone suprastomal stents carry less risk of inducing stenosis at the distal tip of the stent (29).

If the period of stenting is less than 2 weeks and lung function is adequate, consideration may be given to a single-stage procedure, using an endotracheal tube as a stent. This technique is highly dependent upon access to a first-class intensive care unit. Paralysis is best avoided to allow the child an opportunity to maintain his or her own airway in the event of an accidental extubation. Most children younger than 3 years require sedation, whereas many children older than 3 years do not. The period of intubation depends upon the surgery performed and may vary from 1 day for selected anterior cartilage grafts to 14 days for an anterior/posterior cartilage graft.

In some circumstances, a stent may not be required for a two-stage reconstruction. An anterior costal cartilage graft laryngotracheal reconstruction rarely needs a stent, and selected cricotracheal resections may not need a stent.

DECISION MAKING

Before deciding on an open surgical reconstructive technique, conservative endoscopic treatment of laryngeal stenosis should be considered. This approach may include endoscopic dilatation, laser therapy, tissue removal by endoscopic microsurgical techniques, local and systemic steroid therapy, and antibiotic therapy. If these techniques are unsuccessful, open reconstruction of the airway can be considered.

Several factors may influence the timing of surgical correction in children. Patients with acquired laryngeal stenosis caused by long-term intubation frequently have underlying chronic pulmonary disease. Lung disease, such as bronchopulmonary dysplasia, must be addressed medically before surgical correction of the airway. In many children with laryngeal stenosis, other congenital or acquired anomalies require surgical repair. Reconstruction of the airway can be delayed until the other surgical procedures are completed because the existing tracheotomy tube allows easy and safe access to the airway.

In adults and children, any indication of significant GERD should be corrected medically (e.g., histamine [H_2 blockers, antacids] or surgically [e.g., Nissen fundoplication]) before airway reconstruction is undertaken. If this is not successfully treated before reconstruction, the reconstructed airway may suffer repeated injury by acidic gastric contents, causing granulation tissue and further stenosis. Patients with EE also require similar intervention and stabilization prior to undergoing airway surgery.

The variety of open surgical procedures available for reconstruction, including some that are not outlined here, allows the otolaryngologist to manage the stenotic larynx regardless of etiologic factors. Severe stenosis frequently requires more than one surgical correction for successful reconstruction. Therefore, early stenotic lesions should be treated aggressively to maintain an opening in the airway.

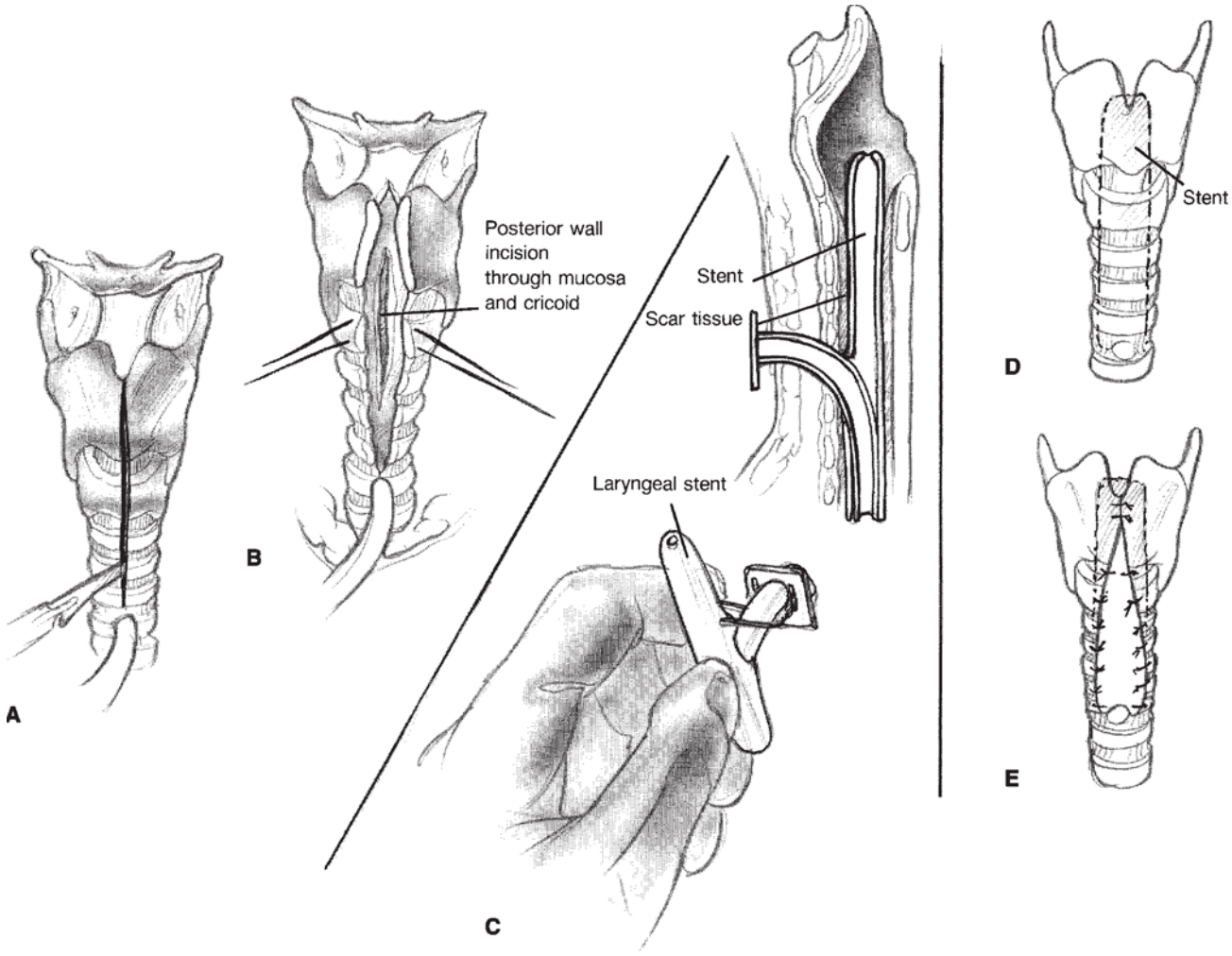


Figure 90.5 Anterior laryngofissure with posterior cricoid lamina split. **A**: Vertical midline laryngofissure from the thyroid notch to the proximal trachea or stoma. **B**: Division of posterior cricoid. **C**: Holinger metal tracheotomy tube wired to Aboulker or Cotton stent. **D**: Stent and tracheotomy tube in place. **E**: Stent and tracheotomy tube in place with an anterior costal cartilage graft.

COMPLICATIONS

Complications related to airway reconstruction may occur intraoperatively, early postoperatively, or late postoperatively. Intraoperative complications include hypoxia, pneumothorax (usually related to harvesting rib cartilage), and pneumomediastinum. Similar problems may occur postoperatively, as may wound infections, graft displacement, stent dislodgement, aspiration, and mucus plugging of the tracheotomy tube. Single-stage reconstruction carries particular risks, including endotracheal tube obstruction, unplanned extubation, glottic edema, and narcotic withdrawal.

All patients who are discharged with tracheotomy tubes should be taught tracheotomy care and given spare tracheotomy tubes, including one a size smaller than that which resides in the patient in case of difficulty with reinsertion in an emergency. The family should be instructed in tracheotomy care, including suctioning and changing the tracheotomy tube.

EMERGENCIES

Emergent complications in the care of laryngeal stenosis include airway obstruction, aspiration of a wire or stent, hemorrhage or hematoma formation, and pneumothorax with resulting respiratory distress.

Airway obstruction may be caused by mucous plugs or granulation tissue. Humidified air should be provided, and changing of the inner cannula or tracheotomy tube should be performed regularly to prevent plugging. Mucous plugs should be carefully suctioned. Granulation tissue may be treated with steroids (e.g., dexamethasone, 0.5 mg/kg/d to a maximum of 20 mg/day) by mouth or with topical or aerosolized steroid/antibiotic drops such as ciprofloxacin/dexamethasone through the tracheotomy tube, depending on the site of granulation tissue. If granulation tissue is causing significant obstruction, the patient may need to be admitted and closely monitored during therapy. Solitary pedunculated granulomas may

be safely removed with forceps during removal of the stent or during an interval examination postoperatively. These patients may be placed on a short-pulsed dose of oral steroids, oral antibiotics, proton pump inhibitors, and topical ciprofloxacin/dexamethasone through the tracheotomy tube.

To avoid some of these complications, the surgical technique should include the use of drains and, in open airway procedures, closure of the skin that allows the escape of air. A radiograph of the chest should always be obtained postoperatively for open reconstructive procedures. If an anterior costal cartilage graft is harvested, sterile saline should be placed in the wound and a positive pressure breath given to determine the possibility of an air leak. Good surgical technique with careful hemostasis and education of ancillary personnel and family can minimize these emergencies.

HIGHLIGHTS

- The narrowest part of the airway in the pediatric patient is the subglottis; in the adult, it is the glottis.
- Symptoms of obstruction differ by location. Supraglottic stenosis presents with inspiratory stridor. Glottic and subglottic stenoses present with biphasic stridor. Lower airway obstruction presents with expiratory stridor.
- Endoscopy is necessary for diagnosing laryngeal stenosis, although lateral and anteroposterior neck radiographs, CT, and fluoroscopy may also contribute information.
- Acquired laryngeal stenosis is much more common than congenital stenosis and is usually more difficult to repair.
- The most important factor in preventing acquired laryngeal stenosis is intubation with an endotracheal tube that is the smallest size permitting adequate ventilation of the patient, while ideally maintaining a leak at less than 20 cm of water pressure.
- Dilatation is usually not successful for long-term management of "fixed" or firm stenosis.
- Successful repair of laryngeal stenosis requires careful evaluation of the patient as well as the airway. Patient factors include evaluation of pulmonary function, esophageal disease, and bacterial colonization. Airway factors include evaluation of the nasopharynx, supraglottis, trachea, and bronchi.
- GERD must be controlled prior to undertaking surgical repair of laryngeal stenosis.
- Measurement of the airway by endotracheal tubes is a reliable and objective method in the diagnosis and follow-up of laryngeal stenosis.

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91 Pediatric Voice

Susan Baker Brehm *Melissa M. Statham*
Alessandro de Alarcón

Pediatric voice disorders comprise a broad spectrum of problems commonly encountered in pediatric otolaryngology practice. Epidemiologic reports estimate that more than 1 million children in the United States are dysphonic, with abnormalities in pitch, quality, and/or loudness (1–3). Given the potentially far-reaching impact that voice disorders may have on the psychosocial development of children, it is imperative that practitioners have a basic understanding of this growing field and a sound working knowledge of contemporary pediatric voice evaluation and management techniques (4,5). To this end, our chapter will present an overview of key voice-related concepts and clinical issues in children.

ANATOMIC CHANGES IN THE LARYNX DURING CHILDHOOD

The Laryngeal Framework

The pediatric larynx continually matures throughout childhood. Maturational changes are particularly rapid during the first several years of life and then gradually slow down until the larynx reaches maturity in young adulthood. Both the thyroid cartilage and the cricoid cartilage undergo significant changes in length, height, width, and weight, though these changes are more pronounced in males. The pediatric larynx is much higher in the airway than the adult larynx and gradually descends with age. In a neonate, the larynx is high in the neck, with the lower border of the cricoid cartilage approximately at the level of C3-C4. By age 2, it descends to approximately C5, and by age 15, it descends to C6-C7. This downward migration is associated with increasing separation between the hyoid bone and the thyroid cartilage, which are contiguous at birth.

Microstructure of the Vocal Fold

Two aspects of the developing pediatric vocal fold play an important role in voice: (a) the relationship between the arytenoid and the musculomembranous fold and (b) the layered vocal fold structure. In neonates, the proportion of the arytenoid and the musculomembranous fold is equal. Over time, this proportion changes, with the musculomembranous fold becoming two-thirds of the vocal fold. The layered structure of the lamina propria also significantly changes. From 2 to 11 months of age, the initial monolayer gradually becomes a bilayered structure. By age 7, it becomes an adult-like three-layered structure (6,7). Collectively, these anatomic and structural changes influence when a voice disorder manifests as well as a clinician's ability to evaluate and initiate treatment. The relationship between these changes and specific voice disorders will be discussed later in this chapter.

VOICE EVALUATION

Optimally, voice evaluation should be carried out in an interdisciplinary setting. This allows close collaboration between otolaryngologists and speech-language pathologists, thus facilitating a more thorough evaluation and the development of a comprehensive, well-coordinated management strategy. Also, it offers parents the convenience of decreasing the number of clinic visits for their child and the number of endoscopies performed.

A comprehensive voice assessment should include a medical history, an endoscopic or videostroboscopic examination, an acoustic evaluation, an aerodynamic evaluation, a perceptual evaluation, and often, a voice-related quality of life or handicapping evaluation. These combined tests provide clinicians with a global perspective on the disorder, facilitate the categorization of the disorder, and ultimately, play a role in treatment decisions.

History

A thorough medical history often allows the clinician to establish a differential diagnosis before proceeding to the endoscopic examination. This history should include relevant information pertaining to the onset of the voice disorder, the sound quality of the voice, and conditions that may alter the sound quality. Prior intubation, prior airway surgery, and prior voice therapy as well as therapeutic approaches used in this therapy should also be documented. Associated symptoms such as coughing, throat clearing, and globus sensation should be noted.

Endoscopy and Videostroboscopy

A successfully performed pediatric endoscopy depends on the child's ability to cooperate during the examination. This is influenced by age, the presence of developmental delay, and the overall comfort level of the child (8). Successfully performing a videostroboscopy depends on whether the child is capable of sustaining a sufficiently long phonation. The choice of instrumentation must consider these two factors.

In most children, endoscopy/stroboscopy is well tolerated and easily performed. Pediatric fiberoptic endoscopes (2.2 to 2.4 mm in diameter) are typically used for children younger than age 4. Although these scopes are well tolerated, they sacrifice image quality for comfort. Pediatric chip-on-the-tip endoscopes (3.1 to 3.2 mm in diameter) provide significantly improved image quality and are generally tolerated by children age 4 and older. These endoscopes allow for the evaluation of connected speech, which plays a role in a number of pediatric voice disorders (Fig. 91.1A and B and Fig. 91.2A and B).

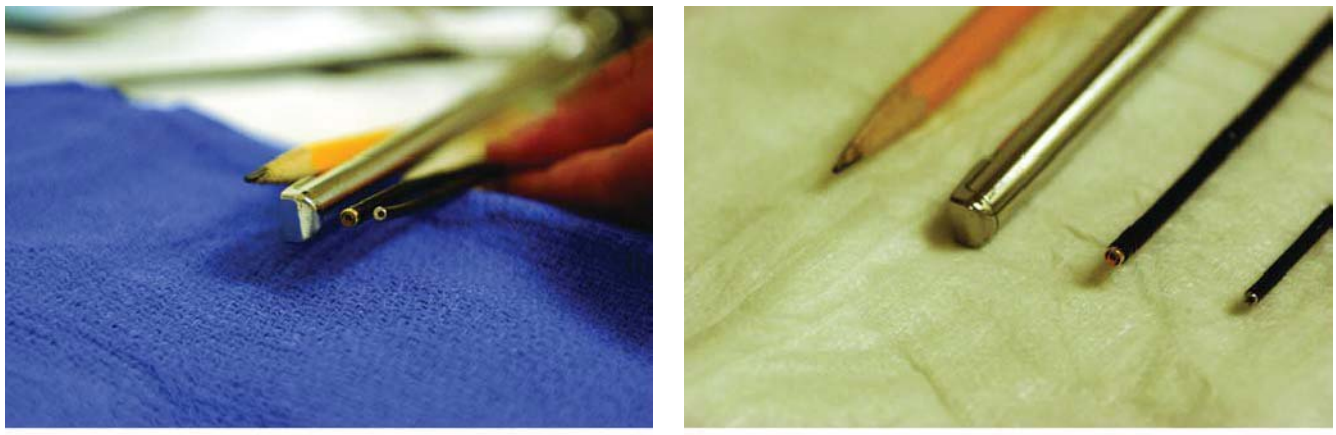
Rigid endoscopy is often reserved for more cooperative children, which typically includes those who are older than age 7. It can be performed using a standard adult rigid stroboscope, a smaller Hopkins rod, or a pediatric rigid stroboscope. These scopes offer better imaging of the vibrating vocal fold than fiberoptic endoscopes.

Videostroboscopy can be employed with either rigid or flexible endoscopes. This technique differs from standard endoscopy, as it uses a strobe light source that is synchronized with the acoustic signal produced during phonation. Furthermore, a video system is used to record the examination. The resulting images show a slow-motion glottal cycle artificially assembled from multiple glottal cycles. These images can then be reviewed to assess vocal fold vibration. Given that videostroboscopy depends on the ability of the child to cooperate, it is often difficult to obtain. Some children may be unable to provide sustained phonation of sufficient duration to allow the strobe light source to synchronize. (For a more in-depth discussion of videostroboscopy, see Chapter 65.)

Acoustic and Aerodynamic Evaluations

Acoustic and aerodynamic evaluations are best performed in a sound-treated, quiet room or a sound booth. Several software programs are available for the completion of the acoustic assessment such as the KayPENTAX computerized speech lab (Lincoln Park, New Jersey). Typical acoustic measures include maximum phonatory frequency range, fundamental frequency, loudness, perturbation (jitter and shimmer), and acoustic signal typing. These measures assist in characterizing voice problems and in helping the clinician make decisions regarding therapeutic interventions (9).

The aim of the aerodynamic assessment is to describe the relationship of the voice disorder to aspects of airflow and pressure during phonation. This assessment measures the rate of airflow through the vocal folds during phonation, breath support, and estimated subglottic pressures. Optimally, this assessment is performed by a speech-language pathologist using instrumentation available through Glottal Enterprises (Syracuse, New York) or KayPENTAX (Lincoln Park, New Jersey).



A B

Figure 91.1 **A:** Endoscopes size tip view. From *right* to *left*, a no. 2 pencil, adult rigid stroboscope, 3.2 mm chip scope, 2.4 mm fiberscope. **B:** Endoscope size lateral view. From *right* to *left*, a no. 2 pencil, adult rigid stroboscope, 3.2 mm chip scope, 2.4 mm fiberscope.

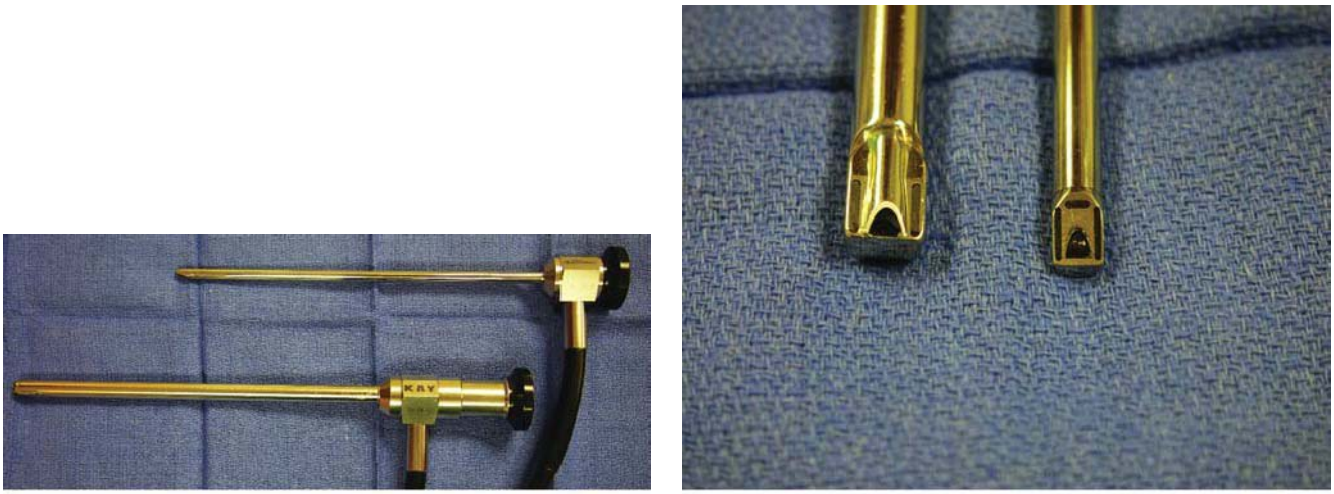


Figure 91.2 **A:** Rigid adult and pediatric stroboscopes lateral view. Images provided courtesy of KayPENTAX. **B:** Rigid adult and pediatric stroboscopes tip view.

Perceptual Evaluation of Voice

A perceptual evaluation can best be described as a standardized expert rating of how voice is perceived. The two most frequently used perceptual tools are the GRBAS (Grade, Roughness, Breathiness, Asthenia, Strain Scale) and the CAPE-V (Consensus Auditory-Perceptual Evaluation of Voice) (10). The CAPE-V evaluation comprises six core perceptual aspects of voice, which include overall severity, roughness, breathiness, strain, pitch, and loudness. Each of these elements is rated using a visual analog system. Ideally, the rating should be performed by at least two speech-language pathologists with expertise in voice disorders.

Voice-Related Quality of Life/Handicapping

Voice-related quality-of-life/handicapping assessments are designed to measure the impact of a voice disorder on a child's daily life. This assessment is more complicated in children than in adults because parental perspectives may be quite different from those of children. These perspectives may be colored by factors such as the child's past airway history, the duration of the voice disorder, and societal influences.

Instruments that have been validated and are widely used include the PVOS (Pediatric Voice Outcomes Survey), the PVRQOL (Pediatric Voice-Related Quality of Life), and the pVHI (Pediatric Voice Handicap Index). A fourth instrument currently being developed is the voice-related PEDS QL 4.0 (Physical, Emotional, Social, Work/School Functioning) (11–15). This differs from the above-mentioned instruments in that it takes into account both the parent's and child's perspectives. At least one voice-related quality-of-life evaluation should be included in the battery of tests used by the practitioner in assessing a voice disorder.

PEDIATRIC VOICE DISORDERS

Laryngopharyngeal Reflux and Eosinophilic Esophagitis

The most common esophageal disorders associated with pediatric dysphonia are laryngopharyngeal reflux (LPR) and eosinophilic esophagitis (EE) (16,17). Children with these disorders generally present with chronic coughing, throat clearing, and globus sensation. These symptoms are often worse in the morning and may improve during the course of the day. The dysphonia is usually perceived as a rough, harsh-sounding voice. Voice quality fluctuates; however, it typically worsens with voice use. Although endoscopic findings are often variable, they may include vocal fold edema, erythema, vocal fold nodules, interarytenoid pachydermia, pseudo-sulculus vocalis, and thickening of the vocal fold cover (Fig. 91.3A–C).

Patients with a suspected diagnosis of LPR or EE are often initially managed with a proton pump inhibitor for a 1- to 2-month period. Parents should be advised that this medication must be taken on an empty stomach 30 minutes before a meal. Most important, it should be given at times which offer maximal convenience and consistency to both the parent and the child. Additionally, the clinician should discuss dietary changes and lifestyle modifications with patients and their families (Chapter 66).

When the dysphonia and related symptoms persist, the patient should be referred to a gastroenterologist for an esophagogastroduodenoscopy (EGD), impedance probe testing, and biopsies. These diagnostic tests will distinguish between LPR, EE, and other disorders. Optimally, otolaryngologists and gastroenterologists work collaboratively to manage these patients. For a detailed discussion of the management of patients with EE, see Chapter 59.

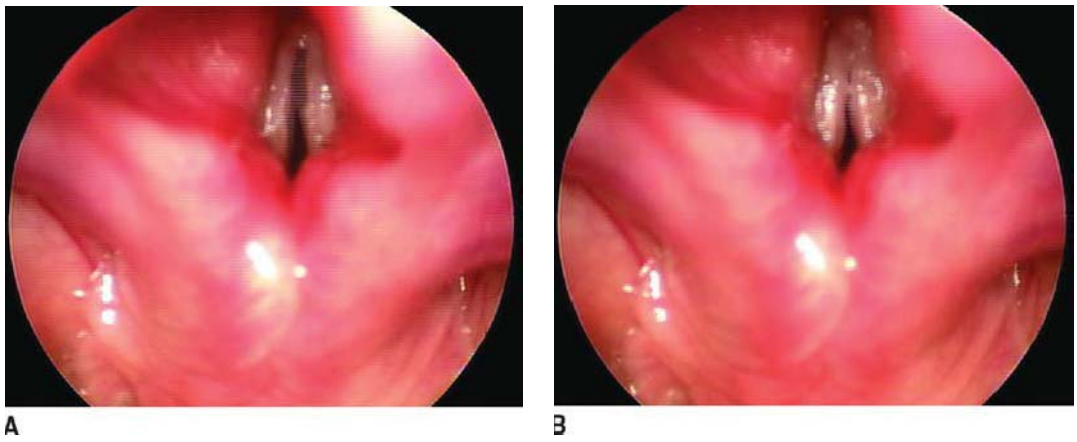


Figure 91.3 Endoscopic views of a child with reflux-induced dysphonia. (**A**,**B**) show sequential images from stroboscopy. (**C**) shows operative microlaryngoscopy performed during an EGD, impedance probe, and biopsies, which confirmed significant reflux.

Vocal Fold Nodules, Cysts, and Polyps

Vocal fold nodules are the most commonly encountered cause of pediatric dysphonia (5% to 40%) (18). Patients generally present with a harsh, breathy voice. They often have limited pitch range and may have voice breaks and aphonia at specific pitches. Also, voice quality often worsens with heavy voice use. These children may be either heavy voice users or vocal abusers who frequently scream and yell. Endoscopic examination often reveals fairly symmetric bilateral lesions in the midmembranous vocal fold. During vocal fold closure, a typical hourglass closure configuration is often seen. (Fig. 91.4A and B) The location and size of the lesions variably affects mucosal wave, vocal fold vibration, and pitch. The perceptual assessment of voice quality varies from mild-to-severe dysphonia (19,20).

The voice perception of patients with vocal fold cysts and polyps is often similar to that of patients with vocal fold nodules. In some cases, however, there may be a history of an acute phono-traumatic event associated with the development of dysphonia. Cyst and polyps are much less common than nodules. Endoscopic examination often demonstrates a large unilateral lesion and a smaller contralateral reactive lesion (Fig. 91.5A–D). As with vocal fold nodules, the size

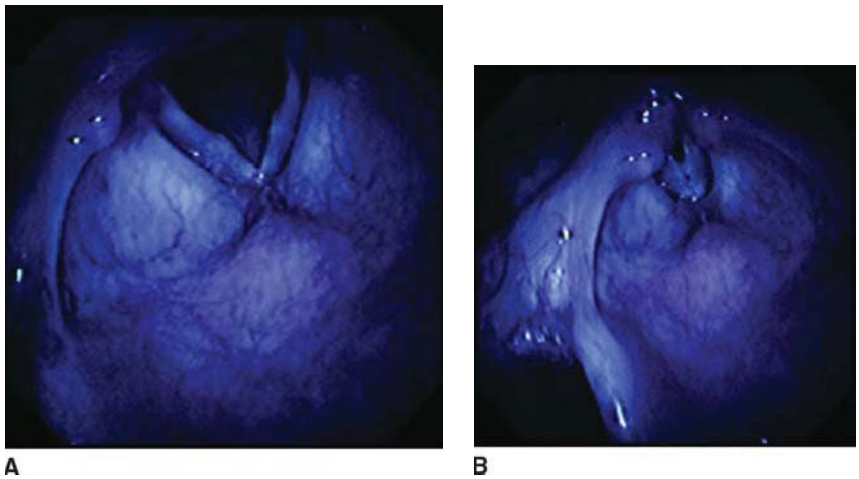


Figure 91.4 Vocal fold nodules. **A:** Open glottis with midmembranous nodules. **B:** Hourglass closure during phonation.

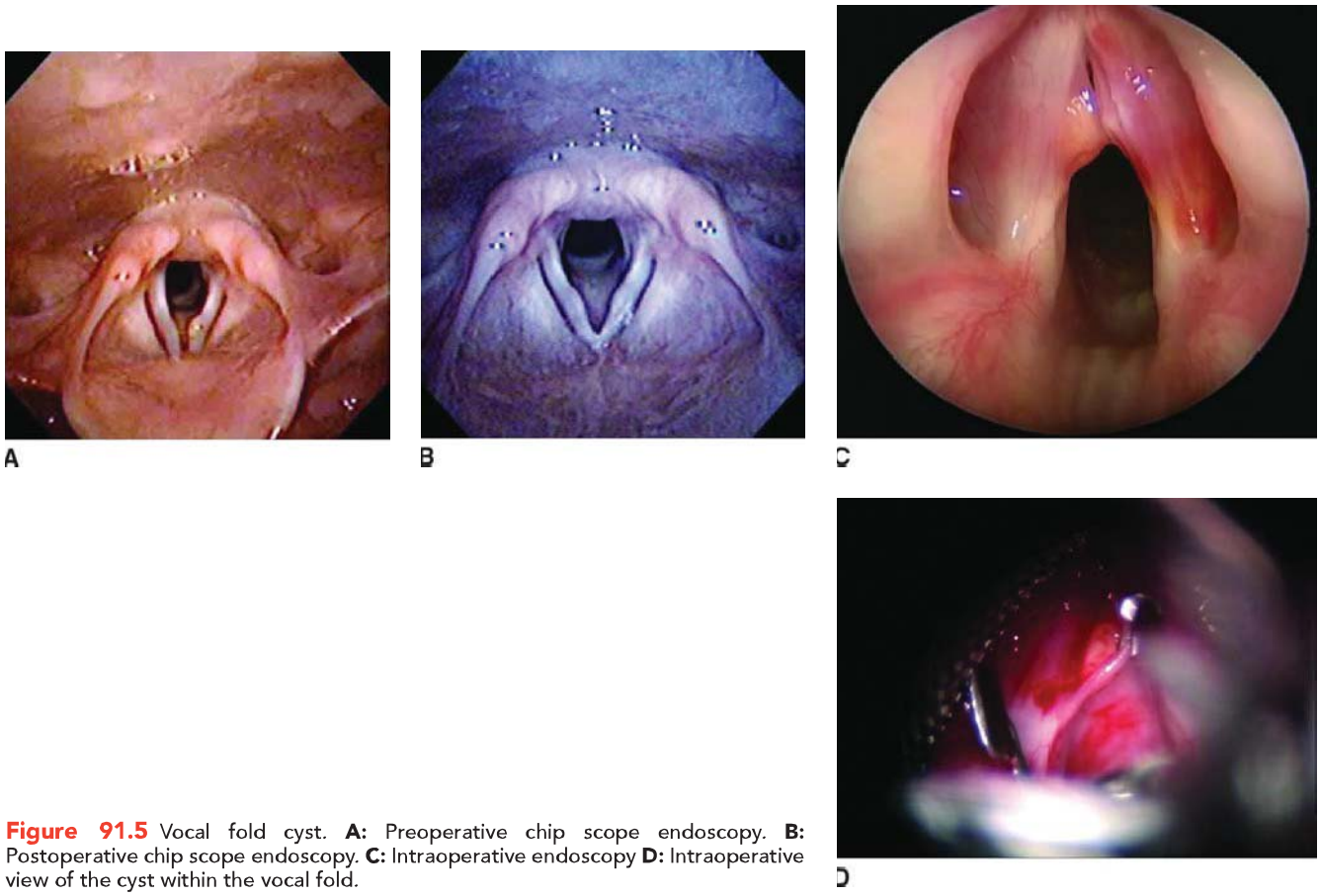


Figure 91.5 Vocal fold cyst. **A:** Preoperative chip scope endoscopy. **B:** Postoperative chip scope endoscopy. **C:** Intraoperative endoscopy **D:** Intraoperative view of the cyst within the vocal fold.

and location of the lesion are often related to the effect on voice. Vocal fold cysts can be mucous or epithelial, and their location can vary from fairly superficial to very deep within the vocal fold. Vocal fold polyps are often exophytic, more pedunculated, and may have an obvious vascular supply. In some cases, imaging of pediatric vocal fold nodules, cysts, and polyps may not accurately differentiate these lesions. The lack of a uniformly accepted nomenclature in pediatric laryngology may also hamper diagnosis and treatment. For a more in-depth description of these benign lesions, see Chapter 68.

Nonoperative Management of Vocal Fold Nodules, Cysts, and Polyps

The initial management of children with vocal fold nodules, cysts, and polyps often involves a course of voice therapy with a speech-language pathologist with expertise in voice disorders (4,5,19,21). Most children who are 4 years of age or older and developmentally normal can actively participate in voice therapy. For children who are younger, developmentally delayed, or unable to participate, reassurance, vocal hygiene counseling, and scheduling routine office follow-up visits may be more appropriate. Typically, voice therapy consists of 10 to 12 sessions over a 2- to 3-month period. After completion of this protocol, we recommend reevaluation of the child to assess voice changes that have occurred as well as the parent's and child's perceptions of changes. The speech-language pathologist plays a crucial role in relating information regarding compliance with voice therapy to the clinician. This information is helpful in that it serves as an indicator of the feasibility of a successful surgical intervention, which requires ongoing postoperative therapy.

Operative Management

Operative management is considered for patients who show little or no improvement in voice quality after completing a course of voice therapy. This approach may consist of an endoscopy to confirm the diagnosis or to determine the possible esophageal contribution to the disorder (i.e., LPR or EE).

Surgical removal of pediatric vocal fold lesions is controversial, and studies comparing nonoperative and operative management are limited (22). Moreover, these studies often show selection bias in patients who undergo surgery. Patients with vocal fold cysts and polyps are more likely to undergo surgical removal than those with vocal nodules because they are less likely to improve with voice therapy. However, the decision to have the child undergo elective surgery should be made jointly by the surgeon, the child, and the caregivers. Children who are compliant with medical therapy, who have a significantly compromised voice-related quality of life, and who have no significant comorbidities that may affect surgical outcome are good surgical candidates. In addition, the surgeon must also consider the child's ability to participate

in the prescribed therapy and the child's past behavior in voice therapy. To decrease the likelihood of a poor voice outcome, surgery should be delayed on children who cannot yet participate in therapy or who are noncompliant.

Surgery should be performed by clinicians who have received training in microflap techniques and should use high-magnification microscopy and microlaryngeal instrumentation. Lesion removal should be performed with the aim of maximally preserving the superficial lamina propria and normal vocal fold architecture (see Chapter 68). The timing of surgery in children is often dictated by the need for postoperative voice rest and how this may affect the child's school schedule. In view of these considerations, surgery is often performed during the summer or during holiday breaks. Relative contraindications to surgery include uncontrolled medical comorbidities such as reflux or EE, poor compliance with voice therapy, significant vocal abuse, and poorly controlled asthma or allergies.

Recurrent Respiratory Papillomatosis (RRP)

Although children with RRP frequently present with airway distress and airway obstruction, a subset of children presents with hoarseness (23). These children often require less frequent surgical debridement. Children who present with dysphonia related to RRP often have a characteristic harsh, raspy voice with voice breaks and periods of aphonia. On endoscopy, papillomatosis is characterized by sessile or pedunculated frond-like growths, which can be seen anywhere within the confines of the larynx (subglottis to supraglottis). The characteristically normal vocal fold structure is often obscured when there is vocal fold involvement. Management involves surgical removal of the papilloma (Chapter 94). To ensure optimization of voice outcomes, utmost care should be taken in using tissue-sparing techniques. To prevent webbing, the surgeon should be mindful of anterior commissure papilloma.

Children with RRP show varying degrees of dysphonia following surgery. Despite the need for frequent surgical intervention, many of these children have surprisingly good voice outcomes (24,25).

Unilateral Vocal Fold Paralysis

Unilateral vocal fold paralysis is more common than bilateral paralysis, and because of the longer course of the left recurrent laryngeal nerve (RLN), left-sided paralysis is more common than right-sided paralysis (4,5). Associated symptoms are typically a weak or breathy cry or a breathy voice quality. Some patients have diplophonia (two voice pitch sounds). To improve glottic closure, some patients compensate by using higher pitch speech. Other patients have frequent bouts of pneumonia or coughing and choking with the ingestion of liquids, which is consistent with aspiration. Dyspnea may be a common complaint; however, this is generally breathlessness and air hunger related to the loss of airway resistance during phonation. The medical history may reveal severe upper respiratory infection, patent ductus arteriosus ligation, congenital heart surgery, anterior approach cervical spine surgery, thyroid surgery, mediastinal surgery, tracheoesophageal repair, or airway surgery (tracheal resection or cricotracheal resection). Children with decreased pulmonary function or those who have undergone recent cardiac surgery are unlikely to compensate for aspiration caused by the vocal fold paralysis. Children with malignancies along the course of the RLN may present with unilateral vocal fold paralysis caused either by pressure on the nerve or direct nerve involvement. Additionally, several case reports suggest an association between vocal fold paralysis and the chemotherapeutic agent vincristine.

Endoscopy and stroboscopy will reveal the paralytic vocal fold. (See Chapter 69 for additional stroboscopic findings.) The position of the fold during phonation and the arytenoid position should be noted during the endoscopic examination, as both can play a role in treatment decisions.

Laryngeal electromyography (LEMG) evaluates electrophysiologic activity in the larynx and may offer useful information regarding the likelihood of the return of purposeful vocal fold function. Additionally, it may help in determining the location of the nerve injury. The reported prognostic value of LEMG in adults is variable; however, the utilization of discreet LEMG criteria improves the accuracy of prognosis for the recovery of vocal fold motion (26). In children, difficulty in electrode placement because of tolerance levels and smaller muscle size is a limitation. In view of this, the role of LEMG in the evaluation of pediatric vocal fold paralysis has not yet been established and is currently being studied (27). To date, there is very little data on the use of LEMG in children.

Treatment of glottal insufficiency is generally determined by patients' symptoms, including the adequacy of their cough, the presence of aspiration, and the degree of phonatory dysfunction. In patients with a known cause of the vocal fold paralysis, a radiologic workup (computed tomography or magnetic resonance imaging [MRI]) is unwarranted. When the etiology of the paralysis is unknown, however, a radiologic study should be performed to evaluate the entire course of the RLN (from the skull base to below the aortic arch). Management strategies include observation, the use of temporizing measures, and longer-term therapeutic interventions. In patients with a minimal voice deficit, observation alone may be used while awaiting possible recovery of vocal fold function. Temporizing measures may be used in patients with a more significant voice deficit. These measures involve the use of short-acting injectable tissue fillers (injection medialization laryngoplasty). Several injectables with varying durations of effectiveness are available (28–30). These injectables include Radiesse Voice Gel, Restylane, and Cymetra (shortest-to-longest acting, respectively). In most children, injection laryngoplasty is performed in the operating room; however, cooperative teenagers may be able to tolerate an in-office procedure (28–30). Longer-term interventions include the injection of longer acting

tissue fillers such as Radiesse Voice and autologous fat (31). Data pertaining to long-term voice outcomes with the use of Radiesse Voice in children is scant. This injectable should be used with caution, as it can be improperly placed within the larynx. Furthermore, with all injectables, increased caution is warranted, as the pediatric vocal folds are small. Meticulous control and placement of an injectate is needed, as injection into the Reinke space will result in impaired vocal fold vibration and distortion of the free edge of the membranous vocal fold. Permanent medialization laryngoplasty with Gore-Tex or silastic is best reserved for children who have gone through puberty and who thus have a fully matured larynx (32). Delaying this procedure until puberty decreases the risk of needing revision laryngoplasty. Also, teenagers are more likely to tolerate an awake procedure, which improves the likelihood of a good voice outcome. Regardless of the material used for medialization, the margin of error is relatively small, and the surgeon should be skilled in the technique that is most suitable for the patient.

An approach that has recently gained wider interest for use in children is ansa-cervicalis to RLN reinnervation with simultaneous injection laryngoplasty (33). The use of this procedure is controversial in adults; however, a recent randomized control trial suggests that it may be advantageous in younger patients (34). The procedure leads to voice outcomes (stroboscopic examination and perceptual evaluation) that are similar to those associated with medialization laryngoplasty. Although reinnervation does not result in return of vocal fold function, it may provide improved tone to the denervated vocal fold and lead to a better position of the "paralytic" vocal fold during phonation. Another potential advantage of the use of reinnervation in children is that it may provide a durable, stable voice without an implant, and it is unlikely to interfere with laryngeal development. Although there are currently no large-scale studies using this approach in children, anecdotal evidence and case series suggest that this may be a viable long-term therapeutic option prior to puberty (35,36). Rigorous studies of voice and swallowing outcomes are needed to better determine the utility of this procedure. Reinnervation does not preclude the use of medialization laryngoplasty at a later date if a satisfactory vocal outcome is not achieved. The procedure requires an open neck approach with the child under a general anesthetic. It should be performed by a surgeon with competency in pediatric open neck surgery. Nevertheless, further research in this area is needed to better define how to incorporate this approach into current treatment algorithms.

Bilateral Vocal Fold Paralysis

Bilateral vocal cord paralysis is sometimes associated with birth trauma, central nervous system abnormalities, and cardiovascular anomalies (37); however, most cases are idiopathic. Affected children usually present with stridor, airway obstruction, aspiration, a strong loud cry, and a good voice. Endoscopy/stroboscopy will reveal the vocal fold paralysis with the vocal folds in the paramedian or median position Also, inhalational collapse of the membranous vocal fold can frequently be visualized. It is often difficult to distinguish between bilateral paralysis, bilateral cricoarytenoid joint fixation, and posterior glottic stenosis on awake endoscopy. Operative endoscopy is often indicated in these cases to distinguish between these disorders. Management of airway obstruction is typically the focus of treatment. Therapeutic interventions include observation, tracheotomy, posterior cordotomy, arytenoidectomy, open or endoscopic vocal fold lateralization, or posterior cricoid expansion using costal cartilage grafting (38). Management of the bilateral paralysis always involves striking a balance in optimizing breathing, aspiration, and voice. Voice outcomes following any intervention have historically included a simple nonvalidated questionnaire or the surgeon's perceptions of the voice result. Important to note, parents' concerns regarding their child's airway obstruction often result in an underestimation of the actual impact of the voice disorder on their child. Further study using standardized voice assessments need to be performed in order to establish a more thorough understanding of the impact of surgery on voice outcome.

Laryngeal Webs

Congenital laryngeal webs result from a failure of airway recanalization during embryogenesis. In many children, webs extend into the subglottis. Given that 40% of children with a congenital laryngeal web also have velocardiofacial syndrome, all children with congenital webs should be evaluated for this syndrome (39). Children with significant webs typically exhibit symptoms of airway obstruction early in life. They often have a weak cry and can be aphonic or mildly dysphonic. Some patients, however, have good voices and strong cries and are minimally symptomatic. The length of the web can influence the vocal quality by altering voice pitch. Endoscopy reveals a web with variable thickness and vibratory qualities. Management of laryngeal webs is often focused on improvement of the airway. The thickness and the length of the web play a critical role in voice outcome following surgery. Treatment of thick webs often yields minimal voice improvement and, in some cases, may result in a worse voice. Postoperatively, the vibrating surface of the vocal fold is scarred and has poor vibratory characteristics. Treatment of thin webs often yields improvement in voice, as the postoperative vocal fold generally has better vibratory characteristics. Treatment of longer webs often has a positive impact on voice outcome, whereas treatment of shorter webs may result in only minimal improvement. Families should be counseled regarding these aspects of web management and should be advised as to specific management goals.

Functional Voice Disorders

The most common functional voice disorders seen in children include muscle tension dysphonia, psychogenic

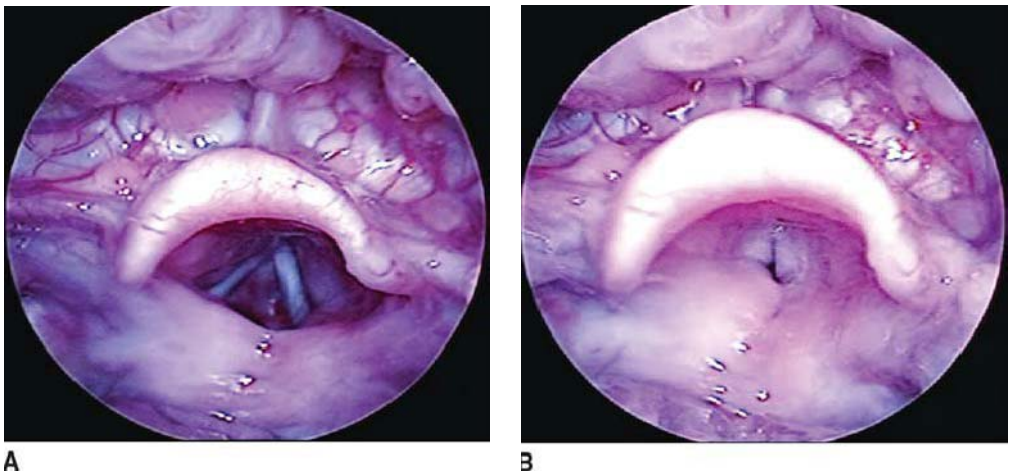
aphonia, puberphonia, spasmodic dysphonia, and paradoxical vocal fold dysfunction (40–42). Children with these disorders may not demonstrate obvious anatomic pathology. Most functional voice disorders manifest during the teenage years, when children present with strained voices, problems with pitch changes, and occasional periods of aphonia. Endoscopy often reveals a structurally normal larynx and vocal folds with dysregulated laryngeal function. The management of children with most functional voice disorders is similar to the management of these disorders in adults. Therapeutic intervention by a speech-language pathologist and behavioral management by a psychologist are usually the mainstays of treatment (21). In contrast to other functional disorders, children with paradoxical vocal fold dysfunction have no voice complaints (43). These patients present with abnormal closure of vocal folds during inspiration and symptoms of airway obstruction. Symptoms are often episodic and occur with specific scenarios. Medical history often reveals that the symptomatic episodes are related to or exacerbated by stressful situations or physical exertion. Patients are frequently misdiagnosed with exercise-induced asthma; however, their symptoms will not respond to asthma medications. The prototypical child with paradoxical vocal fold dysfunction is a high academically functioning athletic female. Evidence also suggests that in some cases sexual abuse may be a contributing factor. As with other functional disorders, management involves the expertise of both a speech-language pathologist and a psychologist, who helps the patient gain insight into what triggers the condition. For recalcitrant cases, further workup and treatment are warranted and may include a MRI brain scan, Botox injection, and testing for myasthenia gravis (44).

Vocal Process Granulomas

Pediatric vocal process granulomas are uncommon and tend to be associated with intubation injury. Symptoms may include chronic coughing, chronic throat clearing, and throat pain. Perceptually, many patients exhibit borderline normal voice quality. Large granulomas can cause significant voice problems by preventing vocal fold closure, which results in a breathy dysphonia. Endoscopic examination reveals a vocal process lesion that is often unilateral. Hyperfunction of the lateral cricoarytenoid muscle is also frequently seen. Treatment includes the use of a proton pump inhibitor, the administration of steroids, and rarely, surgical debridement. Voice therapy plays a crucial role in managing the vocal hyperfunction that is often associated with these lesions.

Dysphonia Following Airway Reconstruction

Nearly 50% of children who undergo airway reconstruction will be dysphonic (45,46). Many children present with complaints years after airway reconstruction, typically during the teenage years. Complaints typically involve concerns about voice quality and loudness. Concerns related to voice quality often stem from social interaction with peers who may call attention to the dysphonia. Loudness concerns involve difficulty being heard in noisy environments and difficulty with voice projection and intelligibility. Postoperative voice disorders are highly variable, with patients exhibiting mild-to-severe dysphonia (47–49). Risk factors for poor voice outcomes include complete laryngofissure, posterior grafting, cricotracheal resection, and multiple airway reconstructions (47,50). On endoscopy, children demonstrate glottic, mixed glottic, or supraglottic phonation. (Fig. 91.6A and B) Patients with supraglottic and mixed glottic phonation will often have perceptually worse voice outcomes (49). Many of these patients have problems with glottic incompetence or diastasis (open glottis); typically, closure of the posterior glottis during phonation is problematic (51). Treatment protocols include voice therapy and, in select cases, surgical intervention. Management of these disorders is an ongoing area of research.



A B

Figure 91.6 Supraglottal phonation after airway reconstruction. **A:** Open glottis. **B:** Phonation of the false vocal folds.

CONCLUSION

Pediatric voice disorders encompass a wide spectrum of conditions. Optimally, these conditions are managed by an interdisciplinary team with special expertise. A standardized approach using validated assessment instruments is recommended. Ongoing research is focused on attaining a more in-depth understanding of these disorders and on developing definitive treatment algorithms.

HIGHLIGHTS

- Pediatric voice disorders are optimally evaluated and managed by an interdisciplinary team with special expertise.
- Endoscopic evaluation of pediatric voice disorders is more commonly performed with flexible endoscopes.
- Vocal fold nodules are the most common cause of dysphonia in children.
- Functional voice disorders in children are primarily treated with voice therapy and behavioral management.
- Treatment algorithms for pediatric unilateral vocal fold paralysis may involve voice therapy, injection laryngoplasty, medialization laryngoplasty, or ansa-RLN reinnervation.
- Nearly half of pediatric patients who undergo airway reconstruction will have dysphonia.

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92 Pediatric Tracheotomy

Jeffrey P. Simons

Airway problems in children are managed with a variety of techniques, depending on their cause, severity, chronicity, and anticipated outcome. The decision of whether a child would benefit from a tracheotomy is often made by the managing airway surgeon or otolaryngologist in the acute or emergent setting. More elective decisions regarding tracheotomy in children with chronic airway obstruction, respiratory failure, prolonged intubation, or the need for pulmonary toilet are often best made by a multidisciplinary team, including otolaryngologists, pulmonologists, critical care physicians, and general pediatricians.

Although pediatric tracheotomy is a relatively infrequently performed procedure, children undergoing tracheotomy still utilize a great deal of health care resources. One study estimated that 4,861 tracheotomies were performed in children in the year 1997 (1). The estimated aggregate inpatient hospital charges for children with tracheotomies in 1997 was about $952 million per year or about $200,000 per child, which would be about $1.34 billion per year or $282,000 per child in 2011 dollars (1). Hospital admissions for tracheotomy rank among the longest hospitalizations for all children with all problems (2). Pediatric patients with tracheostomy tubes have high hospital readmission rates, even 5 years after the tracheotomy was performed (2). Furthermore, parents caring for children with tracheostomy tubes experience considerable caregiver burden. Indeed, having a child with a tracheostomy tube can affect caregivers' emotional well-being, as well as have a significant economic impact on the family (3,4). In one study, caregivers of children with tracheostomy tubes reported adverse effects on many aspects of their quality of life, including sleep, relationships, social life, and ability to work (4).

Although the terms "tracheotomy" and "tracheostomy" have been used interchangeably in the past, they have distinct meanings. The term "tracheotomy," from the Greek word *tome* (to cut), refers to the surgical procedure and the act of making an opening in the trachea. On the other hand, "tracheostomy," from the Greek word *stomoun* (to provide a mouth or opening), refers to the actual opening or hole in the trachea. A tracheostomy tube is the tube that is placed into that opening in the trachea.

HISTORY

The history of tracheotomy is fascinating and a knowledge of that history helps better understand the procedure today. References to making an opening in the windpipe are found in at least two of the three oldest known medical books, including the Rig Veda, a sacred Hindu book written between 2000 and 1000 BC (5). In the eighth century BC, Homer described the operation of cutting open the trachea to relieve a choking person (5). In the fourth century BC, Alexander the Great is reported to have punctured the trachea with the point of his sword to help a soldier choking on a bone lodged in his throat. Asclepiades, who practiced in Rome in the second century BC, was the first surgeon known to perform elective tracheotomies. Galen and Aretaeus both described and discussed tracheotomy in the second century AD (5,6). The procedure was further defined in the second century AD by Antyllus, who recommended that the *arteria aspera* (trachea) be divided with a transverse incision at the third or fourth ring (6). In the seventh century AD, Paul of Aegina repeatedly performed tracheotomy and recorded that one could know when the airway had been entered by the rush of air and the loss of the patient's voice (6). From that time until the 16th century, there is little in written medical history about tracheotomy.

There are frequent references to tracheotomy from the 16th century until around 1830, but most were negative, considering the procedure useless and dangerous (5). During this time period, only 28 successful tracheotomies were described in the literature (6). In 1590, Sanatorius used a trocar to perform a tracheotomy and left a cannula in place for the first time (5). In 1620, Nicholas Habicot

described what was possibly the first successful pediatric tracheotomy in a 14-year-old boy, who swallowed a cloth wrapped around 9 coins. The package of coins lodged in the esophagus and compressed the trachea, causing airway obstruction. The tracheotomy relieved the airway obstruction and the coins were pushed into the stomach, later to pass in the stool (6). Habicot also performed a tracheotomy in another young man as a means to evacuate blood from the airway, which had resulted from a penetrating wound of the larynx (5). In 1650, Theophilus Bonetus recommended the use of tracheotomy for a 7-year-old boy who had airway obstruction from aspirating a piece of bone; unfortunately, he was overruled by the boy's primary physician and the child died (5).

Heister was the first to use the term "tracheotomy". In 1839, he described the operation using a straight tube and a trocar, and suggested that it had been neglected by modern surgeons (5,6). In the early and mid-19th century, tracheotomy became commonly used as a life-saving treatment for diphtheria patients (5). Trousseau (7) reported having performed the operation on more than 200 patients with diphtheria, and saving the lives of about one quarter of them. As a result of the successful use of tracheotomy for airway obstruction in diphtheria patients, the operation became popular for other causes of airway obstruction, including croup, foreign bodies, and trauma (5). Indeed, the medical literature in the second half of the 19th century is full of articles on tracheotomy, including technique, postoperative complications, and indications (5).

Chevalier Jackson (8,9) demonstrated that when tracheotomy is performed with proper technique and postoperative care, the mortality from the procedure is quite low. He recommended using a slow and deliberate technique and avoiding a hasty operation, avoiding general anesthesia when airway obstruction is present, avoiding a "high" tracheotomy or division of the cricothyroid membrane, and dividing the thyroid isthmus (8,9). He also emphasized the importance of proper postoperative care, stating "the 'pipes,' natural and instrumental, must at all times be kept clear" (8).

Tracheotomy was also used in the early administration of general anesthesia in the late 19th century (5). However, by the early 1900s, when endotracheal intubation was popularized, the use of tracheotomy for this indication markedly decreased. In addition, in the early 20th century, immunization for diphtheria and the introduction of sulfonamides significantly decreased airway problems from upper respiratory infections (5).

In the 1930s, tracheotomy again was popularized as a useful procedure for the respiratory care of patients with poliomyelitis (5,10). The introduction of the polio vaccine (Salk vaccine) in the 1950s markedly decreased the incidence of poliomyelitis and the need for tracheotomy for this indication. As late as the 1970s, laryngotracheobronchitis and epiglottitis were common indications for tracheotomy in children, before endotracheal intubation became a popular treatment for acute airway obstruction from inflammation (11). However, vaccination against *Haemophilus influenzae* type B has contributed to significantly decreasing the rates of epiglottitis in children.

Since the 1960s and 1970s, the indications for tracheotomy in the pediatric population have shifted from its predominant use for the treatment of acute airway obstruction from infection and inflammation to the modern indications of the need for prolonged ventilation in patients with respiratory failure (e.g., from prematurity and bronchopulmonary dysplasia), the management of chronic airway obstruction, and the need for pulmonary toilet to manage excessive secretions (12–14).

INDICATIONS FOR TRACHEOTOMY

There are three main indications for tracheotomy in the pediatric population: (a) respiratory failure and anticipated need for prolonged ventilation; (b) upper airway obstruction; (c) providing access for pulmonary toilet. Some children who benefit from tracheotomy have more than one of these indications. Table 92.1 lists many of the indications for tracheotomy in children, divided into these three main categories, although there is some overlap between these categories.

A survey of 85 pediatric otolaryngologists who performed a combined total of more than 2,000 tracheotomies per year demonstrated that about 40% were performed for ventilator dependency, 30% for extrathoracic airway obstruction, 20% for neurologic dysfunction, and 10% for intrathoracic airway obstruction (15). In two separate series of patients separated by a decade, Wetmore et al. (11,13) found that prolonged intubation was the primary indication for tracheotomy in 53% of patients and airway obstruction in 38% or 39% or patients, with the remaining patients having other indications such as pulmonary toilet. In a recent series from Lyon, France, prolonged ventilator dependence was the indication for tracheotomy in 57% of children and upper airway obstruction in 43% (16). Another recent study demonstrated that 46 of 70 children (66%) who underwent tracheotomy had the procedure for prolonged mechanical ventilation (17). This study also found that children who have a tracheotomy for prolonged mechanical ventilation are likely to require a significantly longer hospital stay than children who have a tracheotomy for other reasons (17).

Many studies have demonstrated a significant change in indications for tracheotomy in the past 30 years (12,13,18,19). There has been an increase in tracheotomies for prematurity and chronic lung disease, congenital anomalies, acquired subglottic stenosis, and neuromuscular disease, and a concomitant decrease in tracheotomies for infectious diseases such as laryngotracheobronchitis (croup) and epiglottitis, as well as for short-term airway management (13,18). In one study, infants and young children were most likely to undergo tracheotomy for congenital anomalies, prematurity, lung disease, or some combination of these indications, whereas in adolescents, injury was the most common reason for tracheotomy (1).

TABLE 92.1 INDICATIONS FOR TRACHEOTOMY

Upper Airway Obstruction
- Laryngeal stenosis
  - Subglottic stenosis
  - Posterior glottic stenosis
- Tracheal stenosis
- Severe laryngomalacia
- Severe tracheomalacia
- Micrognathia
  - Macroglossia
  - Laryngeal web
  - Vocal fold paralysis
    - Hydrocephalus
    - Chiari malformation
    - Mobius syndrome
    - Other syndromes
    - Idiopathic
    - Iatrogenic
- Craniofacial syndromes
  - Pierre-Robin sequence
  - Treacher-Collins syndrome
  - Beckwith-Wiedemann syndrome
  - Other syndromes
- Lymphatic vascular malformations
- Trauma
  - Laryngeal fracture
  - Other laryngeal or tracheal injury
  - Facial injury with severe soft tissue edema
  - Trauma to recurrent laryngeal nerves
- Infectious/inflammatory
  - Epiglottitis
  - Laryngotracheobronchitis (croup)
  - Diphtheria
  - Tetanus
  - Ludwig angina
- Neoplastic
  - Laryngeal tumor
  - Tracheal tumor
  - Large tumor of oral cavity or oropharynx
  - Severe papillomatosis
  - Subglottic hemangioma
- Hypotonia secondary to neurologic or neuromuscular disorder
- Severe obstructive sleep apnea

Prolonged Intubation/Respiratory Failure
- Prematurity
- Bronchopulmonary dysplasia
- Congenital heart anomaly
- Hypoplastic lung
- Trauma
  - Traumatic brain injury
  - Pulmonary hemorrhage
  - Crushed chest
- Infectious/inflammatory
  - Pneumonia
  - Bronchiolitis
  - Meningitis
  - Encephalitis
- Neoplastic
  - Brain tumor
  - Spinal cord tumor
- Neurologic impairment
  - Hypoxic-ischemic encephalopathy
  - Myasthenia gravis
  - Guillain-Barré syndrome
  - Central respiratory impairment/central hypoventilation
- Other

Pulmonary Toilet
- Neurological impairment
  - Cerebral palsy/static encephalopathy
  - Hypoxic-ischemic encephalopathy
  - Neuromuscular disorders
  - Traumatic brain injury
  - Hypotonia
- Aspiration secondary to vocal fold paralysis
- Aspiration secondary to decreased laryngeal sensation

In children, respiratory failure and prolonged ventilator dependence are often caused by prematurity and bronchopulmonary dysplasia. In a study of 450 children who underwent tracheotomy, Wetmore et al. (13) found that bronchopulmonary dysplasia was the most common diagnosis.

Upper airway obstruction in children may be caused by craniofacial or structural abnormalities of the upper airway or by dynamic obstruction from hypotonia secondary to neurologic or neuromuscular disorders (12). Such hypotonia also can result in excess secretions or difficulty managing secretions; in these cases, tracheotomy also provides the benefit of easier access for suctioning and pulmonary toilet.

In the pediatric population, more tracheotomies are performed during the first year of life than during any other age group (12). In a series of preterm infants undergoing tracheotomy, Pereira et al. (20) found that 73% were performed for ventilator dependence, 18% for airway obstruction, and 9% for pulmonary toilet (20). Another study of tracheotomy in the preschool population found that tracheotomies are not very commonly performed in preschool-age children and the most common indication in this age group is the need for pulmonary toilet, often due to progressive neurologic disease; trauma was the second most common indication in this age group (21).

TRACHEOTOMY VERSUS ENDOTRACHEAL INTUBATION

Since the late 1970s, endotracheal intubation has replaced tracheotomy as the primary management technique for airway obstruction secondary to infectious etiologies such as laryngotracheobronchitis and epiglottitis (12,18). Anesthesiologists and pediatric intensivists have become more skilled at performing difficult intubations. For example, fiberoptic intubation has permitted some patients with

TABLE 92.2 TRACHEOTOMY VERSUS PROLONGED ENDOTRACHEAL INTUBATION

	Tracheotomy	Prolonged Intubation
Advantages	Shorter, larger tube can be placed Decreased airway dead space Less damage to larynx, including supraglottic, glottic, and subglottic regions More comfortable for the patient May allow child to be discharged from the hospital, even on a ventilator Care for the tracheostomy can be performed by trained caregivers/family who are not health care professionals	Can be performed by a variety of health care providers Does not require a surgical procedure and associated complications
Disadvantages	Requires an experienced surgeon Complications associated with tracheotomy (see Complications section) Requires a surgical procedure	Endotracheal tubes may be plugged easily Increased airway dead space More likely to cause damage to the larynx and trachea Less comfortable for the patient Care cannot be performed easily by patient/family caregivers

craniofacial disorders to have endotracheal intubation rather than a tracheotomy.

In the neonatal and pediatric intensive care units, improved management of endotracheal tubes has both decreased the complication rate from prolonged intubation and improved long-term intubation as an alternative to tracheotomy (18). In one recent 12-year series, the overall rate of tracheostomy tube placement for patients admitted to the neonatal intensive care unit was 0.7% (22). Indeed, the incidence of neonatal-acquired subglottic stenosis has significantly decreased over the past several decades (23).

Endotracheal intubation has the potential to cause injury to the glottis, subglottic region, and trachea relatively quickly, particularly if there is an improperly sized endotracheal tube, over-inflated endotracheal tube cuff, infection, or active gastroesophageal reflux. Perichondritis, infection, and active reflux can lead to delayed healing and scar formation. In adults, tracheotomy is typically recommended when there is an anticipated need for endotracheal intubation for more than 1 or 2 weeks. In infants and children, this time period can be prolonged with proper selection of endotracheal tube size, avoiding cuffed tubes or minimizing the pressure in the cuffs, and restricting movement on the tube. Newborns can tolerate longer periods of intubation (greater than 50 days) with a low risk of subglottic stenosis (24). One study suggested that children between the ages of 1 month and 18 years can also tolerate prolonged intubation well, and that with a properly managed endotracheal tube, 30 to 60 days is a reasonable time period (24). The average intubation period before tracheotomy in children was 32 days in one recent study and 43 days in another (19,25). However, there is no standard timing for tracheotomy after prolonged ventilation in children (17,24). The need for repeated intubation for a variety of reasons or multiple failed self-extubations also may be a reason for an earlier tracheotomy.

Table 92.2 provides a list of the relative advantages and disadvantages of tracheotomy versus prolonged endotracheal intubation. For children who have a relatively short need for intubation and who are not moving around, endotracheal intubation may be a better choice than tracheotomy. One advantage of endotracheal intubation is that it can be performed by many health care providers, whereas tracheotomy requires an experienced surgeon. Endotracheal intubation does not require a surgical procedure with the associated complications. However, disadvantages of endotracheal tubes include that they can become easily plugged, especially in younger children with smaller tubes, they can cause damage to the glottis and subglottis, and they are less comfortable for awake patients.

With tracheotomy, shorter, larger tubes can be placed, leading to decreased airway dead space and easier access for pulmonary toilet. There is less propensity to cause damage to the larynx, including the supraglottic, glottic, and subglottic regions. Tracheostomy tubes tend to be more comfortable for awake patients than endotracheal tubes. Children with a tracheostomy can be discharged from the hospital, even while still requiring a mechanical ventilator. In addition, care for children with a tracheostomy can be provided by trained caregivers/family members and does not necessarily require the constant presence of a health care professional.

There are a variety of techniques available to try to avoid tracheotomy in certain cases of upper airway obstruction (16). For example, some patients with isolated acute subglottic injury from endotracheal intubation can respond to balloon dilation of the airway. In selected cases of patients with recurrent croup and fixed subglottic stenosis, when this is the only airway lesion and the patient has no pulmonary compromise, a single stage laryngotracheal reconstruction



Figure 92.1 Proper positioning of the pediatric patient for a tracheotomy.

can be an alternative to tracheotomy. Some patients with Pierre Robin sequence and airway obstruction from retrognathia and glossoptosis can avoid a tracheotomy by undergoing mandibular distraction osteogenesis as a newborn. The details of these techniques to avoid tracheotomy and their appropriate indications are beyond the scope of this chapter.

TRACHEOTOMY TECHNIQUE

With the exception of a few life-threatening emergencies, tracheotomy in children should be performed in the controlled setting of the operating room under general anesthesia. When possible, the procedure should be performed with the patient intubated with an endotracheal tube to control the airway. If there is significant upper airway obstruction and endotracheal intubation is not possible but a rigid ventilating bronchoscope can be inserted, the procedure can also be performed over the bronchoscope. A laryngeal mask airway (LMA) can also be used when it is not possible to perform endotracheal intubation and a rigid bronchoscope cannot be passed or is not available. In children, awake tracheotomies without a controlled airway should be reserved for the few life-threatening situations in which endotracheal intubation or insertion of a rigid bronchoscope or LMA is not possible. Percutaneous tracheotomy is generally not recommended in children.

The patient is placed supine on the operating table with a shoulder roll to extend the neck (Fig. 92.1). In children with short necks or significant submental fat, tape can be used to help keep the submental pannus out of the way and to hold the head in position. The neck is carefully palpated and the level of the cricoid cartilage, thyroid notch, and sternal notch are marked (Fig. 92.2). The infant larynx is located higher in the neck than in older children and adults, the thyroid cartilage is broader, and the cricoid cartilage is often the most prominent palpable structure. The skin incision is marked between the level of the sternal notch and cricoid cartilage (Fig. 92.3). The skin can be infiltrated with local anesthesia with epinephrine. The neck is then prepared and draped, although the face is often left uncovered in order to provide access to the endotracheal tube by the anesthesiologist.

Either a horizontal or vertical skin incision can be made. Excessive subcutaneous fat deep in the incision can be removed using electrocautery (Fig. 92.4). The platysma fascia is divided. The strap muscles are then divided vertically and retracted (Figs. 92.5 and 92.6). The thyroid isthmus can be retracted superiorly or inferiorly, or divided (Fig. 92.7). If the thyroid isthmus is sitting over the area where the incision in the trachea should be made, the isthmus should be divided with electrocautery and ligated. The trachea is palpated often during the procedure to ensure

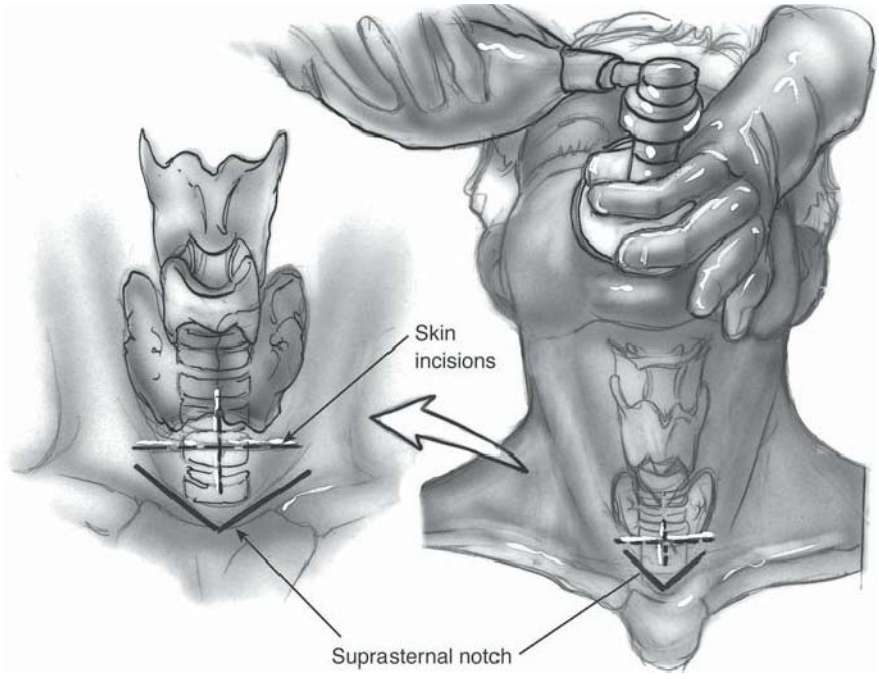


Figure 92.2 Anatomy of the neck and skin incision, which can either be horizontal or vertical.



Figure 92.3 Proper positioning of the pediatric patient for a tracheotomy. The patient is placed supine on the operating table with a shoulder roll to extend the neck. Tape is used to keep the submental fat out of the way and help hold the head in position. The level of the cricoid cartilage, sternal notch, and skin incision are marked.

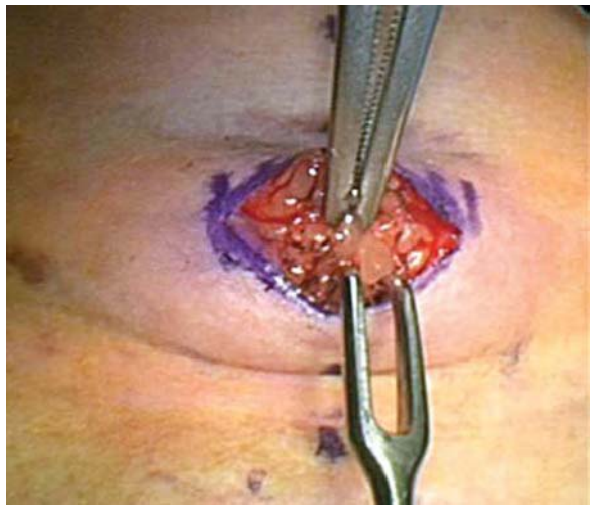


Figure 92.4 Removal of excess subcutaneous fat deep to the skin incision.

that the approach to the trachea remains in the midline (Fig. 92.8). The trachea in children is more pliable and has more lateral mobility than in adults; so it is important to be sure that dissection remains in the midline with the trachea centered in the surgical field. Excessive lateral dissection should be avoided to help minimize subcutaneous air and decrease chance of injury to the dome of the pleura or recurrent laryngeal nerves. When using electrocautery during tracheotomy, the fraction of inspired oxygen (FiO_2) should be kept below 30% to help prevent a surgical fire.

In infants and small children, a vertical incision in the trachea may be preferred (Fig. 92.9). It has been suggested that the vertical incision may decrease the incidence of suprastomal collapse and tracheal stenosis (18). In older children and adolescents, either a vertical incision in the trachea or an inferiorly based flap (Bjork flap) can be employed (11,26,27). Waki et al. (27) have advocated an inferiorly based tracheal flap for all pediatric patients, including infants. However, one survey revealed that most pediatric otolaryngologists (75%) prefer a vertical incision (15).

The vertical incision in the trachea is typically made through rings 2 and 3. Retention sutures (stay sutures) should be placed in a paramedian position on each side of the incision prior to making the incision to help retract the opening in the trachea intraoperatively and facilitate replacement of the tube in case of accidental decannulation in the early postoperative period, prior to the establishment of a mature tracheostomy stoma tract (Figs. 92.10 and 92.11) (15). The importance of these retention sutures cannot be overemphasized, as they can be life saving.

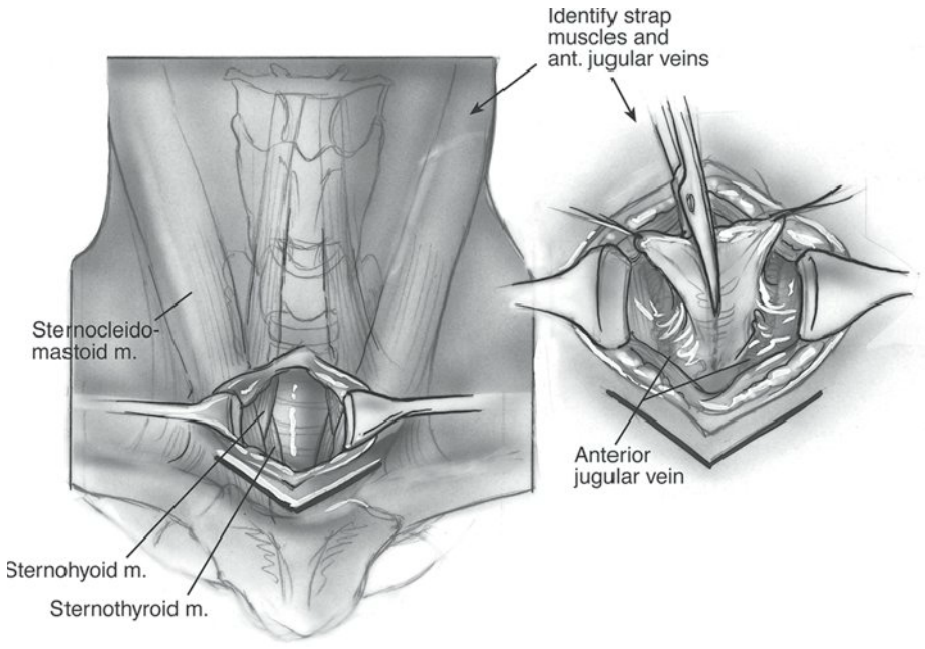


Figure 92.5 Identification and division of the strap muscles.

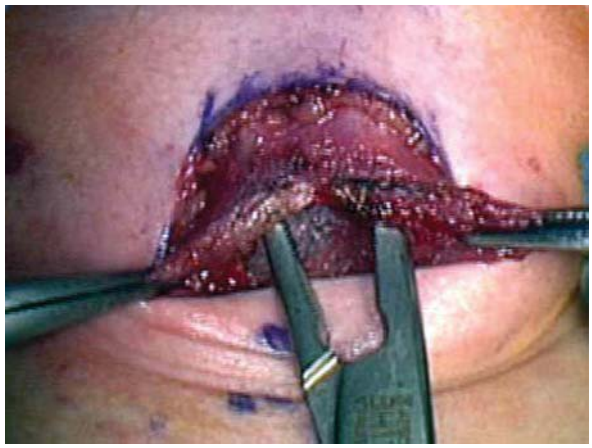


Figure 92.6 The strap muscles are divided vertically in the midline and retracted.



Figure 92.9 The trachea is exposed and a vertical incision is marked in the midline.

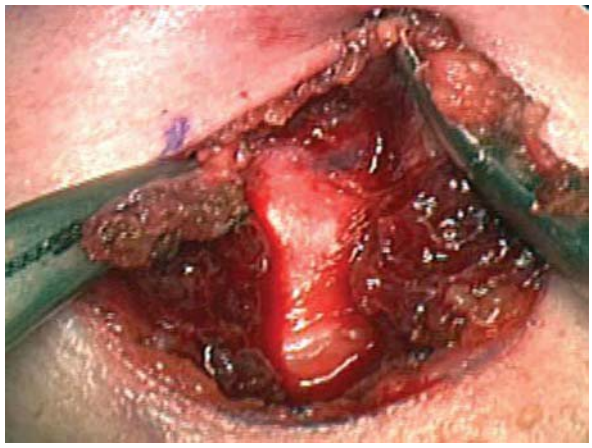


Figure 92.7 Division of the thyroid isthmus. If the thyroid isthmus is sitting over the area where the incision in the trachea is to be made, the isthmus should be divided and ligated.

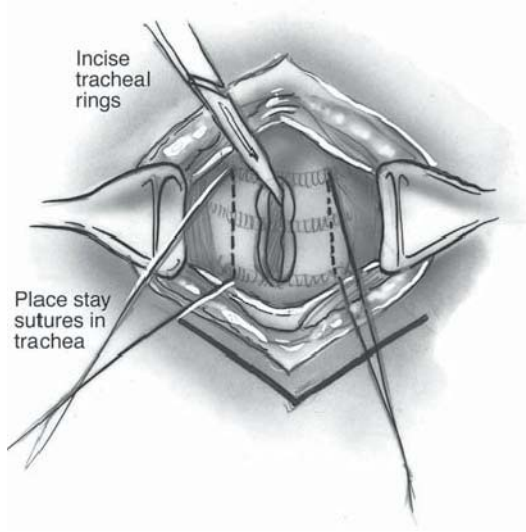


Figure 92.10 Placement of stay sutures on each side of the midline and making a vertical incision in the trachea.

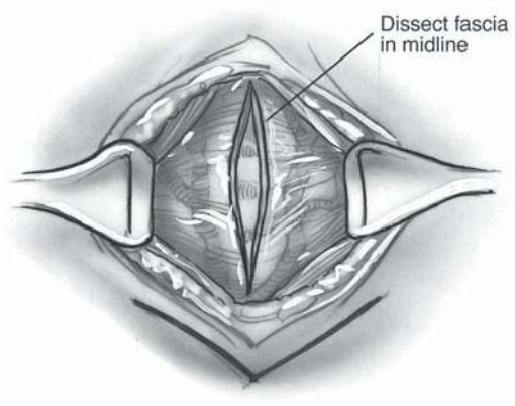


Figure 92.8 Identification of the trachea and dissection of the pretracheal fascia.



Figure 92.11 The vertical incision in the trachea is typically made through rings 2 and 3. Stay sutures are placed in a paramedian position on each side of the incision.



Figure 92.12 Tracheostomy tube is in good position with stay sutures present.

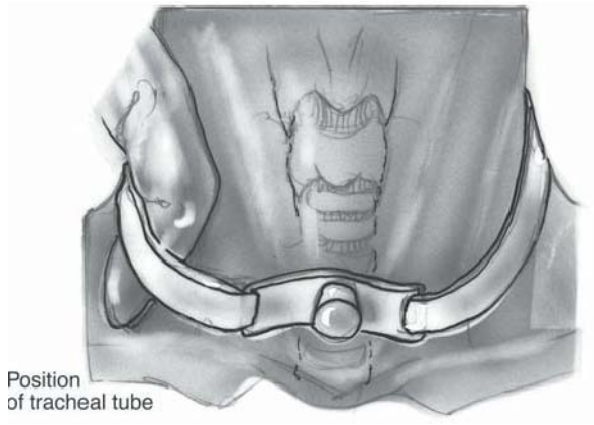


Figure 92.14 Proper position of the tracheostomy tube.

The endotracheal tube is slowly withdrawn to allow for insertion of the tracheostomy tube. However, the tip of the endotracheal tube should remain just below the glottis and should not be completely removed until it is confirmed that the tracheostomy tube is in good position and secure (Fig. 92.12) (11).

Once the tracheostomy tube is in good position and it is confirmed that the patient can be ventilated adequately through the tube, the surgical site is again inspected to ensure that there is good hemostasis. The endotracheal tube can then be removed completely. DuoDERM (ConvaTec Professional Services, Skillman, NJ) can be applied to the neck to help prevent irritation from the tracheostomy tube ties (Fig. 92.13). Cotton tracheostomy tube ties are then placed and tied to secure the tracheostomy tube (Fig. 92.14). In children, it is recommended not to suture the flange of the tracheostomy tube to the skin because children often have shorter tracheostomy tubes, which may be more likely to be displaced from the trachea. If this accidental displacement occurs and the tracheostomy tube is sitting in a false passage, sutured flanges can delay rapid removal of the tracheostomy tube and replacement into proper position.

The stay sutures are then labeled with adhesive tape ("left" and "right") and taped to the chest wall (Fig. 92.15). A flexible tracheoscopy through the tracheostomy tube can be performed to confirm that the tracheostomy tube is the correct size and that the tip of the tracheostomy tube is sitting in good position with respect to the carina. For patients who have had a prolonged intubation, a direct laryngoscopy and rigid tracheoscopy can then be performed to assess for possible injury or inflammation in the area of the true vocal folds, subglottis, and suprastomal trachea.

Pediatric tracheotomy can be performed with or without maturation of the stoma. Maturation of the stoma involves suturing the skin edges to the tracheal cartilage (Fig. 92.16) (28). In a survey of pediatric otolaryngologists performing tracheotomy, 41% routinely matured the

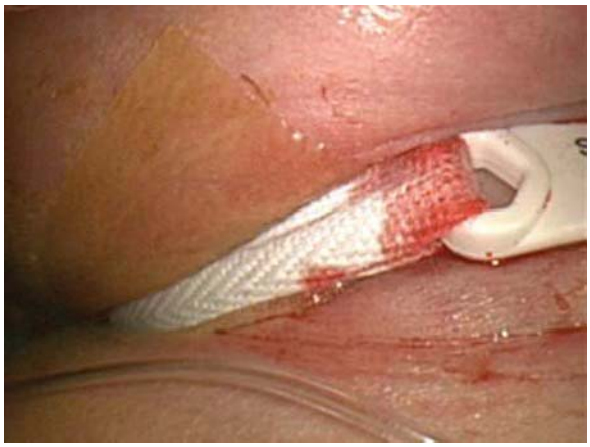


Figure 92.13 Tracheostomy tube is secured with cotton ties and DuoDERM is applied to the neck to help prevent irritation from the tracheostomy tube ties. DuoDERM, ConvaTec Professional Services, Skillman, NJ.

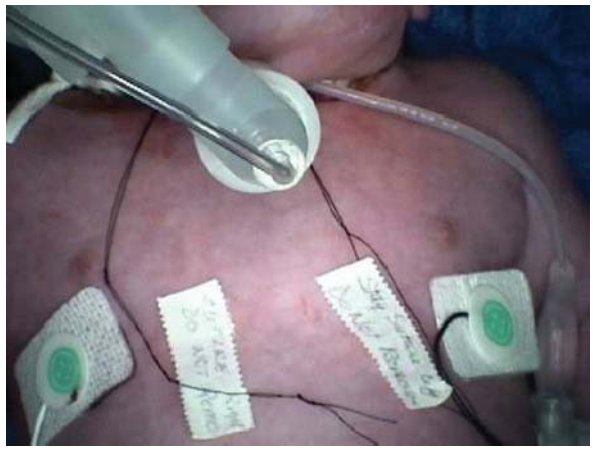


Figure 92.15 Stay sutures are labeled with adhesive tape ("**left**" and "**right**") and secured to the chest wall.

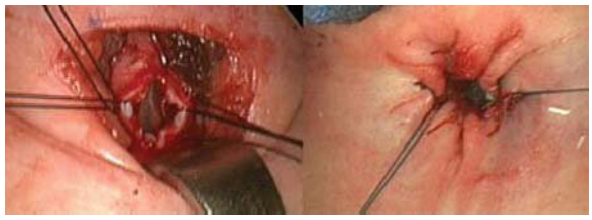


Figure 92.16 Tracheotomy with vertical incision without stoma maturation (**left**) and tracheotomy with vertical incision with stoma maturation (**right**). Stay sutures are in place in both cases. From Colman KL, Mandell DL, Simons JP. Impact of stoma maturation on pediatric tracheostomy-related complications. *Arch Otolaryngol Head Neck Surg* 2010;136:471–474, with permission. Copyright © 2010 American Medical Association. All rights reserved.

stoma (15). Techniques for stomal maturation include suturing four quadrant or vertical skin flaps to tracheal cartilage, suturing an inferiorly-based cartilage flap to the skin (Bjork flap), and a starplasty technique, in which four skin flaps are intercalated among four tracheal cartilage flaps based on Z-plasty principles (26,29,30). One study suggested that maturation of the stoma may decrease the morbidity of early accidental decannulation while leading to no increase in the rate of tracheocutaneous fistula formation (31). These authors felt that tracheostomy tubes in children with matured stomas were easier to replace in the event of accidental decannulation (31). Another study found that the rates of tracheostomy-related complications were similar between matured and nonmatured stomas, including the rates of development of granulation tissue and tracheocutaneous fistulae (28).

The choice of tracheostomy tube depends on the age and size of the child and his or her respiratory status. Patients that require positive pressure ventilation require either a more snug-fitting tracheostomy tube or a cuffed tube to help prevent too large an air leak around the tube, which could make ventilation difficult. Even when there is the need for positive pressure ventilation, smaller children often can be ventilated with an uncuffed tube, which prevents the potential problems associated with a cuff, including overinflation, mucosal injury, and subsequent tracheal stenosis. For children who do not require a ventilator, a smaller tracheostomy tube can be placed, which has the advantage of causing less pressure on the tracheal walls and permitting airflow around the tracheostomy tube to allow for phonation and the use of a speaking valve.

POSTOPERATIVE CARE

Pediatric patients are typically kept in the intensive care unit or a special airway observation unit for at least the first 5-to-7 days after a tracheotomy until the first tracheostomy tube change is performed. By that time, it is less likely that the tube will be placed into a false passage, as the stoma tract is more established. If needed, the patient should be kept sedated and/or restrained until the first tracheostomy tube change in order to help prevent accidental decannulation. The ventilator typically is managed by the pediatric intensivists. Suctioning through the tracheostomy tube should be performed every 1 to 2 hours for the first few days and then, as needed, for secretion control and to help prevent mucus plugging. Care must be taken that the ventilator circuit is not causing traction on the tracheostomy tube, which could contribute to accidental decannulation or erosion of the stoma.

The first tracheostomy tube change, after 5 to 7 days, should be performed by an otolaryngologist or another physician experienced in tracheostomy care in order to determine that the stoma tract has healed well enough to allow nurses, respiratory therapists, and parents to perform future tracheostomy tube changes safely. One author has advocated that the tracheostomy tube can be changed safely as early as 3 or 4 days after surgery but it is more common to wait for 5-to-7 days (32). The tracheostomy tube ties placed at the time of the surgical procedure are often cotton and tied in a knot to help prevent them from loosening in the immediate postoperative period. After the first tracheostomy tube change, the tracheostomy tube ties can also be changed to softer Velcro ties. Also after 5-to-7 days, once a safe tracheostomy stoma tract is established, the stay sutures (retention sutures) can be removed.

A chest radiograph should be ordered in the immediate postoperative period to confirm proper tracheostomy tube position and length with respect to the carina and to rule out pneumothorax or pneumomediastinum (33). As mentioned previously, many otolaryngologists performing tracheotomies in children also perform a flexible tracheoscopy on the operating room table after the tracheostomy tube is inserted to establish that the tube is of correct size with respect to the trachea and carina (33).

Children not on a ventilator are usually able to start oral feedings on postoperative day one. If there is concern for aspiration or dysphagia, an initial bedside clinical swallowing evaluation should be performed by a speech pathologist prior to starting feeding. If there is persistent concern for aspiration, consideration should be given to obtaining an instrumental swallowing assessment such as a videofluoroscopic swallowing study (modified barium swallow study) or a fiberoptic endoscopic evaluation of swallowing (FEES) prior to starting an oral diet.

After the first tracheostomy tube change, the patient's home caregivers then begin to learn routine tracheostomy care, how to manage problems such as mucus plugging and accidental decannulation, and cardiopulmonary resuscitation. Teaching can be performed by physicians, nurse educators, and respiratory therapists experienced in tracheostomy care. The topics include tracheostomy tube-changing technique, frequency of tube changing, suctioning technique and frequency, wound care, recognition of infection and respiratory distress, emergency procedures, and acceptable activities (33,34). Many pediatric otolaryngologists use a tracheostomy management team including

physicians, clinical nurse specialists, respiratory therapists, and other specialists to help with tracheostomy teaching and care (15).

Patients with a tracheostomy tube should not be discharged from the hospital until it is determined that their home caregivers have had adequate training and are comfortable managing the tracheostomy. Proper education and home care help prevent complications after discharge from the hospital (35). In a survey of pediatric otolaryngologists performing tracheotomy, the average time parents were trained prior to a child's discharge from the hospital was 9 days (15). One study found that the average hospital length of stay for children undergoing a tracheotomy was 50.2 days (1).

It is critical that an adult with proper training be present at all times with a child who has a tracheostomy. Home skilled nursing care for children with tracheostomy tubes can be very helpful in aiding parents and preventing complications. Tracheostomy care manuals have been prepared by many children's hospitals and are also available commercially. Proper equipment should be available in the home, including oxygen, suction, suction catheters, saline bullets, apnea monitor, pulse oximetry, and an Ambu bag. The patient should be discharged home with spare tracheostomy tubes of the same size and one size smaller, the latter to be used in the event of an accidental decannulation or tracheostomy tube change in which the original size tube cannot be replaced. Tracheostomy tube changes should be performed on a weekly basis. The electric company, telephone company, emergency services, and local police should be made aware that there is a child in the home with a tracheostomy. It is important that the electricity and telephone service to the home be maintained.

After discharge from the hospital, children who have a tracheostomy must follow up routinely with the otolaryngologist who performed the tracheotomy as well as with their pediatrician. In larger tertiary-care children's hospitals, the trend is for tracheostomy patients to be followed in a multidisciplinary airway center, which may include otolaryngologists, pulmonologists, speech pathologists, respiratory therapists, and other health care providers who can offer different areas of expertise to help manage these often complex patients. Most otolaryngologists perform routine elective interval airway endoscopy in the operating room (3-to-6 month intervals) on all pediatric patients with tracheostomy tubes and feel that it may help prevent complications (35,36). Such endoscopy would include a flexible fiberoptic tracheoscopy, direct laryngoscopy, rigid bronchoscopy, tracheostomy tube change, and possible removal of obstructing suprastomal granulation tissue, if present. Some other otolaryngologists only take patients to the operating room for endoscopy when they present to the office with tracheostomy-related problems. Children with long-term tracheostomies need to have their airways evaluated periodically as they grow to ensure that the tracheostomy tube is the correct size and in the correct position.

COMPLICATIONS OF TRACHEOTOMY

Tracheotomy in children has been associated with a higher rate of complications than adults (11,31). Complications of pediatric tracheotomy can be divided into intraoperative complications, early postoperative complications, and late postoperative complicawtions. Table 92.3 lists the complications of pediatric tracheotomy, divided into these three categories. Early postoperative complications are typically considered to occur within the first week after surgery and late complications occur after 7 days. The overall rates of early complications have been reported to be from 5.0% to 28.0% and late complication rates have been reported to be as high as 63.5%, with as many as 43.0% of these late complications considered to be serious (2,13,14,19,25,28,35–37).

The most common intraoperative complication is hemorrhage. Meticulous dissection technique and control

TABLE 92.3 COMPLICATIONS PEDIATRIC TRACHEOTOMY

Intraoperative Complications
- Bleeding
- Loss of airway or inability to ventilate
- Subcutaneous emphysema
- Pneumomediastinum
- Pneumothorax
- Esophageal injury
- Creation of false passage
- Recurrent laryngeal nerve injury
- Cardiopulmonary arrest, death

Early Postoperative Complications (<7 days)
- Accidental decannulation
- Tracheostomy tube occlusion
- Bleeding
- Subcutaneous emphysema
- Pneumomediastinum
- Pneumothorax
- Creation of false passage
- Stoma/wound breakdown or cellulitis
- Neck skin erosion from tracheostomy tube ties
- Tracheitis

Late Postoperative Complications (>7 days)
- Accidental decannulation
- Tracheostomy tube occlusion
- Peristomal granulation tissue
- Suprastomal granulation tissue
- Stoma/wound breakdown or cellulitis
- Neck skin erosion from tracheostomy tube ties
- Tracheostomy stomal stenosis
- Suprastomal cartilaginous collapse
- Subglottic stenosis
- Tracheomalacia
- Tracheitis
- Tracheal stenosis
- Tracheal granulation tissue
- Airway hemorrhage
- Tracheo-innominate artery fistula
- Persistent tracheocutaneous fistula after decannulation

of bleeding vessels with electrocautery and ties can help prevent intraoperative hemorrhage. It is also recommended that if the thyroid isthmus is divided, it be carefully suture ligated. The possibility of a coagulation abnormality must be considered in any child with excessive bleeding during or immediately after a tracheotomy procedure.

Other intraoperative complications include subcutaneous emphysema, pneumomediastinum, pneumothorax, esophageal injury, recurrent laryngeal nerve injury, creation of a false passage, difficulty ventilating, and cardiopulmonary arrest (14,18,35). Interstitial air such as subcutaneous emphysema often can be prevented by avoiding suturing the edges of the skin incision closed and by confining the dissection to the midline of the trachea without dissecting too far laterally. Pneumomediastinum and pneumothorax can develop from a progression of subcutaneous emphysema or from injury to the dome of the pleura during the tracheotomy procedure. In infants, the apex of the lung can extend into the root of the neck, above the clavicle. Rupture of alveoli caused by excessive coughing in the immediate postoperative period or increased negative intrathoracic pressure also can lead to pneumomediastinum and pneumothorax. Subcutaneous emphysema and pneumomediastinum typically will resolve on their own and can be managed expectantly. Small pneumothoraces can be observed but larger pneumothoraces may require a thoracostomy tube.

Esophageal injury and tracheoesophageal fistula formation also can occur intraoperatively, and usually can be prevented by avoiding making the anterior tracheal wall incision too deep which could cause damage to the posterior tracheal wall (membranous trachea), avoiding forcing the tracheostomy tube roughly into the trachea, and removing esophageal feeding tubes for the procedure. Injury to the recurrent laryngeal nerves can be prevented by keeping dissection close to the midline.

There is some overlap between intraoperative and early postoperative complications, which can also include bleeding, subcutaneous emphysema, pneumomediastinum, and pneumothorax (18).

Certain complications, such as accidental decannulation (3.3% to 11.6%) and tracheostomy tube occlusion (1.8% to 9.9%) can occur in the early or late periods (13,28,35,36,38). Both tracheostomy tube plugging and accidental decannulation are amongst the most common causes of tracheostomy-related morbidity and mortality (12,18,33,38,39). The rates of accidental decannulation are probably higher than reported in the literature, as many episodes of accidental decannulation are not documented unless there is significant morbidity or a requirement to return to the operating room for a stoma revision as a result. Morbidity and mortality from accidental decannulation can be minimized by carefully securing the tracheostomy tube with ties, utilizing stay sutures, and closely observing patients in the intensive care unit or a special airway observation unit until the first tracheostomy tube change. As stated above, some otolaryngologists also feel that maturing the stoma decreases the morbidity from accidental decannulation but this issue is somewhat controversial (31).

Tracheostomy tube obstruction/plugging tends to occur more frequently in premature infants and newborns compared with children older than 1 year (18). This finding likely is due to the smaller diameter tracheostomy tubes used in infants as well as the fact that many premature infants with tracheostomy tubes have bronchopulmonary dysplasia, which can lead to thicker bronchial secretions (18). Appropriate tracheostomy tube care can help prevent tracheostomy tube obstruction. Such care includes frequent suctioning, use of saline with suctioning, and humidifying the inspired air or oxygen. Changing the tracheostomy tube at a proper frequency (ideally every week) can also help prevent mucus plugging.

Stoma/wound breakdown or stoma cellulitis also can occur in the early or late periods. In one study, the rate of wound complications after tracheotomy was 29% (40). Patients less than age 1 year had a higher wound complication rate than older patients (40). It is important to minimize pressure from the ventilator circuit on the tracheostomy tube. The stoma site should be kept as clean and dry as possible to help prevent infection and wound breakdown around the stoma. Barrier protection between the flanges of the tracheostomy tube and the skin can also help prevent early tracheotomy wound breakdown (40). Tracheostomy tube ties that are too tight or moist can lead to skin ulceration. Aggressive local wound care can help prevent early stoma wound breakdown from progressing to more severe wounds. Triple antibiotic ointment can be used to treat mild infection and granulation tissue around the stoma.

Two other common late complications and their reported incidences include the development of peristomal granulation tissue (6.1% to 26.7%) and suprastomal granulation tissue (38.7% to 48.8%) (12,13,28,36,38). Granulation tissue in the peristomal or suprastomal area is quite common and can be harmless (19). However, such granulation tissue can also lead to bleeding, difficulty with tracheostomy tube changes, and suprastomal airway obstruction (Fig. 92.17) (18). Peristomal granulation tissue can be treated with topical triple antibiotic ointment or it can be cauterized with silver nitrate. Severe peristomal granulation tissue can also contribute to the development of tracheostomy stomal stenosis (Fig. 92.18). When such stomal stenosis develops to the extent that tracheostomy tube changes become difficult, a formal stoma revision may be necessary. Obstructing suprastomal granulation tissue can be removed with a variety of techniques, including open excision, endoscopic excision with optical forceps, or excision through the stoma with a small hook and tenotomy scissors, sphenoid punch, or microdebrider (41,42).

Granulomas also can develop at the tip of the tracheostomy tube and can be life threatening in this location by obstructing the tube. Such granulomas can be detected during interval surveillance endoscopy, either performed



Figure 92.17 Endoscopic view of a totally obstructing suprastomal granuloma.

in the office via flexible tracheoscopy or in the operating room during a complete airway endoscopy. When such granulation tissue is detected, changing the tube length, shape, or material may be helpful. Obstructing granulation tissue can be removed endoscopically with a variety of techniques, including optical forceps or laser. Topical steroids applied through the tracheostomy tube also can help decrease the severity of tracheal granulation tissue.

Suprastomal cartilaginous collapse is another late complication. Mild suprastomal collapse is quite common and is not typically a problem. However, more severe suprastomal collapse can lead to significant airway obstruction and interfere with successful decannulation. This complication may be responsible for decannulation failure in 2.4% to 18% of children (43). There are a variety of techniques to manage severe suprastomal cartilaginous collapse, including endoscopic excision with a laser, partial excision of the collapsed segment through the stoma with Kerrison rongeurs, placement of tracheal suspension sutures, and laryngotracheal reconstruction with anterior rib cartilage grafting (43,44).



Figure 92.18 Large peristomal granuloma causing tracheostomy stomal stenosis and difficulty with tracheostomy tube changes.

Another serious late complication of tracheotomy is the development of tracheal stenosis that can develop from pressure from the distal end or cuff of the tracheostomy tube as well as from local infection and inflammation (18). In addition, tracheomalacia can develop as a long-term complication of tracheotomy, particularly involving the suprastomal portion of the trachea.

The incidence of subglottic stenosis as a late complication of tracheotomy has decreased since Chevalier Jackson (8) emphasized the dangers of performing a tracheotomy too "high" in 1921. Subglottic stenosis can be caused by inserting the tracheostomy tube too close to the cricoid cartilage or through the cricoid cartilage. However, subglottic stenosis more frequently occurs as a result of subglottic injury from prolonged endotracheal intubation prior to the tracheotomy being performed and is not considered a complication of the tracheotomy in these cases. Subglottic stenosis as a result of the tracheotomy itself can typically be avoided by careful dissection and placing the incision in the trachea at the correct level.

Development of a tracheo-innominate artery fistula is the most dreaded serious late complication of tracheotomy. Although rare, this complication represents a true emergency and has a high mortality rate. The innominate artery typically comes off of the aorta and crosses the trachea either deep to the sternum or in the inferior portion of the neck in the case of a high-riding innominate artery. Pressure on the anterior tracheal wall from the tracheostomy tube tip or cuff can cause erosion, predisposing to tracheo-innominate artery fistula formation. Although most bleeding from a tracheostomy is caused by granulation tissue, tracheitis, or suction trauma, the possibility of a tracheo-innominate artery fistula must be considered and all children with bleeding from their tracheostomy must be evaluated. When there is bleeding granulation tissue noted on the anterior tracheal wall, there is a high possibility of the presence of a tracheo-innominate artery fistula. Exploration should be performed in the operating room with a pediatric general or cardiothoracic surgeon immediately available. A cuffed endotracheal tube or tracheostomy tube can be placed through the stoma to attempt to tamponade severe bleeding. Placing a finger through the stoma with endotracheal tube intubation from above also may be helpful. Definitive management requires a sternotomy and division/ligation of the innominate artery.

Some series also include tracheitis as an early and late complication of tracheotomy, with an incidence of 8.3% to 48.8% (28,35,36). However, many others do not include tracheitis as a complication, but rather a sequela of having a tracheostomy tube, and its incidence may be underreported. Tracheitis can be treated with nebulized tobramycin or with culture-directed oral or intravenous antibiotics, depending on the severity of the infection.

One study suggested that children with tracheostomy tubes are more likely to have a history of constipation and to take medications for constipation, possibly because the tracheostomy tube prevents the development of adequate subglottic and tracheal pressure during the Valsalva maneuver, which may impair the ability to defecate (45). This study was unable to prove a causal relationship between tracheostomy and constipation, however, because many of the patients with tracheotomy also had neurodevelopmental impairment, which can contribute to constipation (45).

The rate of persistent tracheocutaneous fistula after decannulation is between 2.5% and 37.1% (12,13,28,36,38,46). Persistent tracheocutaneous fistulae may be more likely in children who have a tracheostomy for longer periods of time (12,19). A few studies have found that there was no increase in the rate of tracheocutaneous fistula formation in stomas that have been matured compared with those that have not been matured (28,31). On the other hand, there is a higher rate of tracheocutaneous fistula formation after decannulation when the starplasty technique is used for stoma maturation (30). Most authors recommend waiting 6 to 12 months after decannulation to perform closure of a persistent tracheocutaneous fistula (46). Occasionally, a persistent tracheocutaneous fistula can occur because the airway remains partially obstructed at some level. In these cases, a child may depend on the persistent fistula for respiration. This possibility must be ruled out prior to performing closure of a persistent tracheocutaneous fistula.

Younger patients (less than 1 year) in general have higher complication rates than older patients (13,18,19,28). Colman et al. (28) found that younger patients had a higher rate of suprastomal granulation tissue, tracheitis, persistent tracheocutaneous fistulae, and need for additional surgical procedures for a tracheostomy-related complication. Parrilla et al. (19) also found a higher complication rate in children less than age 1 year (47.4%), compared with children above age 1 year (26.3%). The higher complication rate in younger children is likely due to the narrower diameter and increased pliability of the trachea. Furthermore, children less than 1 year of age who undergo tracheotomy are more likely to have bronchopulmonary dysplasia and abundant, viscous tracheal secretions, increasing their risk of such complications as mucus plugging (19).

Children with a tracheostomy are at risk for frequent hospitalizations for several reasons, including for their primary disease, for respiratory infections such as pneumonia and tracheitis, and for other tracheostomy-related complications (2,17). One study reported that 11% of children required at least four hospitalizations within 6 months of their tracheotomy (17). In another multi-institutional study, 52% of children less than age 1 year at the time of their tracheotomy were readmitted to the hospital within 30 days of discharge (2).

The tracheostomy-related mortality rate in the literature ranges from 0% to 8%, although more recent studies report mortality rates on the lower end of that range (11–13,25,47). There has been a trend toward decreased tracheostomy-related deaths over the past few decades, likely secondary to improved care and monitoring, both in the hospital and at home (12,14). The overall mortality in children who undergo a tracheotomy is as high as 13% to 40%, but the deaths are usually related to the underlying disease process and not the tracheotomy itself (11,12,18,19,36). One study found that children who received their tracheotomy procedure at children's hospitals had lower mortality rates than children who received their tracheotomy at non-children's hospitals. This same study also found that hospitals performing larger volumes of pediatric tracheotomies had lower mortality rates (1). Children with upper airway obstruction as the indication for their tracheotomy tend to have a lower mortality rate than children with chronic lung disease, neurologic impairment, or both (2).

TRACHEOSTOMY TUBES

There are several brands of pediatric tracheostomy tubes available, including Shiley (Covidien-Nellcor, Boulder, CO), Bivona (Smiths Medical, Dublin, OH), Portex (Smiths Medical, Dublin, OH), and Tracoe (Boston Medical Products, Westborough, MA). These tracheostomy tubes are available in different widths, lengths, materials (polyvinyl chloride or silicone), and with or without a cuff. There are also metal pediatric tracheostomy tubes available (Jackson and Holinger tubes), although they are not frequently used and are often reserved for special situations, such as for certain airway reconstruction procedures. The size designations of pediatric tracheostomy tubes are based on the inner diameter of the tubes in millimeters. Neonatal tracheostomy tubes have similar inner and outer diameters to comparable size pediatric tracheostomy tubes but have a shorter length (Fig. 92.19). In contrast to adult tracheostomy tubes, pediatric tracheostomy tubes have a relatively small inner



Figure 92.19 Neonatal tracheostomy tubes have similar inner and outer diameters to comparable size pediatric tracheostomy tubes but have a shorter length. Size 3.5 Neonatal Shiley tracheostomy tube (**left**) and size 3.5 Pediatric Shiley tracheostomy tube (**right**) (Shiley, Covidien-Nellcor, Boulder, CO). Photo courtesy of Charles W. Boig, Jr., BS, RRT, Children's Hospital of Pittsburgh of UPMC.



Figure 92.20 Neonatal and pediatric cuffed Bivona tracheostomy tubes with TTS cuffs (Bivona, Smiths Medical, Dublin, OH). Photo courtesy of Charles W. Boig, Jr., BS, RRT, Children's Hospital of Pittsburgh of UPMC.

diameter, making inner cannulas impractical. Therefore, thoroughly cleaning the tracheostomy tube requires removing the entire tube and replacing it with a new one (34). Most pediatric tracheostomy tubes are uncuffed. Cuffed pediatric tracheostomy tubes are available, but are typically reserved for ventilated patients requiring higher airway pressures. The external connector for almost all pediatric tracheostomy tubes is universally the same size so that it can be attached to the same ventilator circuits, speaking valves, and artificial noses. The shafts of some tracheostomy tubes have wire reinforcement, which can interfere with some radiologic imaging. For example, such wire-reinforced tracheostomy tubes would prevent patients with those types of tubes from having an MRI with the tube in place.

For patients that require intermittent ventilation, Bivona makes a tight-to-shaft (TTS) cuffed tube, in which the cuff is designed to deflate very close to the shaft of the tube with a low profile to minimize contact with the tracheal walls when not in use (Fig. 92.20). Bivona FlexTend tracheostomy tubes have an extension anterior to the flange that can prevent children with excessive cervical/submental fat from occluding the lumen of the tube. Bivona also has a Hyperflex tracheostomy tube that is made of a soft wire-reinforced silicone (Fig. 92.21). This tube is designed to conform to the shape of the airway and can be very useful when the airway is tortuous, such as in patients with severe scoliosis.



Figure 92.21 Assorted Bivona tracheostomy tubes, including standard pediatric tracheostomy tube (**upper left**), FlexTend pediatric tracheostomy tubes (three tubes on **right**), and Hyperflex tracheostomy tube (**left**) (Bivona, Smiths Medical, Dublin, OH). Photo courtesy of Charles W. Boig, Jr., BS, RRT, Children's Hospital of Pittsburgh of UPMC.

DECANNULATION

There has been a trend over the past few decades of fewer tracheotomies overall and lower rates of decannulation, as fewer tracheotomies are being performed for infectious indications and a larger percentage are being performed for chronic lung disease and other chronic disorders (12). The underlying indication for the tracheotomy influences the chance for successful decannulation. In one study, patients with craniofacial abnormalities had a 63% chance of successful decannulation, patients with prolonged intubation had a 47% chance of successful decannulation, and patients with neurologic impairment only had a 12.5% chance of successful decannulation (12). Berry et al. (2) found that children with neurologic impairment had a lower rate of successful decannulation and a higher mortality rate than those without neurologic impairment.

In a study of children who underwent tracheotomy in the first year of life, 36.3% of term infants and 30.6% of preterm infants were decannulated successfully (14). The average length of tracheostomy use prior to successful decannulation was 458 days for term infants and 736 days for preterm infants (14). In a series of 181 children undergoing tracheotomy, Tantinikorn et al. (36) found that 64.1% were able to be decannulated successfully. In another study, successful decannulation was achieved in 62% of surviving children who underwent a tracheotomy while in the neonatal intensive care unit (22). Improvements and advances in the management of airway obstruction from subglottic stenosis and craniofacial abnormalities have improved decannulation rates in children with these problems.

For decannulation to be successful, there must be adequate improvement or resolution of the original problem that led to the requirement for a tracheotomy, whether it be respiratory failure and prolonged ventilation, upper airway obstruction, or the need for access for pulmonary toilet (48). The decision to proceed with decannulation is often multidisciplinary, and involves the patient's pediatrician, otolaryngologist, pulmonologist, gastroenterologist, and neurologist (49). Prior to decannulation, an endoscopic evaluation of the airway, including flexible fiberoptic laryngoscopy, direct laryngoscopy, and rigid bronchoscopy, should be performed to make sure that there is no supraglottic obstruction from granulation tissue or cartilaginous collapse, to assess vocal fold function, and to determine that there is no other site of airway obstruction that would

prevent successful decannulation (49). The tracheostomy tube is then downsized so that there is room in the airway to breathe around the tube while it is plugged. The tracheostomy tube is then plugged under supervision to determine whether the patient can breathe easily through the larynx and upper airway. Tracheostomy tube-plugging trials can occur during the daytime while the child is at home or out of the hospital. If the child does well with the tracheostomy tube capped during the daytime, he or she is typically admitted to a monitored bed in the hospital for a trial of nighttime capping of the tracheostomy tube prior to decannulation. At our institution, these nighttime capping trials are performed in the pediatric intensive care unit. If this nighttime capping is tolerated, the patient is then decannulated and observed for another night or two in a monitored setting prior to discharge. Once the tube is removed, a mild-pressure dressing is applied to the stoma area.

If there is concern for significant upper airway obstruction, dynamic airway collapse, or obstructive sleep apnea, a polysomnogram can be performed with the tracheostomy tube plugged prior to decannulation (50). In small infants, it may not be possible to downsize the tracheostomy tube to a small enough size to allow for a capping trial, as even the smallest tubes can fill the trachea completely. In these cases, the tracheostomy tube may occasionally be removed without a capping trial. A few otolaryngologists have advocated the use of fenestrated tubes as part of the decannulation process in children (51). However, fenestrated tracheostomy tubes are not generally recommended as part of the decannulation process in the pediatric population, as the fenestration can create significant irritation to the tracheal mucosa and promote granulation tissue formation.

COMMUNICATION CONCERNS

Children with tracheostomy tubes can have a delay in speech acquisition and decreased receptive and expressive language skills (52–54). There is a higher risk for communication disorders in children with tracheostomy tubes who already have neurodevelopmental impairment (15,53). Indeed, children with tracheostomy tubes can be significantly limited by their lack of voice (4). One study suggested that achieving the earliest decannulation possible can improve the chance of normal speech and language development (53).

It is helpful for children with tracheostomy tubes to be evaluated by a speech pathologist, both to assess swallowing function and to address communication issues. In patients who can tolerate them, speaking valves (e.g., Passy-Muir valves) can help with both verbal communication and swallowing (11,34). Contraindications to speaking valves include significant laryngeal stenosis or other forms of airway obstruction that would prevent adequate exhalation and severe neurologic dysfunction. Speech therapy for children with tracheostomy tubes can improve communication skills.

Many children with tracheotomies are able to attend school (15). Children with a tracheostomy should be allowed to have as normal a childhood as possible. A developmentally normal child who has a tracheostomy tube should not be placed in a learning situation designed for children with learning disabilities, such as special education classes.

SWALLOWING

Although tracheostomy tubes do provide easy access for pulmonary toilet, they can impair swallowing function. The tracheostomy tube can partially tether the laryngotracheal complex and impair laryngeal elevation during swallowing (55,56). An open tracheostomy tube can also reduce cough effectiveness as a protective mechanism from aspiration (55). The tracheostomy tube may cause a relative esophageal obstruction, particularly tubes that have a cuff. Furthermore, there is a blunting of the laryngeal adductor reflex in patients with a tracheostomy, which can impair airway protection during swallowing (55). In addition, an open tracheostomy tube also prevents the buildup of subglottic pressure that normally occurs during the physiologic swallow. Gross and others have demonstrated that patients with tracheostomy tubes that utilize a speaking valve such as a Passy-Muir valve are able to generate higher subglottic pressure and may be less likely to exhibit aspiration or deep penetration (55,56). Children with tracheostomy tubes should have their swallowing assessed by a speech pathologist. For patients who can tolerate them, speaking valves may not only help with communication, but also with swallowing function.

SUMMARY

The indications for tracheotomy in children have changed over the past several decades. The most common indication for tracheotomy in the pediatric population is currently respiratory failure and prolonged intubation, followed by upper airway obstruction and the need for pulmonary toilet. In general, children with tracheotomies have become more complex, as there has been a decrease in the use of tracheotomy for acute airway management and infectious diseases and an increase in tracheotomy for chronic lung disease, congenital anomalies, and neuromuscular disorders. For similar reasons, there has been a trend toward lower rates of decannulation, as the underlying reason for the tracheotomy influences the chance for successful decannulation. Children can tolerate longer periods of endotracheal intubation than adults but there is no standard timing for tracheotomy after prolonged ventilation in children. Meticulous surgical technique and appropriate postoperative care can help prevent tracheotomy complications, both intraoperatively and in the postoperative period.

Patients with tracheostomy tubes are often complex and may benefit from management by a multidisciplinary

team, including otolaryngologists, pulmonologists, speech pathologists, and respiratory therapists. Proper education and home care can help keep children with tracheostomy tubes safe and avert complications after discharge from the hospital. Tracheostomy tubes are available in a broad range of sizes, materials, and types, and it is important to select the appropriate tracheostomy tube for each child. Children who have a tracheostomy can have both impaired communication skills and abnormal swallowing function as a result of their tracheostomy. It is important to involve speech pathologists in the care of children with tracheostomy tubes to help address both of these issues. When possible, children with tracheostomy tubes should be encouraged to attend school and participate in activities in order to have as normal a childhood as possible.

HIGHLIGHTS

- Children with tracheostomies utilize a great deal of health care resources.
- There is significant emotional, social, and economic burden on caregivers taking care of children with tracheostomy tubes.
- Although the terms "tracheotomy" and "tracheostomy" have been used interchangeably in the past, "tracheotomy" refers to the surgical procedure and the act of making an opening in the trachea and "tracheostomy" refers to the actual opening or hole in the trachea.
- The history of tracheotomy dates back several thousand years and its popularity as a procedure has been influenced by various diseases and their treatment developments (such as diphtheria, poliomyelitis, and epiglottitis).
- The most common indication for tracheotomy in the pediatric population currently is respiratory failure and ventilator dependence followed by upper airway obstruction and the need for pulmonary toilet.
- In general, infants and children can tolerate longer periods of endotracheal intubation than adults; however, there is no standard timing for tracheotomy after prolonged ventilation in children.
- There are both advantages and disadvantages of tracheotomy versus prolonged intubation and several factors must be considered in determining which is the most appropriate course for each child.
- There are a variety of techniques available to try to avoid tracheotomy in certain cases of upper airway obstruction.
- With few exceptions, tracheotomy in children should be performed in the operating room, under general anesthesia, with a secure airway.
- In infants and small children, a vertical incision in the trachea may be preferred. In older children and adolescents, either a vertical incision in the trachea or an inferiorly based flap can be employed.
- Stay sutures should be placed prior to making the incision to help retract the opening in the trachea intraoperatively and facilitate replacement of the tube in case of accidental decannulation in the early postoperative period.
- Pediatric tracheotomy can be performed with or without maturation of the stoma. Some surgeons feel that maturation of the stoma may decrease the morbidity of early accidental decannulation while leading to no increase in the rate of tracheocutaneous fistula formation.
- Children undergoing tracheotomy should be observed in the intensive care unit or in a special airway observation unit postoperatively for 5-to-7 days, until the first tracheostomy tube change, to help prevent morbidity from early postoperative complications, such as accidental decannulation and tracheostomy tube occlusion.
- Proper education and home care can help keep children with tracheostomy tubes safe and avert complications after discharge from the hospital.
- There are a variety of complications of pediatric tracheotomy that can be divided into intraoperative complications, early postoperative complications (less than 7 days), and late postoperative complications.
- There are several types of pediatric tracheostomy tubes available, in different widths, lengths, and materials; it is important to select the appropriate tracheostomy tube to meet each child's needs.
- The underlying reason for the tracheotomy influences the chance for successful decannulation; there must be adequate improvement in the problem that led to the tracheotomy prior to decannulation.
- Prior to decannulation, a complete airway endoscopy should be performed to evaluate for any tracheostomy-related problems and determine that there is no concerning areas of airway obstruction.
- Children who have a tracheostomy can have both impaired communication skills and abnormal swallowing function; it is important to involve speech pathologists in the care of children with tracheostomy tubes to help address both of these issues.

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93 Ingestion Injuries and Foreign Bodies in the Aerodigestive Tract

Warren K. Yunker *Ellen M. Friedman*

Children less than 5 years of age routinely explore their environment by placing objects in their mouths. As such, they are at a significantly increased risk for both the accidental ingestion of harmful substances and foreign bodies becoming lodged within the aerodigestive tract. These events are potentially life threatening. As such, it is necessary for all Otolaryngologists to be familiar with the diagnosis and management of these conditions.

INGESTION INJURIES

Otolaryngologists have always been at the forefront of the diagnosis and management of caustic ingestion. In 1927, Dr. Chevalier Jackson was successful in lobbying for the special labeling of caustic materials. His campaign, which resulted in the prominent printing of "Poison" on various products, heralded the beginning of an overall increase in public awareness regarding the handling and storage of hazardous substances. Subsequent legislations, such as regulating maximum concentrations of hazardous agents and requiring child-resistant containers, not only further increased public awareness, but also significantly decreased the impact of hazardous chemical ingestion.

Over the last 100 years, the mortality from esophageal burns has decreased, while the management of their sequelae has improved. In the early 1900s, chronic esophageal strictures alone accounted for a mortality rate of more than 40%, with management of the unvisualized esophagus centering primarily on supportive care (1). With the evolution of diagnostic imaging and aerodigestive tract endoscopy, practitioners are able to more accurately diagnose and treat esophageal injuries.

Mechanism of Injury

The most common agents responsible for caustic ingestion fall into one of three categories: (a) alkalis, (b) acids, and (c) bleaches. Each of these three categories causes a distinct histologic reaction when it comes into contact with the mucosa of the upper aerodigestive tract.

Alkali agents cause liquefaction necrosis, wherein the mucosa disintegrates, allowing the agent to penetrate into the surrounding tissues. This is reflected in the finding of more oral and upper esophageal injury. Alkalis are usually odorless and tasteless, which, in the case of accidental ingestion, may allow for the consumption of large volumes. Ingestion of compounds with a pH between 9 and 11, such as many household detergents, rarely cause serious injury. However, ingestion of even small quantities of an alkali with a pH above 11 may cause severe burns. Specific examples of strong alkali are sodium hydroxides (lye, drain and oven cleaner, and dishwashing detergents) and sodium phosphates (dishwashing detergents and laundry detergents). Granular forms of detergents and cleaners are associated with a higher rate of injury than liquid forms because of their adherence to the mucosa. Another commonly ingested alkaline agent is hair relaxer (2–5). These agents denature structural proteins, thereby straightening curly hair. Fortunately, the degree of mucosal injury following hair-relaxer ingestion has been found to be mild with little to no adverse clinical effect. Unfortunately, alkaline agents may not be perceived by families to represent a potential hazard because of their ubiquitous nature and lack of childproof packaging.

Acidic agents result in coagulation necrosis, which causes a coagulum to form on the mucosa, thereby limiting deeper absorption until the agent reaches the stomach. In addition, these agents tend to have a low viscosity, which facilitates rapid transit to the stomach. Gastric injury following ingestion may result in gastric outlet obstruction or perforation, which is a potentially life-threatening complication as there can be multiorgan injury and rapid clinical decompensation (6). Fortunately, the bitter taste of acidic compounds may help to lower the volumes of accidental

ingestion. Examples of strong acids that may be found around the home are sulfuric acid (drain cleaner), hydrochloric acid (toilet bowl cleaner), sodium bisulfate (toilet bowl cleaner), and hydrofluoric acid (metal cleaner) (6).

Bleaches, which are essentially of neutral pH, are considered esophageal irritants. Large series of patients with bleach ingestion have shown no significant morbidity or mortality. For this reason, extensive workup of patients following bleach ingestion is not warranted (7).

The amount and type of agent ingested, the presence of food in the stomach, gastrointestinal transit time, and the presence of gastroesophageal reflux will all contribute to the extent and severity of injury following caustic ingestion. Initial contact of the caustic agent with the mucosa produces immediate changes that then progress over the following 2 to 3 days. After this acute phase, a latent period begins, during which stricture formation may occur. This process may proceed as rapidly as within 1 month, or slowly evolve over years. Superficial mucosal burns tend to heal without sequelae. Burns that are deep enough to disrupt the submucosa and muscular layer tend to be complicated by a significant loss of mucosa. In these cases, an intense inflammatory response develops in the burned area, with accompanying esophageal dysmotility. In response to the injury, fibroblasts produce a matrix of newly formed collagen fibers, which begin to contract 3 to 4 weeks after the initial insult. Contraction enables adhesive bands to form, which can then lead to the development of both pseudodiverticula and endoluminal strictures. Stricture formation may evolve to include both the submucosal and muscular layers. In general, only circumferential esophageal injuries lead to strictures severe enough to cause clinically significant morbidity.

Clinical Presentation

Caustic ingestions occur most frequently in children younger than 6 years, with the majority of cases occurring in children between 12 and 48 months of age (6). In general, the child has to be ambulatory and have access to cabinets or other areas where cleaning products are stored. The most common symptoms following a caustic ingestion are dysphagia, drooling, food avoidance, and vomiting. More ominous signs and symptoms, such as severe retrosternal or thoracoabdominal pain or tachycardia with hypotension, may be associated with significant gastrointestinal injury. Dysphonia or stridor may herald progressive airway obstruction. The prognostic significance of the presenting clinical signs and symptoms following caustic ingestion has been widely addressed in the literature (8,9). Although minor symptoms do not rule out the presence of relevant injury, an increased number of symptoms do correlate with a greater likelihood of significant injury. A recent Italian study of 102 children reported that the presence of three or more symptoms was an important predictor of severe esophageal burns (10). In the same series, the absence of signs and symptoms was associated with a very low relative risk of severe lesions. However, it is important to note that in this series, 2 of the 70 patients (2.8%) without symptoms had severe injuries on endoscopy.

Even the presence or absence of oral injuries, such as lip or buccal mucosa burns, does not accurately predict the presence or absence of more distal involvement. In a recent survey by Dogan et al. of 473 pediatric caustic ingestions, 240/389 (61%) patients without oral cavity burns had esophageal lesions found at endoscopy (11). A study by Hawkins et al. showed that 70% of patients with oropharyngeal burns did not manifest associated esophageal injuries (12). Therefore, neither the presence nor absence of visible injury on physical exam should influence further investigation.

Diagnosis and Treatment

The initial management of ingestion injuries focuses on the ABCs of resuscitation: airway, breathing, and circulation. Most childhood ingestions occur while the child is unsupervised. As a result, it may not be possible to obtain an accurate history, or information regarding the quantity and type of agent. Whenever possible, the parent or guardian should be asked to bring the container of the suspect agent to the physician's office or emergency room. In addition, in the United States there is 24-hour-a-day Poison Center hotline (1-800-222-1222) that should be contacted for help in identifying the pH of the ingested substance as well as for specific treatment recommendations. Any patient with stridor or drooling should undergo emergent laryngoscopy.

Patients with severe laryngopharyngeal injuries, including but not limited to edema, burns, or necrosis, should undergo emergent tracheotomy, rather than endotracheal intubation, in order to maintain and protect the airway. At the present time, it is unclear if either acids or alkalis present a greater risk, either short-term or long-term, to the airway and larynx following ingestion. Similarly, there is little to no published literature focusing on treatment algorithms for ingestion-related laryngeal injuries. As such, at present, we believe that the safest and most prudent course of action is to leave the tracheotomy in place until such time that the laryngopharyngeal injuries have fully evolved and stabilized. Only then the airway can be completely and thoroughly evaluated and decannulation contemplated. Due to a lack of evidence, we do not advocate the routine use of either prophylactic antibiotics or systemic steroids in these cases.

Once the airway is secure, direct endoscopic visualization of the esophagus is the most reliable and accurate method of determining the extent of esophageal injury. However, the timing of endoscopy is crucial. If the examination is performed earlier than 12 hours following ingestion, adequate time may not have passed for the injury to fully manifest, and as a result the examination may underestimate

the extent of injury. Yet, examination during the period of structural weakness of the esophageal wall will increase the risk of iatrogenic injury during the examination. Therefore, endoscopy should be performed between 12 and 48 hours following ingestion to achieve the highest degree of patient safety while yielding the most information (8).

Esophageal injury is graded at the time of endoscopy to direct therapy, as the degree of injury is correlated with the likelihood of complications, morbidity, and mortality. Several esophageal injury-grading systems have been proposed in the literature (13–16). Unfortunately, there is no one system that has been widely adopted. Regardless of the grading system used, the goal is to risk-stratify patients and direct subsequent therapy. The classification system proposed by Estrera et al. segregates injuries into four grades (Table 93.1) (16). Grade 1 injuries consist of mucosal edema and erythema. Grade 2 injuries consist of mucosal erythema, sloughing, superficial ulceration, and noncircumferential exudates. Grade 3 injuries are associated with deep mucosal ulceration or circumferential sloughing. Grade 4 injuries are characterized by eschar, full thickness changes, or perforation. Another commonly employed esophageal injury grading system is the one proposed by Zargar et al. (14). However, for purposes of brevity and clarity it will not be reviewed here.

Traditionally, in these patients esophagoscopy was performed using a rigid, open tube endoscope, and the teaching was that the endoscope should not be advanced beyond areas of transmural or circumferential injury due to the heightened risk of iatrogenic perforation. In recent years, a considerable number of patients with ingestion injuries are now being initially assessed with flexible endoscopes. There is little to no published literature comparing the risk of rigid and flexible esophagoscopy in inducing esophageal perforations following caustic ingestion. As such, at present, we believe that the safest and most prudent course of action is still to avoid advancing the esophagoscope, be it flexible or rigid, beyond areas of transmural or circumferential injury.

If patient assessment occurs more than 72 hours postingestion, esophagoscopy should be avoided. In this situation, radiographic contrast studies should be used for initial assessment.

TABLE 93.1 ESOPHAGEAL INJURY GRADING SYSTEM

Grade	Description
1	Mucosal edema and erythema
2	Mucosal edema, sloughing, ulceration, and noncircumferential exudates
3	Deep mucosal ulceration or circumferential sloughing
4	Eschar, full thickness changes, and perforation

Patients with grade 1 injury on endoscopy can usually be managed with 24 to 48 hours of nothing by mouth (NPO) with IV hydration and subsequently restarted on a regular diet and discharged from hospital. Patients grade 2 and 3 injuries should be kept NPO with nutrition supplied either enterally (via a nasogastric [NG] tube that was inserted under direct vision in the operating room or using fluoroscopy) or parenterally. NPO status is usually maintained for 7 to 10 days, followed by a contrast swallow study prior to commencing PO feeds. In the event of a perforation, emergency surgery may be required. In rare instances, an emergency esophagectomy or gastrectomy may be needed.

The use of neutralizing agents is not recommended because they have not been shown to be efficacious and may lead to increased thermal injury. Gastric lavage and induced vomiting with emetics, such as ipecac, are also contraindicated as vomiting will cause repeated exposure of the agent to the esophageal mucosa and potentially increase the degree of injury. Similarly, blind passage of an NG tube should be avoided due to the potential for iatrogenic esophageal perforation.

Starting in the 1960s, patients with esophageal ingestion injuries were frequently treated with systemic steroids in an attempt to decrease or prevent stricture formation. However, patients with isolated grade 1 burns rarely, if ever, develop strictures (14). In comparison, most patients with grade 3 burns develop strictures regardless of therapy (17). Patients with severe burns are at high risk for other complications, such as infection and perforation, and the use of steroids may, in fact, make the esophageal tissue more prone to perforation. In addition, a recent systemic review on the use of steroids in second-degree caustic esophageal injuries did not support the use of steroids in these patients (18). As such, it is our recommendation that systemic steroid therapy no longer be routinely employed in the management of caustic esophageal injuries.

Similarly, the use of prophylactic antibiotics does not appear of benefit in managing caustic esophageal burns (19). It is our recommendation to withhold antibiotics unless the patient develops signs or symptoms of a secondary infection.

Postinjury gastroesophageal reflux may act synergistically to further damage the esophagus, thereby promoting granulation tissue and possibly increasing scar formation. As such, the routine use of antireflux therapy has been recommended to help prevent secondary reflux-associated esophageal injury (20–22).

Complications

Complications arising from caustic ingestion may arise either acutely following ingestion or arise over a period of months to years. Acute complications include, but are not limited to, esophageal perforation, tracheoesophageal fistulae, gastric perforation, mediastinitis, peritonitis, pneumonia, sepsis, and death. If the patient develops sepsis,

or other signs of esophageal perforation or mediastinitis, urgent exploration and drainage is indicated.

The most common long-term complication of caustic ingestion is stricture formation. Strictures may be mild, requiring only slight alterations of diet, or may be severely debilitating. In addition, they may form in multiple locations and can vary in length or severity (Fig. 93.1). Since the 1920s, esophageal dilatation has been used to improve the esophageal lumen. Balloon catheter dilation can be used safely and effectively in children in whom esophageal strictures develop after caustic injury, although it may be associated with higher complication and failure rates when compared to its use in children with congenital esophageal strictures (23). Long-term management of esophageal strictures secondary to caustic ingestion involves repeated serial dilations. Recently, the topical application of the fibroblast inhibitor mitomycin C has emerged as a successful adjunctive therapy in the management of esophageal strictures (24,25). Although the data regarding the use of mitomycin C is promising, the optimal frequency of application and long-term outcomes are, as of yet, unclear.

Other long-term sequelae of caustic ingestion include the development of a hiatal hernia, reflux esophagitis, peptic stricture, and esophageal cancer. The association with esophageal carcinoma is unusual in that an equal male-to-female ratio of occurrence exists and it presents in a younger age group than is usually affected. In a large series of esophageal carcinomas, a 1% to 4% incidence of caustic ingestion was found in the clinical histories (23). Although the exact degree of increased risk for carcinoma is unknown, it has been estimated to be 1,000-fold. Fortunately, because these carcinomas tend to arise within the scar tissue, their tendency for distant metastasis is lower, and potential cure with resection is higher. For this reason alone, long-term follow-up of patients with esophageal stricture is warranted, regardless of their symptoms. Any patient who develops dysphagia years after a caustic injury should undergo radiographic evaluation and endoscopy.



Figure 93.1 Barium swallow demonstrating esophageal stricture formation following caustic ingestion. This stricture developed within 1 month of lye ingestion.

AERODIGESTIVE FOREIGN BODIES

Life-threatening foreign-body incidents occur in two forms: (a) foreign-body aspiration, wherein the object is lodged within the laryngotracheobronchial axis; and (b) foreign-body ingestion, in which the object is lodged within the esophagus. Both forms can present with the acute onset of airway symptoms, and share significant associated morbidity and mortality.

Foreign-Body Aspiration

In the United States, over the last quarter century the incidence of foreign-body aspiration has remained relatively consistent, and this is unlikely to change as long as children continue to place objects in their mouth as a means of exploring their surroundings. Fortunately, there has been a dramatic decrease in childhood deaths from asphyxiation by ingested objects; although the associated morbidity in survivors or prolonged hypoxia remains considerable (26).

The most common age group affected is toddlers between 2 and 4 years of age. Case series from the last decade reflect that children younger than 5 years account for approximately 84% of cases, while children younger than 3 years account for 73% (27). The high incidence in this age group reflects the oral tendency of these children. In addition, children of this age often do not have full posterior dentition or mature neuromuscular mechanisms for appropriate swallowing and airway protection. Boys are affected more frequently than girls in a ratio of approximately 2:1. The acute episode is heralded by gagging and choking; however, because the toddlers may be out of the parents view during the acute episode, this period of acute distress may go unwitnessed, making it more difficult to be sure of the diagnosis. If the foreign body descends further down the tracheobronchial axis, active distress may subside. Overall, symptoms vary in severity depending on the size and composition of the foreign body, as well as its location, degree of airway obstructing, and the surrounding tissue reactions.

Since up to 50% of aspirations may go unwitnessed, the differential diagnosis for a patient with nonspecific pulmonary complaints, such as intermittent coughing or wheezing, must include airway foreign body. Without a high degree of suspicion for foreign-body aspiration, physicians may proceed with allergy testing, asthma therapy, or treatment of a presumed pulmonary infection, while

overlooking the possibility of foreign body. It is not uncommon for a patient to be treated for several months, including repeated hospitalizations, before proceeding to bronchoscopy for diagnosis and removal of the retained foreign body. Therefore, any patient with a prolonged nonspecific pulmonary complaint, even in the absence of an aspiration history, should raise the question of a retained foreign body. It is not surprising that in a review by Cohen et al. of 143 cases of foreign-body aspirations in children demonstrated that only 41% were seen by a physician 1 day following the aspiration event (28). Likewise, Reilly et al. noted that 15% of pediatric aerodigestive foreign-body injuries were incorrectly diagnosed at the time of initial physician assessment and that foreign-body aspirations were seven times more likely to have a delay in diagnosis than were foreign-bodies lodged in the esophagus (29).

The most commonly aspirated objects in the pediatric population are food products. Most are peanuts, but raisins, seeds, and other nuts are also commonly encountered. Beans and seeds absorb water over time and with subsequent swelling can rapidly result in a complete bronchial obstruction. Other organic foreign bodies can also illicit an inflammatory reaction in the surrounding tissue, and may result in arachnoid bronchitis. This is seen as a spidery pattern on chest radiograph, even if the foreign body itself is radiolucent. Inert foreign bodies are less inflammatory and may remain in one position for extended periods of time without causing increasing degrees of obstruction. The most common inert bronchial foreign bodies are pieces of toys. In the past, plastic toy pieces were often radiolucent and therefore undetectable on chest radiograph. Several companies, including 3M and Mattel, have sponsored research into, and the development of, radiopaque plastic. Unfortunately, however, this material is not routinely employed by all toy manufacturers. Another common childhood toy associated with aspiration is the latex balloon. The aspiration of latex balloon has a high morbidity and has prompted the move toward Mylar balloons for children.

McGuirt et al. found that the elderly also have a significant incidence of foreign-body aspiration, which is perhaps due to their lack of dentition (30). The foreign bodies most commonly aspirated by adults include food products and portions of dental prosthesis.

Workup

Chest auscultation most commonly will reveal decreased breath sounds on the obstructed side, in addition to wheezing and decreased localized air entry. The chest findings may be misinterpreted as asthma or pneumonia. As such, in the setting of prolonged, or unusual symptoms that are not responsive to routine management a bronchoscopy is indicated.

The most important noninvasive study to evaluate for foreign bodies is the chest radiograph (Fig. 93.2). However, Strome showed that up to 25% of plain chest radiographs of patients with known foreign bodies are within normal limits (31). This may be due to the fact that the hallmark radiographic signs, associated with foreign-body aspiration, mediastinal shift, and air trapping, are most readily demonstrated only on expiratory plain film or fluoroscopy, instead of a single inspiratory view (Fig. 93.2). In children unable to comply with inspiratory and expiratory radiographs, right and left lateral decubitus films may be helpful. In the unobstructed setting, the dependent lung will deflate on lateral decubitus positioning. If the dependent lung remains fully aerated, obstruction exists, suggesting the presence of an obstructing foreign body (Fig. 93.3).

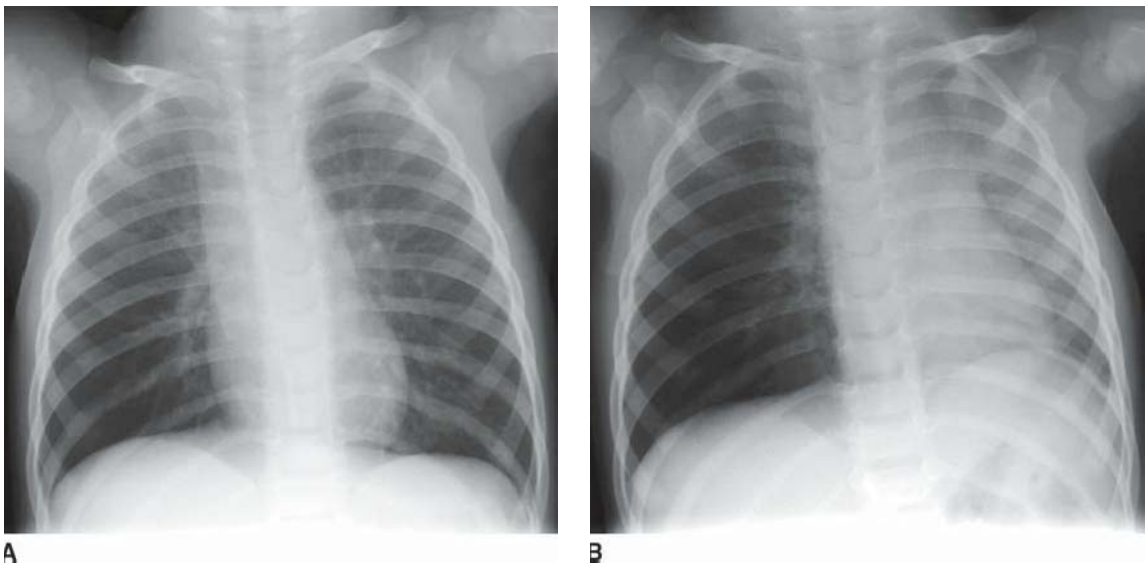


Figure 93.2 Inspiratory and expiratory radiographs of a child who aspirated a peanut into his right mainstem bronchus. **A:** Inspiratory view. **B:** Expiratory view. Note how the right lung remains inflated on expiration. *Image courtesy of Dr. C. Branstetter.*

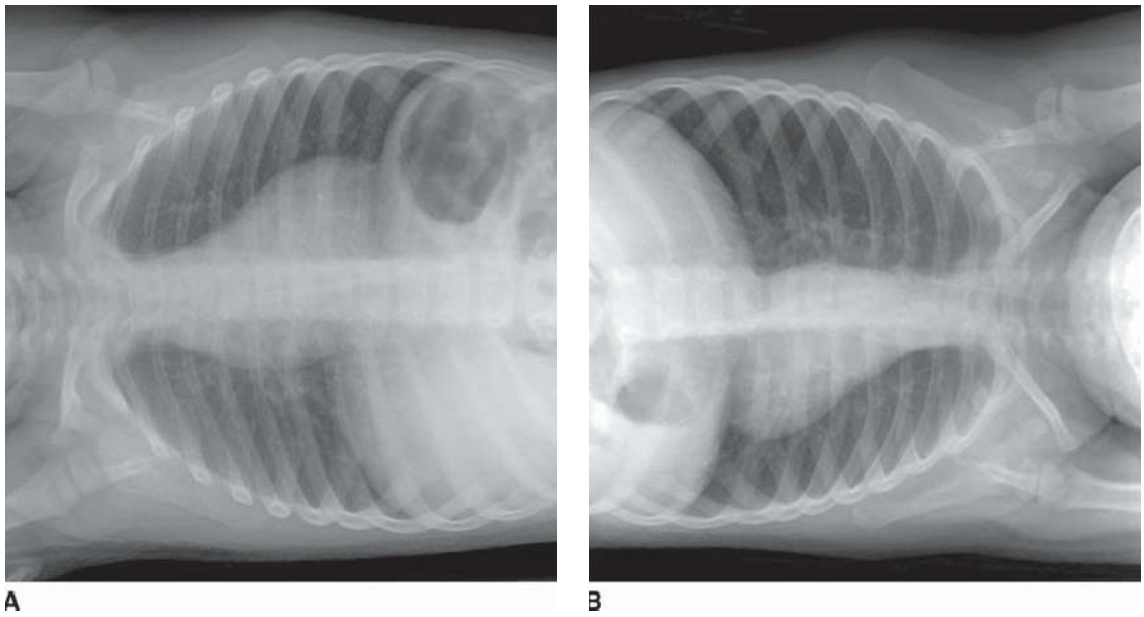


Figure 93.3 Right and left lateral decubitus radiographs of child who aspirated a pumpkin seed into her left mainstem bronchus. **A:** Right lateral decubitus position. **B:** Left lateral decubitus position. Note how the left lung does not change in volume despite changes in patient position. *Image courtesy of Dr. J. Crowe.*

However, even with the use of fluoroscopy, approximately 10% of patients with an aspirated foreign body will be missed. Therefore, even in the presence of a normal radiographic exam, a patient with a suspicious history and clinical course should be considered for endoscopic evaluation.

Making the accurate diagnosis of an airway foreign body is complicated due to the frequent combination of an unwitnessed aspiration episode, clinical picture consistent with several other common entities, and a lack of foolproof confirmatory diagnostic tests. For this reason two different outcomes may arise; in one group the diagnosis of an aspirated foreign body may be delayed and another group of patients may undergo negative bronchoscopy in search of a foreign body when the patient actually has pneumonia, asthma exacerbation, or bronchitis. CT scans and virtual bronchoscopy can significantly help in accurately diagnosing airway foreign bodies. Specifically, chest CT scans are able to reliably identify nonradioopaquic foreign bodies and can deliver a relatively low dose of radiation exposure. Hong et al. (32) showed that chest CT was highly sensitive in identifying a foreign body as well as surrounding secondary parenchymal changes and mediastinal diseases. Earlier consideration of the use of chest CT scans in the evaluation of these children could decrease the delay in reaching the correct diagnosis in positive children and could also decrease the number of negative bronchoscopies performed in children with other processes.

Treatment

An experienced team that includes an anesthesiologist experienced in spontaneous ventilation anesthesia, an endoscopist, and a nurse or surgical technician should perform bronchoscopy. To help ensure that a patient with a precarious airway does not deteriorate into a critical situation, excellent communication among all team members is absolutely essential. The endoscopist must remember to exclude the possibility of multiple foreign bodies, which can occur in up to 5% of cases (30). After the removal of a foreign body, the endoscope is reintroduced into the trachea to search for additional foreign bodies and to assess any trauma to the tracheal mucosa.

The actual removal of the foreign body presents its own set of challenges. Edema, granulation tissue, and bleeding frequently impede the visualization and extraction of the foreign body. In addition, postinstrumentation airway edema, which may further impair the patient's airway, is not uncommon. Fortunately, this usually responds to intravenous dexamethasone and nebulized epinephrine. Attempts to manipulate the location of the foreign body through patient positioning should be avoided, as it is rarely successful and may dislodge the object and allow it to progress to an even more distal location in the tracheobronchial tree.

Foreign-Body Ingestion

It is estimated that approximately 1,500 people die annually from complications related to foreign-body ingestion, with children being the most common victims (33). Presenting symptoms depend upon the size of the foreign body, its location, and duration of impaction. In children, esophageal foreign bodies frequently present with a mild to moderate degree of respiratory distress (33,34). This is a result of the extreme compliance of the party wall between the

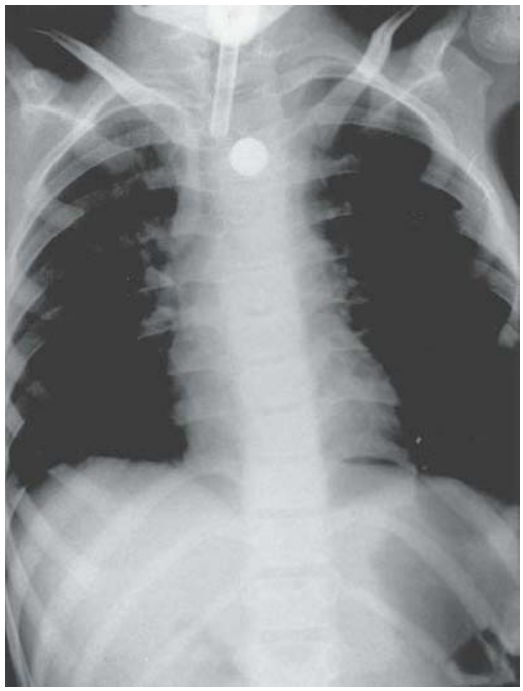


Figure 93.4 Chest radiograph of a child with a coin lodged in the esophagus. In this case, an emergency tracheotomy had been performed to relieve the severe airway distress the unsuspected foreign body was causing.

esophagus and trachea. The mass effect of an impact object in the esophagus, therefore, can have significant impact on the airway. Figure 93.4 is a radiograph of a patient who presented to the emergency department in severe respiratory distress and underwent emergency tracheotomy. On the postoperative chest radiograph, the source of the airway obstruction was found to be an esophageal foreign body. It is important to recognize that dysphagia and drooling may actually present as late, rather than as the initial symptoms of an esophageal foreign body.

In the Unites States and Europe, coins are the most commonly ingested pediatric foreign body. Other commonly ingested items include toys, toy parts, sharp objects, disc batteries, fish bones, and food. The most commonly ingested foreign body resulting in fatality is a segment of hotdog. Coins that lodge in the esophagus typically settle in one of three locations. Approximately 60% to 70% become lodged at the upper esophageal sphincter or cricopharyngeus muscle, 10% to 20% impact in the mid-esophagus at the level of the aortic notch, and 20% are held up by the lower esophageal sphincter (Fig. 93.5) (34). If a foreign body becomes lodged elsewhere in the esophagus, the possibility of an underlying abnormality, such as a congenital esophageal stricture, should be considered.

Whenever possible, evaluation of patients with a suspected esophageal foreign body should include both anteroposterior and lateral x-rays to verify that the object is indeed in the esophagus rather than in the airway (Fig. 93.5). Endoscopy under general anesthesia with a protected airway is the mainstay of esophageal foreign body management. However, esophagoscopy is not without risks, including pharyngeal bleeding, accidental extubation, hypoxia, esophageal perforation, and mediastinitis. Emergent removal of the foreign body should be performed in symptomatic patients unable to swallow their own secretions or who are experiencing acute respiratory symptoms. However, in these situations

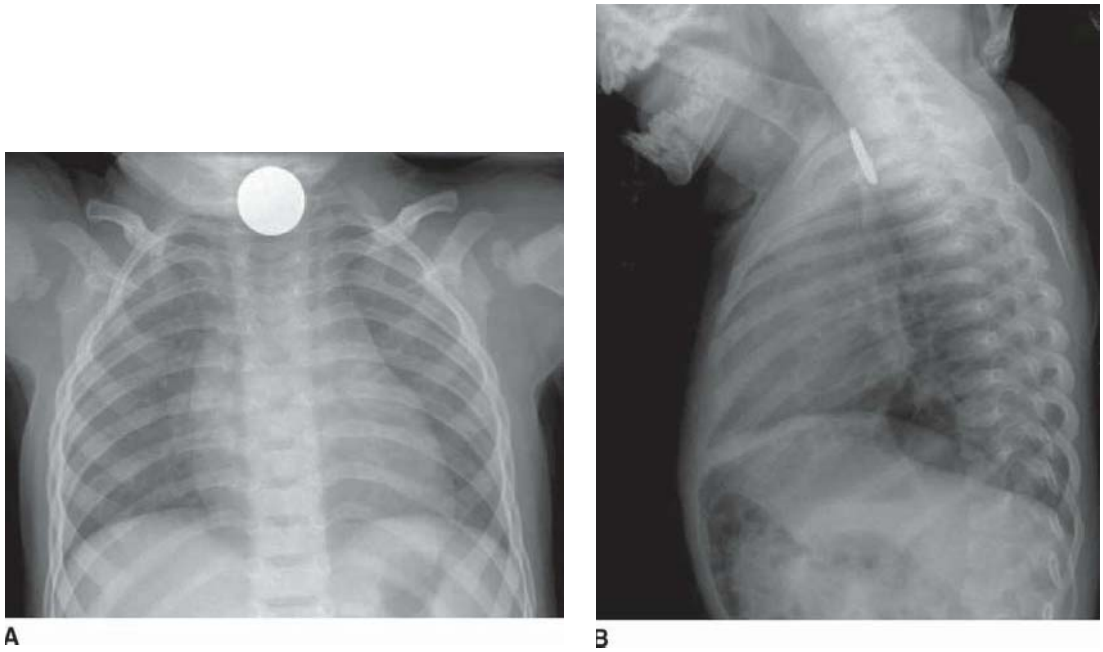


Figure 93.5 Radiographs of two different children with foreign bodies lodged at the level of the upper esophageal sphincter (UES). Anteroposterior (AP) **(A)** and lateral **(B)** view of coin lodged at the UES. AP *(Continued)*

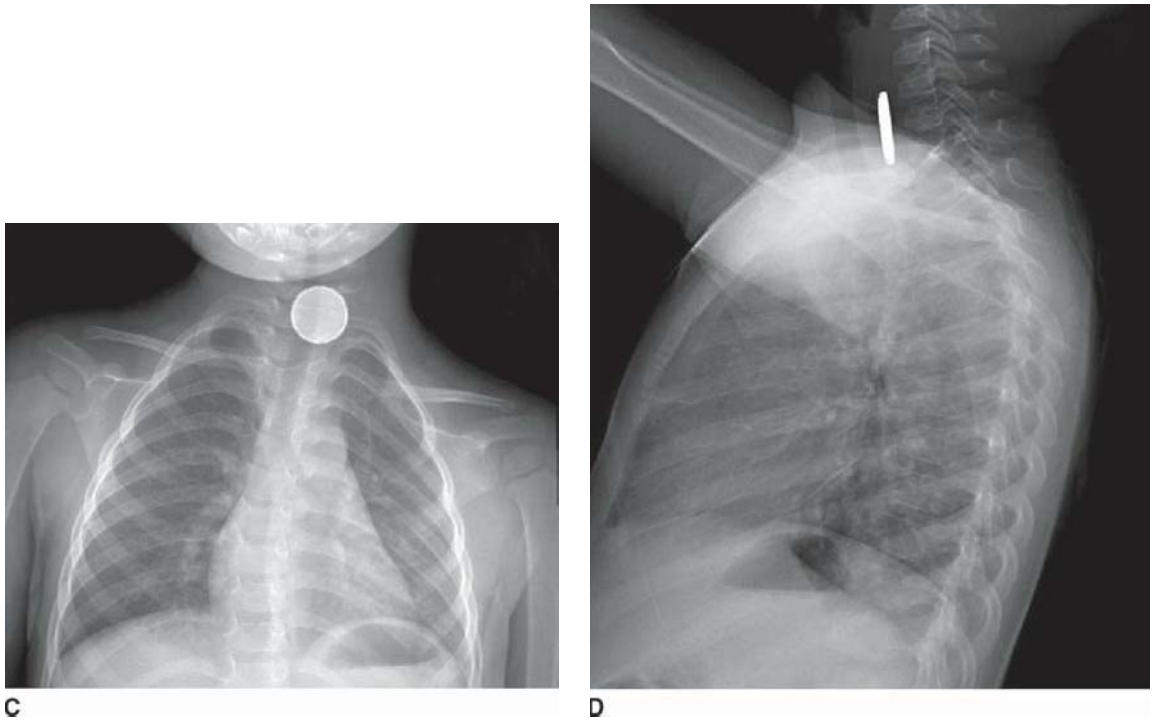


Figure 93.5 *(Continued)* **(C)** and lateral **(D)** views of a disc battery lodged at the UES. Note the "double-ring" that is characteristic of a disc battery in **C**. Also note the step that can be seen along the edge of the disc battery in **D** as compared to the profile of the coin in **B**.

the risk of aspiration of gastric contents is higher and appropriate precautions should be taken. In patients who are asymptomatic, endoscopy can be postponed for 12 to 24 hours. There are two important exceptions to this principle. The first is if the foreign object appears to be a disc battery. The second is if the foreign object is sharp and/or has the potential to perforate the esophagus, such as an open safety pin. In these situations, emergency endoscopy is required. If there is a significant delay between the time of diagnosis and endoscopy, a repeat radiograph should be obtained immediately prior to the procedure to verify that the object has not passed into the stomach. Following extraction of the foreign body, the esophagoscope should be reinserted to rule out the potential of a second foreign body, as well as to evaluate and document any mucosal injury (35). In instances where the object has passed into the stomach, the patient can usually be managed expectantly.

Although it is technically possible to remove an esophageal foreign body under fluoroscopy in the radiology suite with the use of a balloon catheter, it is potentially dangerous. Although dislodging a foreign body from the esophagus into the larynx, resulting in airway obstruction, is uncommon, it does not seem to be a justifiable risk in the presence of a safer alternative.

Disc Battery Ingestion

The disc battery is the most potentially harmful of the esophageal foreign bodies, and as such deserves special comment. These batteries are becoming increasingly common in children's toys, and, not surprisingly, so is their ingestion. In 1998, the American Association of Poison Control Centers reported a total of 2,063 disc battery ingestion, while in 2007, 10,213 cases of battery exposures were documented across the United States in 2007 (36).

A classic feature of disc battery ingestion is the "double-ring" seen on chest x-ray (Fig. 93.5). However, the absence of this finding does not exclude the possibility of a disc battery and the clinician must maintain a high index of suspicion. The damage caused by these batteries is a combination of leaking alkaline contents, low-voltage electrical discharge and pressure necrosis, and substantial injury to the esophageal mucosa may occur as early as 1 hour after ingestion (37,38). Given the rapidity of onset and potential for extensive injury, a disc battery lodged in the esophagus mandates emergency esophagoscopy. When substantial esophageal erosion is detected, bronchoscopy to evaluate the tracheal wall for a fistula, as well as a postoperative chest x-ray and esophagogram are recommended to evaluate for esophageal perforation (39,40). Management of foreign body-induced esophageal injuries, be it disc battery or other foreign body, is similar to that of caustic ingestion.

In contrast, batteries that have traversed the esophagus and are situated in the stomach require a less urgent approach as they are likely to uneventfully pass through the remainder of the gastrointestinal tract, typically within 48 hours (34).

OTHER CONSIDERATIONS

An interesting finding concerning caustic ingestions and foreign-body aspirations is the possibility of child abuse (41–43). Negligence, or an act of omission, may result in an accident, but it may also be the sign of a troubled family and a child at risk. Intentional abuse, or an act of commission, is much more worrisome. There have been an increasing number of cases demonstrating child abuse or Munchausen syndrome by proxy with foreign-body or caustic ingestions. Some cases are obvious, others are more difficult to recognize. Increased vigilance will aid and protect children at risk. Most states mandate the reporting of suspicious episodes.

HIGHLIGHTS

- Caustic ingestion can be classified as alkaline, acidic, or neutral.
- Alkaline substances cause liquefaction necrosis, whereas acidic substances cause coagulation necrosis. Neutral agents, such as bleach, are mild esophageal irritants.
- The initial management of a caustic ingestion focuses on the ABCs of resuscitation: airway, breathing, and circulation. Poison control should be contacted at time of presentation.
- Esophagoscopy should be performed 12 to 48 hours following caustic ingestion for both diagnostic and prognostic purposes.
- Current literature does not support the use of either prophylactic antibiotics or systemic steroids in the management of caustic esophageal injuries.
- An esophageal foreign body may present with respiratory distress rather than dysphagia or drooling.
- An airway foreign body should be suspected in any patient who presents with prolonged or unusual pulmonary symptoms.

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Recurrent Respiratory Papillomatosis

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Craig S. Derkay *Cristina M. Baldassari*

In discussing recurrent respiratory papillomatosis (RRP) of the aerodigestive tract, it is helpful to review our current knowledge regarding the etiology of the disease, including some basic information on human papillomavirus (HPV), the histopathology of respiratory papillomas, as well as the epidemiology of the disease and risk factors for its transmission. This chapter also addresses the common clinical features seen in children with RRP, including the pertinent findings on history, physical examination, endoscopy, and imaging studies. Surgical treatments, including the use of laser and nonlaser technologies, also are addressed. Additionally, potential nonsurgical adjuvant therapies and their current indications for use are discussed. Complications of the disease itself as well as of its treatment are covered. A staging system for following patients with RRP is presented along with other new horizons for research and treatment of this frustrating entity.

RRP is a disease of viral etiology, caused by HPV types 6 and 11, associated with exophytic lesions of the airway. Although it is a benign disease, RRP has potentially morbid consequences due to its involvement of the airway, propensity to recur, and to the risk of malignant conversion.

RRP is both the most common benign neoplasm of the larynx among children and the second most frequent cause of childhood hoarseness (1). The disease is often difficult to treat because of its tendency to recur and spread throughout the respiratory tract. Although it most often involves the larynx, RRP may involve sites anywhere in the entire aerodigestive tract. The course of the disease is variable, with some patients experiencing spontaneous remission and others suffering from aggressive papillomatous growth, requiring multiple surgical procedures over many years.

In most pediatric series, RRP is diagnosed between 2 and 4 years of age with a delay in diagnosis from the time of onset of symptoms averaging about 1 year (2,3). Seventy-five percent of the children have been diagnosed before their fifth birthday (4). It is estimated that 1,500 to 2,500 new cases of childhood-onset RRP occur in the United States each year. The incidence among children in the United States is estimated at 4.3 per 100,000 children, translating into more than 15,000 surgical procedures at a total cost of more than $100 million per year (5). Anecdotal observations suggest that most patients are first born; have young, primigravid mothers; and come from families of low socioeconomic status (5–7). The clinical course is unpredictable, with malignant transformation possible in patients with long-standing aggressive disease.

RRP may have its clinical onset during either childhood (juvenile onset recurrent respiratory papillomatosis, JORRP) or adulthood (adult onset recurrent respiratory papillomatosis, AORRP). Of these two distinct forms, JORRP is generally more aggressive. The aggressive form of RRP, although most prevalent in children, can also occur in adults. Children whose RRP was diagnosed at younger ages (less than 3 years) have been found to be 3.6 times more likely to have more than four surgeries per year and almost 2 times more likely to have two or more anatomic sites affected than were children whose RRP was diagnosed at later ages (greater than 3 years) (8,9).

ETIOLOGY

Human Papillomavirus

HPV is a small DNA-containing, nonenveloped icosahedral (20-sided) capsid virus with a double-stranded circular deoxyribonucleic acid 7,900 base pairs long. Until the 1990s, HPV had been suspected but not confirmed as the causative agent in RRP. This uncertainty developed from an inability to culture the virus *in vitro*, and from the failure to demonstrate viral particles consistently in papilloma lesions using electron microscopy or HPV antibodies. Today, with the use of viral probes, HPV DNA has been identified in virtually every papilloma lesion studied. The

most common types identified in the airway are HPV 6 and HPV 11, the same types responsible for genital warts. Specific viral subtypes may be correlated with disease severity and clinical course. Children infected with HPV 11 appear to have a more obstructive airway course early in the disease and a greater need for tracheotomy (9,10).

HPVs are grouped on the basis of genetic homology, with viruses that exhibit less than 90% identity in specific regions of the viral genome being defined numerically as separate types. On this basis, nearly 100 different HPV types have been identified. These groupings correlate with tissue preference as well as similarities in pathophysiology. Groups associated with mucosal lesions in the aerodigestive and genital tracts include HPV types 6 and 11 with a low malignant potential; HPV 16 and 18 with a much higher malignant potential; and HPV 31 and 33 with a malignant potential that lies somewhere in between. At least 90 different types of HPV have been identified and are designated by numbers (i.e., HPV 6). The closer the numbers, the more similar the viral subtypes are in their clinical manifestations.

The induction of cellular proliferation is a fundamental property of HPV though its mechanism of action remains unclear. The present understanding is that HPV establishes itself in the basal layer, where viral DNA enters the cell and is transcribed into RNA which is then translated into viral proteins. The genome consists of three regions: an upstream regulatory region and the two regions named according to the phase of infection in which they are expressed, the early (E) and late (L) regions. The E region genes are involved in potent oncogenes that are responsible for the replication of the viral genome, interaction with host cell intermediate filaments, and transforming activities. The L region genes encode the viral structural proteins (11). Several factors are involved in the regulation of cell proliferation.

It is likely that the host immune system plays an important role in the pathogenesis of HPV-induced lesions. Both humoral and cellular immune responses may be compromised in children with RRP and a patient's immunocompetence may also influence the clinical course of disease. The role of cytokines such as interleukin-2, interleukin-4, and interleukin-10 and expression of the major histocompatibility complex antigens in the malfunction of the cell-mediated immune response in children with RRP have been demonstrated (12). Papillomas with a reduced expression of these antigens may evade immune surveillance and allow the disease to progress more rapidly.

HPV is thought to infect stem cells within the basal layer of epithelium (13–15). Following infection of the stem cells, the viral DNA can either be actively expressed, or it can exist as a latent infection in epithelium that remains clinically and histologically normal. During latency, there is very little viral RNA present. In fact, HPV DNA can be detected in normal-appearing mucosa in RRP patients who have been in remission for years, explaining why reactivation and clinical recurrence can occur following many years of remission (16–18). Thus, reactivation of viral expression can occur any time following establishment of a latent infection. Adult-onset respiratory papillomas could reflect either activation of virus present since birth or an infection acquired in adolescence or adult life. Gene products of early genes E6 and E7, and possibly E5, are required for papilloma induction, but the details of the mechanism of HPV activation are unknown. In order to "cure" RRP, it is necessary to modulate the host response to the virus and, ideally, eliminate the latent infection.

The universality of HPV in the lower genital tract rivals that of any other sexually transmitted disease in humans. It is estimated that at least 1 million cases of genital papillomas occur per year in the United States, affecting about 1% of the population (19). These most often manifest as condylomata acuminata involving the cervix, vulva, or other anogenital sites in women or the penis of male sexual partners of affected women. In addition, it is estimated that colposcopic (subclinical) changes affect nearly 5 million US women. An additional 14 million women, or about 10% of the female population of child-bearing age, are DNA positive but have no visible lesions while more than 80 million women, or 60% of the at-risk population, are HPV antibody positive but DNA negative. The incidence of HPV infections in sexually active young college women is high, with a cumulative incidence of 43% over a 36-month period in a recent study (20). Clinically apparent HPV infection has been noted in 1.5% to 5% of pregnant women in the United States (21). As in RRP, HPV 6 and 11 are the most common subtypes identified in cervical condylomata.

Recurrent Respiratory Papillomatosis

Histologically, RRP appears as pedunculated masses with fingerlike projections of nonkeratinized stratified squamous epithelium supported by a core of highly vascularized connective tissue stroma (Fig. 94.1). The basal layer may be either normal or hyperplastic, and mitotic figures are generally limited to this layer. Cellular differentiation appears to be abnormal, with altered expression and production of keratins. The degree of atypia may be a sign of premalignant tendency.

RRP lesions occur most often at anatomic sites in which ciliated and squamous epithelium are juxtaposed (22). The most common sites for RRP are the limen vestibuli, the nasopharyngeal surface of the soft palate, the midline of the laryngeal surface of the epiglottis, the upper and lower margins of the ventricle, the undersurface of the vocal folds, the carina, and at bronchial spurs (6). In tracheotomized patients, RRP is often encountered at the stoma and in the mid-thoracic trachea, areas that might be considered iatrogenic squamociliary junctions.

Papilloma lesions may be sessile or pedunculated and often occur in irregular exophytic clusters (Fig. 94.2). Typically, the lesions are pinkish to white in coloration. Iatrogenic implantation of papilloma may be preventable

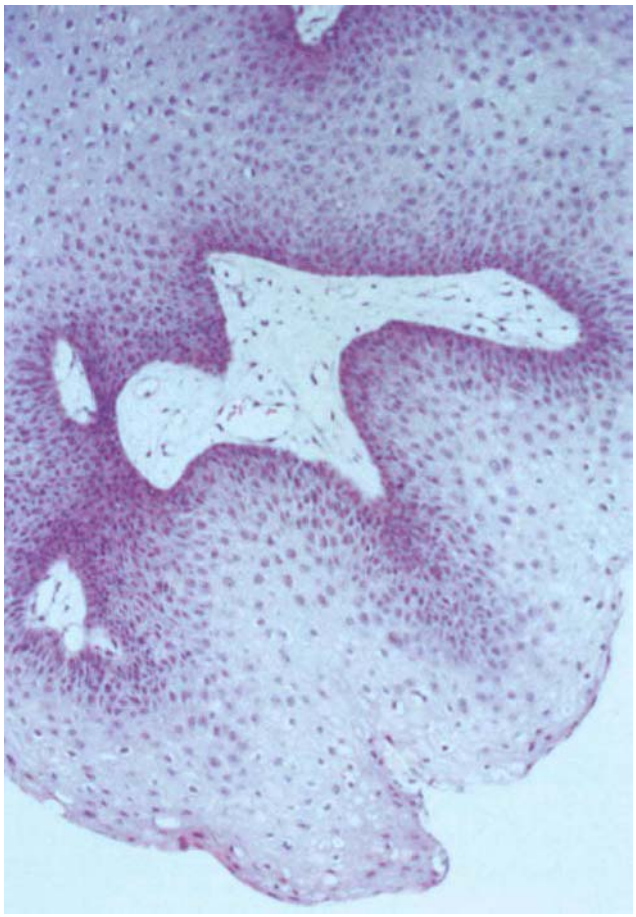


Figure 94.1 Histologic section of papilloma, demonstrating fingerlike projection of nonkeratinized stratified squamous epithelium and vascularized connective tissue stroma.

by avoiding injury to nondiseased squamous or ciliated epithelium adjacent to areas of frank papilloma. Ciliated epithelium undergoes squamous metaplasia when exposed to repeated trauma and is replaced with nonciliated epithelium that creates an iatrogenic squamociliary junction.

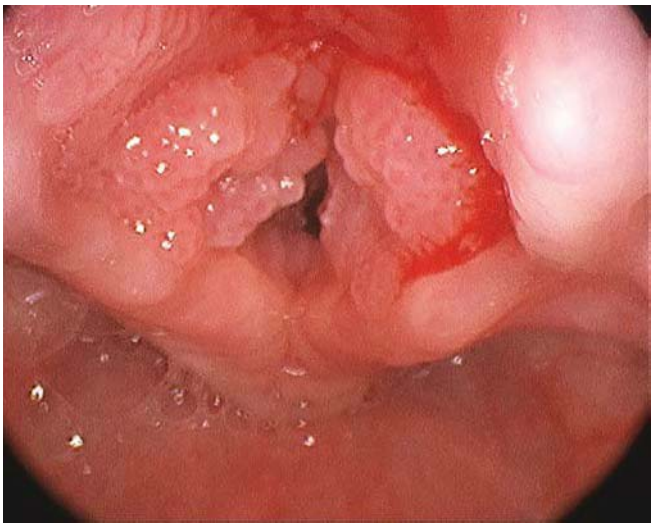


Figure 94.2 Papilloma lesions involving the laryngeal inlet.

This may also explain the observation that RRP flourishes in the presence of uncontrolled gastroesophageal reflux with an increased incidence of laryngeal scarring (23).

EPIDEMIOLOGY

RRP may affect people of any age, with the youngest patient identified at 1 day of age and the oldest at 84 years (5). JORRP (arbitrarily defined as patients diagnosed at less than 12 years of age) is most often diagnosed between 2 and 4 years of age. The distribution of RRP among boys and girls is approximately equal, and there are no apparent differences in surgical frequencies by gender or ethnicity (8). AORRP peaks between the ages of 20 and 40 years and has a slight male predilection. The mode of transmission for AORRP is unknown. While it is postulated that transmission is from either latent virus present from birth or adult exposure through sexual contact, these theories have yet to be fully substantiated.

Numerous studies have been performed to elucidate the true incidence of RRP. The national registry of children with RRP, composed of the clinical practices at 22 pediatric otolaryngology sites (arguably a skewed population of more severely affected children), calculates a mean number of procedures at 19.7 per child, with an average of 4.4 procedures per year (8). Children diagnosed before 3 years of age were found to be 3.6 times more likely to require more than four surgical procedures per year and 2.1 times more likely to have two or more anatomic sites involved than those diagnosed after their fourth birthday (8). Children with disease progression are diagnosed at younger ages than those who remain stable or become disease-free (24). Younger children are more likely to have persistent disease and more often experience an increased number of surgeries in the first year following diagnosis (25).

In a survey of practicing otolaryngologists in the United States, half of the adults with RRP had required fewer than five procedures over their lifetime compared with less than 25% of the children. Approximately equal percentages of children and adults (17% children vs. 19% adults) had very aggressive RRP (defined as requiring more than 40 lifetime operations), although adults had more years to accumulate these operations (5). The true incidence and prevalence of RRP are uncertain. In a Danish subpopulation incorporating 50% of the population of that country, the incidence of laryngeal papillomatosis was 3.84 cases per 100,000 (26). The rate among children was 3.62 per 100,000, whereas adult-onset cases occurred at a rate of 3.94 per 100,000. These figures are comparable with those found in a US survey, which estimated an incidence in the pediatric population of 4.3 cases of RRP per 100,000 children and 1.8 cases of RRP per 100,000 adults (5). Armstrong et al. (27) estimated that there are 80 to 1,500 incident cases of JORRP annually in the United States and 700 to 3,000 prevalent cases of JORRP based upon a 1999 epidemiologic analysis of two US cities.

Recently, Campisi et al. created a national database incorporating all children (less than 14 years old) with RRP in Canada treated by Pediatric Otolaryngologists. This study found the national incidence of JORRP from 1994 to 2007 to be 0.24 per 100,000 with a prevalence of 1.11 per 100,000 (28). These estimates are significantly lower than several previous studies, but similar to a population-based study of RRP patients in Seattle and Atlanta (27). The authors attribute this discrepancy to either over-estimation by other studies based on extrapolated data or higher incidences in other countries.

Interestingly, a recent pilot study of a large database of publicly and privately insured patients in the United States consistently showed that RRP incidence was higher in publicly insured patients compared to those with private insurance (3.21 vs. 1.98 per 100,000, respectively) (29). An explanation for this finding is that patients with public insurance often come from a lower socioeconomic level than those with private insurance. A cross-sectional study of all active JORRP patients from the Hospital for Sick Children in Toronto showed that nearly half of these patients were below the poverty line in Canada (30). This study, however, showed no correlation between socioeconomic status and severity of disease.

RRP places a large economic burden on individual patients and their families as well as our society as a whole. On average, a child presenting to an academic center in the United States with RRP requires 19.7 procedures over their lifetime, with a mean frequency of procedures being 4.4 per year (5). Approximately equal numbers of adults and children with RRP (17% vs. 19%, respectively) will have aggressive disease requiring more than 40 lifetime procedures. The average lifetime cost to treat one patient with RRP has been estimated at $60,000 to $470,000 in the United States (29).

In addition to the economic burden, RRP significantly impacts quality of life. Lindman et al. (31) utilized a validated quality of life instrument to assess patients with JORRP. Compared with healthy controls, children with RRP self-reported significantly poorer quality of life in the areas of psychosocial health, social functioning, and school functioning. Children with RRP had quality of scores similar to children with other chronic medical conditions.

Transmission

The precise mode of HPV transmission remains unclear. Several studies have convincingly linked childhood-onset RRP to mothers with genital HPV infections, whereas circumstantial evidence suggests that adult disease may be associated with oral–genital contact. Retrospective and recent prospective studies have confirmed that HPV may be passed by vertical transmission from mother to child (32–34). Silverberg showed that children born to mothers with active condylomata had a 231-fold increased risk of developing RRP when compared to children born to disease-free mothers (35). In addition, they showed that children born to women with active condylomata had a twofold higher risk of developing RRP if labor lasted more than 10 hours. Kashima found that childhood-onset RRP patients were more likely to be first born and vaginally delivered than were control patients of similar age (36). The authors hypothesized that primagravid mothers are more likely to have a long second stage of labor and that the prolonged exposure to HPV in the birth canal leads to a higher risk of infection in the first born child. They also suggested that newly acquired genital HPV lesions are more likely to shed virus than long-standing lesions. This would explain the higher incidence of RRP observed among the offspring of young mothers of low socioeconomic status—the same group that is more likely to acquire sexually transmitted infections such as HPV.

Hallden showed that 54% of JORPP patients were born to mothers with a history of vulvar condylomata at the time of delivery (37). Despite this apparent close association, few children exposed to genital warts at birth actually develop clinical disease (38). It is not well understood why RRP develops in so few children whose mothers have condylomata. Although HPV could be recovered from the nasopharyngeal secretions of 30% of infants exposed to HPV in the birth canal the number of infants expected to manifest evidence of RRP is only a small fraction of this (39). Based on these data, it appears that secondary factors including patient immunity; timing, length, and volume of virus exposure; and local traumas (intubation, extraesophageal reflux) must be important in the development of RRP. Reports of neonatal papillomatosis suggest that, in at least some cases, development of the disease may occur *in utero*. Because caesarean section does not seem to prevent the development of RRP in all cases, a better understanding of the risk factors associated with RRP is needed before the efficacy of caesarean delivery in preventing papilloma disease can be fully assessed (40).

A case-control study found that patients with AORRP had more lifetime sexual partners and a higher frequency of oral sex than matched controls (36). This data would suggest patients with AORRP are exposed later in life than patients with JORRP. However, HPV has the disturbing capability to form latent infections in the basal cell layer of otherwise healthy appearing mucosa (16–18). It has been suggested that AORRP may represent a reactivation of HPV infection acquired during birth instead of a *de novo* exposure during adulthood.

Viral DNA has been detected in areas of "normal appearing mucosa" adjacent to papilloma lesions, suggesting a possible explanation for the recurrence of the disease following thorough surgical removal (18,38). Brandsma reported finding HPV DNA in 4% of random, clinically normal biopsies of the airway (41). AORRP, thus, could reflect either activation of virus present since birth or an infection acquired in adolescence or adult life. Nosocomial acquisition of virus by patients in the operating room



Figure 94.3 Papilloma lesions involving the trachea in a child with extralaryngeal disease.

(OR) also may result theoretically from improper equipment sterilization or room preparation. However, current Occupational Safety and Health Administration recommendations have virtually eliminated this risk.

Although any site along the upper aerodigestive tract can be affected, HPV shows a predilection to infect sites where ciliated columnar and squamous epithelia are juxtaposed (8). This explains the frequent involvement of the false vocal folds, the upper and lower margins of the ventricle, and the undersurface of the true vocal folds. In tracheotomized patients, papillomas often are encountered at the stoma and in the mid-thoracic trachea, which are areas where iatrogenic trauma to ciliated epithelium often induces squamous metaplasia (see Fig. 94.3). It is postulated that an eddying flow of the mucous blanket at squamociliary junctions may concentrate infectious viral particles at these sites. Children with bronchopulmonary dysplasia who require prolonged endotracheal intubation also may be at increased risk for development of RRP. An endotracheal tube may play the same role in the mechanical dissemination or implantation of papilloma virus as a tracheotomy in this setting, through the interruption of the continuous respiratory mucosal surface. Gastroesophageal reflux disease (GERD) also has been identified as a potential risk factor for disease persistence, although additional research is necessary to verify this anecdotal observation.

CLINICAL FEATURES

Because the most common symptoms of RRP are related to airway obstruction, it is not uncommon for children to be misdiagnosed initially as having asthma, croup, or chronic bronchitis. The hallmark of RRP in children is the triad of relentlessly progressive hoarseness, stridor, and respiratory distress. Hoarseness in children tends to be overlooked or at least accepted until it reaches a certain level of severity. However, any infant or young child with symptoms of voice change, along with obstructive airway symptoms or recurrent croup, warrants laryngoscopy to rule out neoplasia, with RRP being the most likely lesion.

Children with RRP most often present with some degree of dysphonia. Stridor is often the second clinical symptom to develop, beginning as an inspiratory noise and becoming biphasic with progression of the disease. Less commonly, chronic cough, recurrent pneumonia, failure to thrive, dyspnea, dysphagia, and acute life-threatening events may be the presenting symptoms. The duration of symptoms prior to diagnosis varies with a typical period of about 1 year from onset of symptoms till a diagnosis of RRP is made. Not uncommonly, a mistaken diagnosis of asthma, croup, allergies, vocal nodules, or bronchitis is entertained before arriving at the definitive diagnosis of RRP.

Because of the rarity of RRP and the slowly progressive nature of the disease, some cases may go unrecognized until respiratory distress results from papillomas obstructing the airway. The result is a relatively high need for tracheotomy to be performed in these children. Shapiro et al. (42) noted that RRP tracheotomy patients presented at a younger age and with more widespread disease, often involving the distal airway prior to tracheotomy. In the Centers for Disease Control and Prevention (CDC) registry, children with tracheotomy were initially diagnosed with RRP at a younger age (2.7 years) than those without a tracheotomy (3.9 years) (7). Both prolonged tracheotomy and the presence of subglottic papilloma at the time of tracheotomy have been associated with an increased risk of distal tracheal spread.

Extralaryngeal spread of respiratory papillomas has been identified in 13% to 30% of children and in 16% of adults with RRP (5,43). The most common sites of extralaryngeal spread were, in order of frequency, the oral cavity, trachea, and bronchi (5). In a recent review of the experience at three academic medical centers, 12% of the children with RRP had distal tracheal spread of their disease and 7% had pulmonary dissemination. One common thread in the children with distal spread was the use of jet ventilation anesthesia techniques in the surgical management of their disease (44). Pulmonary RRP begins as asymptomatic, peripheral nodules and progresses to enlarging lesions with central cavitation and necrosis. Pulmonary RRP is insidious and progresses over years. It can eventually manifest as respiratory failure due to destruction of the lung parenchyma and malignant transformation.

The course of RRP is variable with some patients experiencing spontaneous resolution. However, RRP is frequently characterized by relentless recurrence and most patients necessitate frequent surgical debridements. Certain patient factors such as younger age at diagnosis and HPV 11 subtype are linked to aggressive progression of RRP. A possible

link between RRP and immunodeficiency states also has been observed. Both children and adults with acquired immunodeficiency syndrome, congenital immunodeficiencies, or those on immune suppression after organ transplantation have been identified with RRP (7). Respondents in a recent American Society of Pediatric Otolaryngology (ASPO) survey related at least one death from RRP in their clinical practices (43). When death occurs, it is usually associated with a complication of frequent surgical procedures or caused by respiratory failure due to distal disease progression.

Dysplastic and malignant transformation have been reported in RRP. In a recent study by Sajan et al. (45), RRP biopsy specimens of 20 patients with JORRP were examined. Only 1 of 123 specimens (less than 1%) had evidence of dysplasia. Dysplasia in AORRP appears to be more prevalent with 22% to 55% of patients demonstrating evidence of dysplasia on histopathology (46,47). An RRP task force survey reported malignant transformation of RRP into squamous cell carcinoma (SCC) in 26 cases (43). The mechanism of RRP transformation remains poorly understood. In a recent study by Lee in which six AORRP patients developed laryngeal carcinoma, the only risk factor associated with malignant transformation was an absence of HPV DNA on polymerase chain reaction of papilloma specimens (48).

PATIENT ASSESSMENT

History

Persistent or progressive stridor and dysphonia, with the possible development of respiratory distress, are the most consistent signs and symptoms of RRP in children (Table 94.1). In the absence of severe respiratory distress, a careful history should be obtained. Information regarding the time of onset of symptoms, possible airway trauma including a history of previous intubation, and characteristics of the cry are obviously important. Hoarseness, although a common and often benign clinical complaint in young children, always indicates some abnormality of structure or function. Because of the precision of laryngeal mechanics, hoarseness may result from a remarkably small lesion and thus be an early sign in the course of a disease process. On the other hand, if the lesion's origin is remote from the vocal cords, hoarseness may present as a late sign. Although histologically the same lesion, a papilloma that produces hoarseness in one patient may produce stridor and obstruction in another, depending on the size and location of the lesion. The quality of the voice change may give only limited clues to its etiology, whereas other characteristics such as age of onset, rate of progression, associated infection, history of trauma or surgery, and the presence of respiratory or cardiac distress may be of much greater significance. A low-pitched, coarse, fluttering voice suggests a subglottic lesion, whereas a high-pitched, cracking voice, aphonia, or a breathy voice suggests a glottic lesion. Associated high-pitched stridor also suggests a glottic or subglottic lesion. Although stridor that has been present since birth is more often associated with laryngomalacia, subglottic stenosis, vocal cord paralysis, or a vascular ring, it should be realized that neonates also can present with papillomatosis.

Associated symptoms such as feeding difficulties, allergic symptoms, vocal abuse, and the presence of hereditary congenital anomalies may help distinguish RRP from alternative diagnoses, including vocal fold nodules, vocal fold paralysis, subglottic cysts, subglottic hemangioma, and subglottic stenosis. In the absence of any history suggesting these lesions, review of the perinatal period may reveal a history of maternal or paternal condylomata. If the onset of stridor and dysphonia is gradual and progressive over weeks or months, then neoplastic growth compromising the airway must be considered and investigated.

Certainly not every child with a hoarse voice or cry merits investigation beyond an assessment of the symptom. However, in the presence of hoarseness with respiratory distress, tachypnea, decreased air entry, tachycardia, cyanosis, dysphagia, chronic cough, failure to thrive, recurrent pneumonia, or dysphagia, the larynx must be visualized and a firm diagnosis of the cause of hoarseness must be made. Any child with slowly progressive hoarseness merits investigation and the clinician should not wait until total aphonia or airway problems occur.

TABLE 94.1 COMMON PRESENTING SYMPTOMS IN CHILDREN WITH RRP

Progressive hoarseness
Stridor
Increasing dyspnea

Physical Examination

Children presenting with symptoms consistent with RRP must undergo a thorough and organized physical examination. The child's respiratory rate and degree of distress must first be assessed. The physician should observe the child for tachypnea or the onset of fatigue that may indicate impending respiratory collapse. The child should be observed for flaring of the nasal ala and the use of accessory neck or chest muscles. Increasing cyanosis and air hunger may cause the child to sit with the neck hyperextended in an attempt to improve airflow. If a child is gravely ill, additional examination should not be undertaken outside the OR, the emergency room, or the intensive care unit, where resuscitation equipment for intubation of the airway, endoscopic evaluation, and possible tracheotomy are readily available.

In the stable, well-oxygenated child, additional examination can proceed. The most important part of the examination is auscultation with the aid of a stethoscope. The physician should listen over the nose, open mouth, neck, and chest to help localize the probable site of the respiratory obstruction. A useful technique is to pull the bell off the stethoscope and listen over these areas with the open tube. The respiratory cycle, which is normally composed of a shorter inspiratory phase and a longer expiratory phase, should then be observed. Stridor of a laryngeal origin is most often musical and may begin as inspiratory, but will progress to biphasic with worsening airway narrowing. Infants with stridor should be placed in various positions to elicit any changes in the stridor. A child with RRP would not be expected to demonstrate much change in the stridor with position change in contrast to infants with laryngomalacia, a vascular ring, or a mediastinal mass. Pulse oximetry can add an accurate quantitative analysis of the child's respiratory state. In the stable patient in whom asthma is a likely diagnosis, pulmonary function testing combined with arterial blood gas evaluation also may be helpful.

Airway Endoscopy

The preoperative diagnosis of RRP is best made with a flexible fiberoptic nasopharyngoscope. Careful, sequential inspection of the pharynx, hypopharynx, larynx, and subglottis provides the critical information necessary to make the diagnosis of RRP and allows estimation of lumen size, vocal cord mobility, and the urgency of operative intervention. Advances in instrumentation of flexible nasopharyngoscopes have resulted in instruments as small as 1.9 mm in diameter that allow passage in even the smallest newborns. Even the smallest diameter scopes provide images that can be seen on a video monitor and recorded for later review. Recording of sequential endoscopic examinations allows for assessment of disease progression. Topical decongestion and local anesthesia can be applied by spray, dropper, or pledget. Oxymetazoline is the decongestant of choice because of its lack of cardiac side effects. Either topical tetracaine or lidocaine may be used to enhance patient cooperation, but the dosage must be critically monitored in the small infant to avoid cardiotoxicity.

Most clinicians find that visualization with the flexible nasopharyngoscope is far superior to that obtained with indirect mirror laryngoscopy in young children. Patient cooperation, however, is required even with good topical anesthesia. In infants, this is not a large issue because they can easily be restrained in a sitting-up position in the parent's or nurse's lap for evaluation. Likewise, most patients over 6 or 7 years of age can cooperate with the examination. It is the intermediate age group, between 1 and 6 years of age, who may be the most difficult to examine, taxing the patience and skill of even the most experienced clinicians. Although dynamic evaluation may be appreciated when children are spontaneously breathing, endoscopy in the OR under anesthesia is warranted in any child suspected to have RRP who cannot be fully examined in the outpatient setting.

OTHER CONSIDERATIONS

Children newly diagnosed with RRP warrant a substantial time commitment on the part of the otolaryngologist to engage the family in a frank and open discussion of the disease and its management. Support groups such as the Recurrent Respiratory Papilloma Foundation (RRPF: www.rrpf.org; PO Box 6643 Lawrenceville, NJ 08648-0643) and the International RRP ISA (Intl RRP ISA: www.rrpwebsite.org; PO Box 30821, Seattle, WA 98113-0821) can be a vital resource for information and support.

RRP patients require frequent office visits and endoscopic procedures at the outset to establish the aggressiveness of their disease. They are encouraged to return to the office or call as often as necessary while family members and the health care team become familiar with the child's symptoms and level of distress. Although infant home intercom-type monitors are often recommended, apnea/bradycardia monitors and pulse oximetry are generally not necessary. Repeat flexible fiberoptic laryngoscopy may be used in the office setting, as may speech and language therapy if offered early in the course of the disease. Control of other medical factors such as reflux and asthma is also aggressively pursued.

SURGICAL MANAGEMENT

No single modality has been consistently effective in eradicating RRP. The current standard is surgical therapy with a goal of maintaining an airway and doing no harm. For patients with anterior commissure disease or highly aggressive papilloma, the goal may be subtotal removal to avoid excessive scarring. Overzealous surgical therapy, however, can lead to significant scar injury that can leave the patient with continued airway or vocal dysfunction once the disease goes into remission. When in doubt, it is best to leave the disease behind in the anterior commissure and interarytenoid areas because the majority of complications following disease remission are related to damage in these areas. Most patients with JORRP require repeated surgery with a median of 7 surgeries in Lindeberg and Elbrond's series, 13 surgeries in that of Morgan and Zitsch's, and 19 in Derkay (1,5,26).

Currently, there are no medical or surgical cures for RRP. Goals of any therapeutic RRP regimen include eradication of disease from the airway, improvement in voice quality, control of disease spread, and decrease in the number of trips to the OR for surgical debridement. Surgical management remains the mainstay of therapy for RRP. A balance must be achieved between returning to the OR frequently, which carries the risks of stenosis, webbing, and anesthesia, versus prolonging intervals between operative interventions.

TABLE 94.2 POTENTIAL SURGICAL MODALITIES FOR RRP

Microlaryngoscopy with cup forceps removal
Microdebrider powerized resection
CO_2 laser
KTP laser
Pulse-dye lasers

RRP, recurrent respiratory papillomatosis.

Longer intervals between procedures, however, may allow for disease spread and increasing tumor burden.

There are multiple different surgical techniques that can be utilized to treat RRP. These include the use of the microdebrider, the laser, and sharp dissection (Table 94.2). Traditionally, the CO_2 laser has been favored over cold instruments in the treatment of RRP involving the larynx, pharynx, upper trachea, and nasal and oral cavities (49). The CO_2 laser has an emission wavelength of 10,600 nm, and converts light to thermal energy. It provides a controlled destruction of tissues with vaporization of water and also cauterizes tissue surfaces. When coupled to an operating microscope, the laser vaporizes the lesion with precision while causing minimal bleeding. When used with a no-touch technique, the CO_2 laser minimizes damage to the vocal folds and limits scarring.

In recent years, the utilization of the microdebrider for endoscopic management of RRP has gained popularity. In a survey of pediatric otolaryngologists conducted in 2002, the majority of respondents (52%) identified the microdebrider as the preferred technique for papilloma removal (43). Similarly, our current surgical preference for debulking of RRP involves the use of the microdebrider. Advantages of this technique include: improved voice outcomes, minimal collateral laryngeal mucosal thermal trauma, less procedure time, fewer personnel required in the OR, reduced cost when compared to the laser, and no increase in pain scores (49–52). Safety advantages include no risk of laser fire or burns and reduced risk of exposure of OR personnel to aerosolized viral particles.

Technologic advances in fiberoptic laser delivery and endoscopy using distal-chip scopes have made office-based therapy of AORRP a viable, cost-effective option. In addition to being safe, office-based airway laser procedures are well tolerated by patients. A recent study reported 87% of patients preferred office-based laser procedures to similar OR-based upper aerodigestive tract laser procedures (53). For the most part, pediatric patients still require general anesthesia for treatment of their RRP. This is due to problems with cooperation and a smaller airway.

In the past several years, the pulse dye laser (PDL) has been gaining popularity for the treatment of RRP, and it is now recognized as a viable treatment option. Patients with sessile lesions, disease involving the ventricle, and areas with the potential for significant scarring may benefit from the use of the PDL. The PDL is a nonablative laser that selectively targets the microvasculature of the lesion, thus sparing the epithelium, a photoangiolytic effect. The wavelength of the PDL is 585 nm. The PDL takes advantage of the chromophore in oxyhemoglobin, which has peaks at both 540 and 585 nm (54).

The PDL can be employed in either the OR or in an office-based setting. Hartnick et al. demonstrated that the 585 nm PDL was safe and effective for use in RRP in the pediatric population. In their small (n = 23), prospective, longitudinal study, they noted no events of anterior commissure webbing or true vocal cord scarring on lesions treated with the PDL. Additionally, they found no evidence of damage to the normal epithelium during PDL therapy. This finding would allow bilateral anterior commissure therapy to be performed during one surgery and could potentially lead to improved voice outcomes. They also commented that the flexible fiberoptic delivery of PDL energy made it advantageous for lesions in hard-to-treat locations including the ventricles, infraglottic area, and trachea (55). Koufman and Mouadeb promote the effectiveness of the PDL in the office setting (56,57). Using little to no topical anesthesia, Koufman's group performed 212 PDL procedures on 59 RRP patients with an average of 3.6 procedures per patient and a mean follow-up of 17 months. They noted no complications associated with the PDL procedures. Mouadeb performed office-based PDL therapy on 21 RRP patients with similar results of no anterior glottic webbing or vocal cord scarring. Additionally, they noted a statistically significant improvement in Voice Handicap Index (VHI) on the patients in their study.

Thus, PDL promises to be a part of our expanding armamentarium for JORRP and AORRP. With current third-party reimbursement rates, there are perverse financial disincentives preventing the widespread utilization of office-based PDL therapy for RRP. Rees et al. found a potential $5,000 per case savings when PDL therapy was performed in the office instead of under general anesthesia, yet the existing reimbursement scheme does not cover the cost for the surgeon of using the laser in the office. Until there is reconciliation of the cost-payment issues, this office-based technology and its benefits will be largely unavailable to RRP sufferers (58).

Two other lasers that can be delivered via a flexible fiberoptic medium for treatment of RRP are the pulsed potassium-titanyl-phosphate (KTP) laser and the flexible CO_2 laser. The KTP laser has a wavelength of 532 nm, which is similar to one of the peak absorption wavelengths of hemoglobin. The KTP laser can be used in either the office or the OR setting to treat papillomatous lesions in a similar, photoangiolytic, fashion to the PDL. Burns conducted a prospective pilot study of the KTP laser in 55 AORRP patients using disease regression as a primary endpoint (54). At least 90% disease regression was achieved in 80% of AORRP patients. Despite having 93% of their

cases with anterior commissure disease, they reported no new webbing. The authors prefer the KTP laser to the PDL because of the extended pulse width of the KTP. This extended pulse width allows for enhanced clinical efficacy and uses a wavelength closer to an absorption peak of oxyhemoglobin (54). No study yet has determined the optimum energy delivery necessary to affect tissue coagulation and/or effectively cause photoangiolysis (59).

The flexible CO_2 laser allows access to previously difficult to reach areas including the trachea, tongue base, and hypopharynx. This laser uses a hollow core fiber that allows passage of both the laser beam and nitrogen flow for cooling. It enables the surgeon to change focus and intensity manually without adjusting a micromanipulator. The fibers are only 1.8 mm in diameter and fit easily through the suction port of both a ventilating bronchoscope and a Lindholm microlaryngoscope. Additionally, the CO_2 laser fiber can be used with a variety of angled handpieces that allow access to the oral and nasal cavities.

SPECIAL CONSIDERATION

Surgical management of RRP is challenging. Whenever possible, utilize the most-experienced pediatric-trained anesthesiologist and OR staff available.

Tracheotomy is occasionally used as an alternative or an adjuvant to repeated endoscopic surgery. However, it has been suggested that tracheotomy may activate or spread disease lower in the respiratory tract. Cole reported on the Cincinnati Children's Hospital JORRP experience in which tracheal papillomas developed in half of their tracheotomy patients. Despite attempts to avoid this procedure, 21% of their patients still required a long-term tracheotomy (60). Shapiro, on the other hand, described a favorable experience with the placement of tracheotomies in children with JORRP treated at the Children's Hospital of Pittsburgh (61). While 37% of the patients in this study required a tracheotomy, the presence of the tracheotomy did not change the incidence of extralaryngeal spread of disease. Most clinicians agree that tracheotomy is a procedure to be avoided in RRP patients unless absolutely necessary. When a tracheotomy is unavoidable, decannulation should be considered as soon as the disease is managed effectively with endoscopic techniques.

Recurrent Respiratory Papillomatosis Surgery

Current procedures for managing papilloma disease in the larynx with the microdebrider will be described; we will then briefly review our CO_2 laser technique. These techniques are modified depending on the location of the disease, the amount of previous laryngeal surgery, and the degree of airway obstruction. In some circumstances, papillomas may best be removed with the use of the microdebrider, in others the CO_2 or KTP laser via the ventilating bronchoscope. When determining which surgical procedure will be utilized, consideration must also be given to which anesthetic technique will be employed. When using the laser, the operating surgeon may choose to intubate the patient with a laser-safe endotracheal tube. Alternatives to this approach of securing the airway include apneic technique without intubation, insufflation techniques, or the use of jet ventilation.

Preoperative Planning

Regardless of the technique planned for removal, before the child enters the operating suite, the surgeon, anesthesiologist, and OR team must select the proper size endotracheal tubes, laryngoscopes, and bronchoscopes and ascertain that all ancillary equipment, including telescopes, light cords, suction tips, and forceps are available. The surgeon, along with the OR team, should check that all equipment used for the procedure, including the surgical microscope with appropriate size lens, the laser or microdebrider unit, the micromanipulator, filtered suction, and smoke evacuation units, are all properly functioning. In our institution, if the laser is going to be utilized, the surgeon personally checks the laser for beam alignment by test-firing it prior to the child entering the room. Laser safety is carefully monitored in our institution by the laser safety committee. This includes a laser safety officer, a physician for each specialty that uses the laser, nurses from the OR, a hospital administrator, and biomedical engineer. All OR personnel are required to wear eye protection whenever working around the laser. Specially designed laser masks are required to be worn by OR personnel during the surgery to prevent the inhalation of viral particles liberated during the laser procedure.

Before the institution of any anesthesia, the surgeon should discuss the pathology with the anesthesiologist. The ultimate decision about the technique of anesthesia, whether to use an endotracheal tube or to use a total intravenous technique (apnic or spontaneous ventilation), should be shared between the anesthesiologist and the surgeon. When the child's pathology permits, we prefer the total intravenous technique with propofol. In this technique, there is no endotracheal tube to limit access to the papillomatous lesions and to distort laryngeal anatomy. If the laser is going to be utilized, the smallest possible laser-safe endotracheal tube that allows for adequate ventilation should be used. If a cuffed tube is necessary, then the cuff should be filled with saline so that, if it is inadvertently struck by the laser beam, the saline acts as a heat sink and fire extinguisher. Some surgeons prefer to use methylene blue in saline to provide an additional warning in case the cuff is penetrated.

The majority of pediatric anesthesiologists at children's hospitals are familiar with papilloma surgery in children. However, in institutions where there are a limited number of anesthesiologists experienced in pediatric papilloma surgery, then whenever possible these individuals should be involved. This type of surgery is not well suited to the

novice surgeon, anesthesiologist, or OR nurse. It is our practice to insist that the attending anesthesiologist be present and involved "hands on" with all critical portions of the surgical procedure, including induction, changing of anesthesia techniques from an endotracheal tube to apnea technique, and extubation. We try to avoid the use of premedications and insist on having the bronchoscopes and laryngoscopes set up in advance in case the child develops airway obstruction or experiences a laryngospasm on anesthesia induction.

To this end, the staff within the OR also should be informed of the surgeon's concerns so that appropriate instrumentation is ready. When performing surgery for RRP, it is advisable to have an experienced team of OR nurses familiar with the sequence in which equipment is used. Intraoperative teamwork is enhanced with the availability of video monitors during the operation because this allows the entire OR staff to follow the operation as it progresses. Dialogue between the surgeon, nursing staff, and the anesthesiologist continues throughout the procedure regarding the current status of ventilation, the amount of bleeding encountered, the motion of the vocal cords, the timing of laser use in conjunction with respiration, and the concentration of oxygen in the anesthesia mix.

Operative Technique—Endoscopic Microdebrider

When comparing the removal of papillomas with the microdebrider and with the CO_2 laser, many of the steps are similar. We will highlight the major differences between these two techniques. When the microdebrider is used, there is a need for one less person on the OR team; the laser nurse. Likewise, all of the precautions described below regarding laser safety and aerosolizing or disseminating of HPV particles do not apply. Additionally, the anesthesia provider is not required to keep the FiO_2 below 40% which may minimize patient desaturation during the procedure.

The typical room setup includes a suspension microlaryngoscope (Lindholm), a full set of Parson laryngoscopes (Karl Storz Endoscopy America, Culver City, CA), two appropriately sized ventilating bronchoscopes, and a 7,200-A Hopkins rod telescope (Karl Storz Endoscopy America, Culver City, CA). The microscope is fitted with a 400-mm lens. An assortment of suctions, alligators, cup forceps, and light cords, as well as a pack of neuropathies and topical oxymetazoline, are also standard. An endoscopy video cart equipped with color television monitor, digital recorder, photo printer, three-chip camera, and xenon light source is also used. Additionally, a pediatric tracheotomy set is brought into the room, although the pack is not opened.

In conjunction with the nursing staff, a proper length laryngeal Skimmer blade is chosen (18 cm vs. 22 cm depending on the relative size of the child), and the microdebrider unit is typically set at between 600 and 1,000 rpm on oscillation mode.

After informed consent has been obtained from the appropriate caregivers, the child is brought to the OR that has been prepared and inspected by the surgeon. Time-out and surgical marking procedures are followed in our hospital for all OR cases. The surgical sequence begins with an anesthetic mask induction using sevoflurane and the establishment of intravenous access. Dexamethasone at 0.25 to 0.5 mg/kg is routinely administered perioperatively. The larynx is exposed using the Parsons laryngoscope attached to 6 L/min of oxygen flow through the insufflation port. The vocal folds are then sprayed with a weight appropriate dose of 2% lidocaine using a syringe attached to a Cass needle. A diagnostic laryngoscopy is performed using the 7,200-A telescope under video control to assess the degree of papilloma disease and its encroachment on the laryngeal airway. Depending on the extent of disease, the child's history, and the interval since the last endoscopy, a full tracheoscopy, and bronchoscopy also may be performed. Again, depending on the child's level of preoperative and operative distress, the surgeon may choose to perform this maneuver with either the 7,200-A telescope (if there is a low likelihood of discovering distal disease) or with an appropriate size ventilating bronchoscope (if there is high likelihood of discovering distal disease). Still photography with the 7,200-A telescope is then performed at this stage in the procedure. Photographs are useful in documenting disease extent and can be printed for inclusion in the medical record and for discussions with the family.

Once the airway has been assessed, either an endotracheal tube will be placed by the surgeon or an apneic technique with intravenous propofol and insufflated sevoflurane will be adopted. The Lindholm microlaryngoscope is then inserted and positioned. We prefer to suspend the microlaryngoscope to a Mayo stand attached to the OR table. This device allows the microsuspension system to be moved along with the patient and also allows for angulation of the laryngoscope over a 120-degree range. If a biopsy specimen is desired, we generally begin the surgery by obtaining this from the bulkiest portion of the papilloma and then apply a neuropathy soaked in oxymetazoline to the biopsy site to minimize bleeding. We prefer to operate under the highest magnification available with the light source turned to the maximal setting. It is advisable to attach the microscope camera to the video monitor so that all OR personnel, including the anesthesia team, can follow the progress of the surgery. Our preference is to begin debriding the papillomas in the supraglottis first and then work our way toward the true vocal cords. The surgeon must be comfortable working with the microdebrider in either hand; the removal of papilloma from the left side of the larynx is best accomplished when the device is used in the right hand, while disease from the right side should be removed with the microdebrider in the surgeon's left hand. The hand opposite of the device holds a microsuction

which is used to help retract tissue and evacuate blood. In order to minimize the risk of web formation, it is essential to avoid creating opposing, raw surfaces at both the anterior and posterior commissure with the microdebrider. Care should also be taken when removing sessile papillomas from the true vocal cord surface, erring on the side of leaving disease as opposed to sacrificing a portion of the vocal fold. The microdebrider does allow for removal of papillomas in the subglottis and proximal one-third of the trachea by placing a 7,200-A telescope in one hand and the microdebrider in the other.

Because of the relative increased speed in removing of the papillomas with the microdebrider technique, the entire procedure typically takes less than 45 minutes. Humidified air and occasionally, racemic epinephrine are administered postoperatively in the recovery room. The patient is then closely monitored for several hours prior to discharge, and occasionally an overnight stay in a monitored bed unit is necessary. As a general rule, the more extensive the papilloma disease and the more compromised the airway, the more important it is for the child to be monitored postoperatively in an intensive care or step-down unit. Additional doses of steroids can be administered at 6-hour intervals if needed, and continuous pulse oximetry is mandatory.

Operative Technique—CO_2 Laser

Many of the steps described above in the microdebrider technique also apply when utilizing the CO_2 laser. When performing laser surgery for RRP, it is advisable to have an experienced team of OR nurses familiar with the sequence in which equipment is used and instructed in the proper use of the laser. In our facility, we also have a laser safety team that provides yearly updates for the OR staff to ensure everyone's familiarity with the equipment and its potential complications. The laser team consists of a scrub nurse, a circulating nurse, and a laser nurse. The laser is the responsibility of the laser nurse, allowing the circulator and scrub nurse to concentrate on their duties. All OR personnel are equipped with micropore laser filtration masks and approved goggles. All equipment is set up in advance including fitting the microscope with the CO_2 laser attachment and the laser is pretested before the child enters the room to assure its alignment.

After informed consent has been obtained from the appropriate family members, including a discussion regarding potential laser complications, the child is brought back into an OR that has been prepared and inspected by the surgeon and the laser team. If the extent of disease is such that an endotracheal tube will initially be utilized to secure the airway, then the surgeon begins by intubating with a laser-safe tube (metal Xomed-Treace, Medtronics, Minneapolis) of the smallest caliber that will allow the anesthesiologist adequate ventilation. (Commercially available laser-safe tubes are preferable to aluminum-wrapped red rubber tubes.) Once the airway has been secured with the endotracheal tube, then the anesthesiologist has the option to administer muscle relaxants. However, it is often preferable to use continuous or intermittent propofol infusions to keep the child anesthetized during the procedure. It should be stressed that no muscle relaxants are administered until the surgeon has assessed the degree of laryngeal obstruction and secured the airway. This precaution serves to prevent the situation in which the child obstructs his/her airway due to papilloma, blood, or mucus, precipitating hypoxia and possible laryngospasm.

Once the airway has been secured, the endotracheal tube is anchored in place with a single piece of tape (allowing the surgeon easy access for removal of the endotracheal tube in the case of an airway fire). The child is then placed in suspension using the microlaryngoscope. Lubricant is placed in the patient's eyes. The child is further protected against laser beam exposure by placing moist, saline-soaked gauze pads over the eyes. Next, the operative field is draped with moistened towels. The surgeon confirms that all OR personnel are equipped with ocular protection, including side shields. A sign is posted outside the OR warning that a laser procedure is in progress and a spare set of safety glasses is left outside the door for OR personnel who wish to come inside the room while the laser is in operation. Special laser masks with extremely small pores are worn to minimize exposure to the laser plume. A high-volume smoke evacuator is attached to one port of the microlaryngoscope to collect the laser plume. A second suction attached to the smoke evacuator is used by the surgeon. By this point, the inspired FiO_2 delivered to the patient should be as close to a room-air mixture as possible. Ideally, the laser is not used until the oxygen in the mixture is between 26% and 30%. In selected circumstances, it may be warranted to proceed with an FiO_2 at or below 40%. These precautions are taken to minimize the possibility of a laser-induced endotracheal tube fire.

As an initial procedure, a microcup forceps is used to obtain a biopsy specimen from the bulkiest portion of papilloma. The CO_2 laser, delivered via a micromanipulator attached to the operating microscope at initial settings of 4 W power, 0.1-second intervals, and repeat mode, is then used to remove papilloma lesions. Moistened neuropathies are placed at the laryngeal inlet to decrease the air leak and to provide a backstop for errant laser shots. (These must be kept moist because they too can act as a source of combustion.) Bulky papilloma is handled by defocusing the laser. With the laser refocused, lesions are gradually vaporized to the level of the mucosa, avoiding entry into Reinke space and the deeper vocalis muscle. During papilloma removal, we prefer using low-power laser settings to limit thermal injury to the surrounding tissue, although this technique may prolong operating time. A small-caliber suction device is kept close to the laser impact site to remove the hot steam of vaporization. The suction can also be used to remove eschar and as a retractor of the vocal folds to allow for exposure of the subglottic

region. Neuropathies soaked in neosynephrine are used for both removal of eschar and debris and hemostasis. Care is taken to avoid injuring the anterior commissure, and at least 1 mm of untreated mucosa should be left in this region so that a web does not develop during the healing period. Similar precautions are taken when addressing the posterior commissure.

Papillomas in the supraglottic larynx are addressed first, by disease involving the anterior half of the true vocal cords. Surgical access to papilloma in the posterior glottis or subglottis is often obstructed by the endotracheal tube and thus an alternative means of anesthesia is sought. We prefer an apneic or spontaneous respiration technique with insufflation of oxygen and sevoflurane while the endotracheal tube is removed intermittently. An alternative technique is the use of jet ventilation.

Once a decision is made to utilize the apnea technique, the anesthesiologist increases the FiO_2 to 100%. The child is extubated but left in suspension, and the smoke evacuation port of the microlaryngoscope is disconnected. Oxygen tubing is then connected to the microlaryngoscope port to initiate flow of 6 L/min of oxygen. The carbon dioxide and oxygen levels are closely monitored and the length of "laser on" time is adjusted appropriately. The laser is used for 2- to 6-minute intervals and the child is periodically reintubated with a polyvinyl chloride endotracheal tube directly through the microlaryngoscope. (A stylet is useful to stiffen the tube and improve the angulation during intubation.) Typically, the child is reoxygenated for the same period of time that he or she was apneic before proceeding with the next laser cycle. At the end of the case, the child is then reintubated with a standard endotracheal tube using a Selinger technique to avoid any difficulty in reestablishing the airway upon removal of the microlaryngoscope. The child is extubated only when fully awake.

An alternative anesthetic technique that can be utilized during laser removal of laryngeal papillomas is jet ventilation. Jet ventilation eliminates the potential fire hazard of the endotracheal tube and allows good visualization of the vocal cords. The jet cannula can be placed either above or below the vocal cords. We prefer placement of the cannula proximal to the end of the laryngoscope to decrease the risk of possible pneumothorax or pneumomediastinum. With large laryngeal lesions, narrowed airways, and ball-valve lesions, a high degree of outflow obstruction may develop that could lead to increased intrathoracic pressure and a subsequent pneumothorax. These complications can also occur if there is inadequate muscle relaxation. Additional limitations of this technique are the possibility of transmission of HPV particles into the distal airway, excessive mucosal drying, and insufflation of air into the stomach causing gastric distention. Thus, jet ventilation requires constant communication between the operating surgeon and the anesthesiologist.

Potential complications of laser surgery include the development of anterior commissure webs, laryngeal and subglottic stenosis, burns to the patient or OR personnel, and laser-induced endotracheal tube fire. A laser fire is more likely to occur in the setting of high oxygen concentrations and in the presence of a polyvinyl chloride endotracheal tube. Direct thermal injury to local tissues or a chemical burn may result from such a mishap. In order to prevent a laser fire, the oxygen concentration should be limited to less than 40%, or alternately the patient can be ventilated with room air. In the event of a laser fire, emergency care consists of immediate extubation of the patient and disconnection of the tube from its oxygen source. The child is then reintubated and examined through a ventilating bronchoscope. Antibiotics are given and a tracheotomy may be necessary based on the degree of damage. Tertiary care consists of positive end expiratory pressure and reverse isolation.

POSTOPERATIVE CARE

Children with stable papilloma disease requiring fewer than four laser procedures per year and whose caregivers reliably follow-up prior to the child showing signs of respiratory distress can be monitored at home with commercially available infant home intercom-type monitors. Patients with rapidly reforming papillomas and those whose caregivers wait until the child is in distress before seeking medical attention may warrant home pulse oximetry with frequent home health visits. Children with RRP are encouraged to return to the office or call as often as necessary. We give them "carte blanche" within our practice and explain to them that their children have a special problem that allows them access to speak with the doctors and nurses and come to the office whenever they feel their child is in need. We have yet to experience a family that has abused this privilege. Instead, this policy has enhanced the family's trust in the health care team and has decreased the need for urgent and emergent laser procedures.

RECURRENT RESPIRATORY PAPILLOMATOSIS STAGING

A staging system for RRP is essential. Such systems are useful when tracking a child's disease progression, communicating with other surgeons, and treating patients in a protocol or study format. Although several scoring and staging systems have been proposed, clinicians have yet to adopt a uniformly acceptable nomenclature for describing RRP lesions that is both simple and comprehensive. Failure to adopt such a system has created confusion in the RRP literature and in physician-to-physician communications regarding patient's response to therapies. In addition, the absence of an accepted staging system has hampered our abilities to accurately document the natural course of the disease and to report the results of adjuvant treatments. We have proposed a severity/staging system for RRP in a format that incorporates the best qualities of the existing systems by numerically grading the extent of papillomatosis at defined aerodigestive

subsites. The staging system also assesses functional parameters, diagrammatically catalogs subsite involvement, and assigns a final numeric score to the patient's current extent of disease (Fig. 94.4) (62). Using software designed at the University of Washington (Seattle) and licensed to the ASPO, this staging system is now computerized and available to pediatric otolaryngologists and bronchoesophagologists to allow them to objectively and subjectively measure an individual patient's clinical course and response to therapy over time. Encryption technology with this software offers promise to allow clinicians from around the world to anonymously share some of their patient data in a HIPPA-compliant format to enhance our knowledge of this disease and promote multi-institutional investigations.

MEDICAL MANAGEMENT

Though surgical management remains the mainstay of therapy for RRP, ultimately more than 20% of patients with the disease require some form of adjuvant therapy (43) (Table 94.3). The most widely adopted criteria for initiating adjuvant therapy are a requirement of more than four surgical procedures per year, distal or metastatic disease, and/or rapid regrowth of papilloma disease with airway compromise (63).

ADJUVANT THERAPIES

The most commonly utilized adjuvant medical therapy for RRP is intra-lesional cidofovir (Vistide) (43). Cidofovir is a nucleoside analog of deoxycytidine monophosphate. Once converted to its active form, this prodrug becomes incorporated into DNA and produces toxicity against the herpes virus family. It is FDA approved only for intravenous use in the treatment of cytomegalovirus retinitis in patients with HIV. However, laboratory and clinical studies have demonstrated its effectiveness in the intralesional treatment of RRP in adults and children (64–66). Cidofovir is relatively widely used "off label" for severely affected RRP patients (43). When we utilize cidofovir, our approach is to inject 5 mg/mL into the papilloma bed after microdebriding to a total volume of 2 mL and will commit to repeating this procedure at 4- to 6-week intervals for up to 6 months.

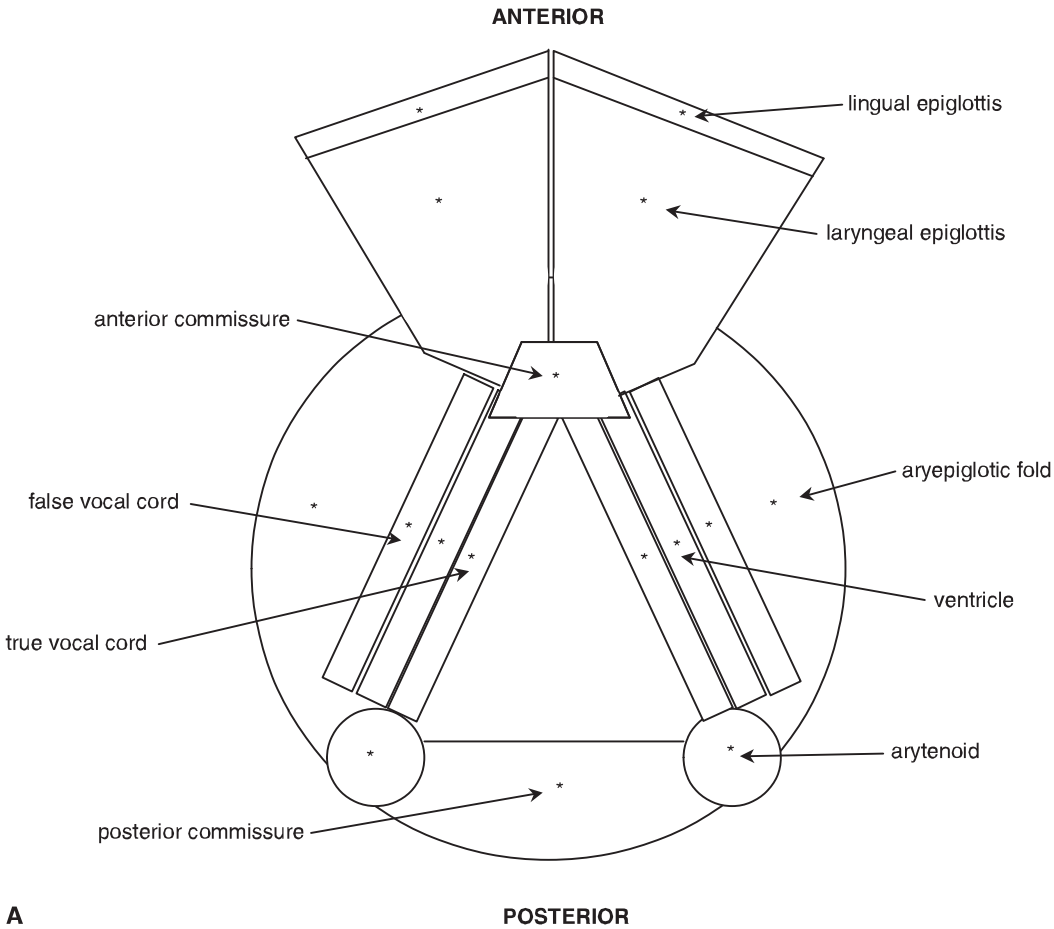


Figure 94.4 Coltrera/Derkay staging and severity scheme. **A:** Representation of diagram of scorable laryngeal sites. *(Continued)*

A. Clinical Score

DATE OF SURGERY_____ SURGEON_____
INSTITUTION_____

1. Describe the patient's voice today:
   normal___(0), abnormal___(1), aphonic___(2)
2. Describe the patient's stridor today:
   absent___(0), present with activity___(1), present at rest___(2)
3. Describe the urgency of today's intervention:
   scheduled___(0), elective____ (1), urgent___(2), emergent___(3)
4. Describe today's level of respiratory distress:
   none___(0), mild___(1), moderate___(2), severe___(3), extreme___(4)

Total score for questions 1 through 4 = _____

B. Anatomical Score

For each site, score as: 0=none, 1=surface lesion, 2=raised lesion, 3=bulky lesion

LARYNX:
- Epiglottis: Lingual surface___ Laryngeal surface___
- Aryepiglottic folds: Right___ Left___
- False vocal cords: Right___ Left___
- True vocal cords Right___ Left___
- Arytenoids: Right___ Left___
- Anterior commissure_____
- Posterior commissure_____
- Subglottis_____

TRACHEA:
- Upper one-third_____
- Middle one-third_____
- Lower one-third_____
- Bronchi: Right___ Left___
- Tracheotomy stoma____

OTHER:
- Nose_____
- Palate_____
- Pharynx_____
- Esophagus___
- Lungs_____
- Other_____ Total Score for Anatomical _____

C. Total Score

Total Anatomical Score plus Total Clinical Score

B

Figure 94.4 *(Continued)* **B:** Laryngoscopic and clinical assessment scale for RRP.

Chadha performed a 10-year systematic review of the literature regarding RRP treated with intralesional cidofovir and reported complete disease resolution in 57% of patients and a partial response in 35% of patients. Despite these promising numbers, the authors note a tremendous variability in dosage, interval of administration, and number of injections. They also point out the need for a well-designed, placebo-controlled, double-blinded, randomized trial to better study this adjunct (67). In contrast, McMurray found no statistical difference when comparing cidofovir and placebo RRP treatment groups. Both arms of the study showed statistically significant improvements in Derkay severity score, VHI, and a quality of life. Limitations of this study include a small sample size (n = 19), low dose of cidofovir (0.3 to 5 mg/mL), and a short follow-up period (68). Despite its weaknesses, this study highlights the importance of the placebo group in demonstrating the effectiveness of surgical debridement in the successful treatment of aggressive RRP. Donne's recent work provides additional insight into the variable responses described when using intralesional cidofovir in RRP patients. The authors found that while cidofovir was effective against HPV 16 infected cells, it had only marginal effectiveness against HPV 6 infected cells. This study was performed in

TABLE 94.3 ADJUVANT TREATMENT MODALITIES FOR RRP

Cidofovir
Celebrex
α-Interferon (pegylated)
Anti-reflux therapy
Indole-3-carbinol
Therapeutic vaccination—HspE7
Bevacizumab (Avastin)

RRP, recurrent respiratory papillomatosis.

an isogenic system in which low- and high-risk viral proteins are expressed in the same genetic background. The authors concluded that cidofovir might have little selectivity for low-risk HPV (type 6)-related disease (69).

Based upon animal toxicity studies and case reports, there are concerns regarding the side-effect profile of cidofovir including the induction of dysplasia and malignant degeneration of papilloma lesions following intralesional injection (51). Naiman et al. (70) looked at cidofovir plasma concentrations after intralesional airway injection in patients with RRP. They found that intralesionally injected cidofovir was absorbed to some degree in the bloodstream. Of 35 patients (adults and children), one adult reached levels at the upper end of recommended therapeutic levels to prevent nephrotoxicity. During a 26-week intravenous toxicology study in rats, similar levels of cidofovir were shown to cause a significant increase in mammary adenocarcinomas (71). However, Lacy et al. (72) showed that no tumors were detected in cynomolgus monkeys who were injected with intravenous cidofovir (with and without oral probenecid) once weekly over a 52-week period. In a thorough review of the side effects of cidofovir in RRP, Broekema identified 31 articles meeting the inclusion criteria (73). The results showed that dysplasia occurred in 2.7% of all patients treated with intralesional cidofovir. This percentage is concurrent with the reported incidence of spontaneous malignant degeneration of RRP (2.3%). They concluded that intralesional cidofovir use in RRP does not increase the risk of laryngeal dysplasia. Lindsay reported on a retrospective review of pediatric operative biopsy specimens from JORRP patients treated with cidofovir and found no cases of dysplasia identified in those specimens (74).

Until additional studies have been performed demonstrating its safety, it is our opinion that use of cidofovir in RRP follows the recommendations of the Task Force on RRP (51) listed below:

I. Given the promising results reported in pediatric and adult patients, cidofovir should be routinely presented as a treatment option in moderately-to-severely afflicted RRP patients, that is, those patients whose disease is not improving on surgical therapy alone or in conjunction with less potentially morbid adjuvant measures and/or requiring surgical intervention greater than three times a year.
II. With appropriate consent, cidofovir therapy should be a viable option in patients whose disease severity is resulting in a need for frequent surgery, worsening airway compromise, severely impaired communication, or those who otherwise may be considered candidates for tracheotomy.
III. Patients with more mild disease, particularly children, should be discouraged in most cases from seeking treatment with cidofovir, until a better understanding of the long-term implications of the use of this drug have been established. With appropriate informed consent, cidofovir could still be utilized on a case-by-case basis, at the discretion of the prescribing physician, for the more mildly affected patient.
IV. As with all surgical procedures, informed consent should be obtained and documented in the patient's record. At a minimum, this should include a frank discussion of the nephrotoxic and carcinogenic potential of this drug: limiting usage of adjuvant cidofovir to treatment in only severe or recalcitrant cases in children.

When a decision has been reached to begin a trial of cidofovir, we recommend administering the drug at the 5 mg/mL concentration as an intralesional injection following debridement of papillomas. The authors usually try to avoid using more than 2 mL during a single procedure. Administration may be repeated at 4- to 6-week intervals for a 6-month trial period. The trial can be abandoned if no demonstrable clinical benefit is achieved after this time interval.

Celecoxib (Celebrex)

Recent research into the molecular biology of RRP, specifically the signaling cascades leading to regulation of cyclooxygenase-2 (COX-2), has revealed that HPV-infected cells behave differently. The individual elements of these unique signaling cascades may present themselves as new targets for therapeutic regimens in the treatment of RRP and other HPV-induced diseases (75). Favorable anecdotal results with the use of Celecoxib (Celebrex) have resulted in the initiation of a multi-institutional study of COX-2 inhibitors in the treatment of adults and children with RRP.

Interferon

Interferon has been used as an adjuvant therapy in patients with RRP since the 1980s. In addition to being one of the initial adjuvant therapies, interferon was formerly the most common adjuvant therapy for treatment of RRP. Interferons are a class of proteins manufactured by cells in response to a variety of stimuli, including viral infection. The exact mechanism of action is unknown, but interferon is thought to inhibit viral protein synthesis by modulating the host

immune response (76). In 1995, 9% of children with RRP received the drug, and the most recent survey of pediatric otolaryngologists demonstrates its use has been cut to less than 4% (5,43). This decline in the use of interferon as an adjuvant treatment for RRP is due to several factors, including the high side-effect profile and the emergence of cidofovir. The most frequently utilized product, recombinant alpha-interferon (Roferon, Roche), has recently been taken off the market and replaced by peginterferon alfa-2a (Pegasys, Roche). A special strand called a "peg" has been attached to this interferon molecule to increase the half-life of the drug. Once attached, the peg helps protect the interferon from being destroyed by the host immune system. In addition to increased effectiveness, peginterferon alfa-2a also has a better safety profile and a simpler dosing regimen. The newer formulation needs to be administered only once weekly by subcutaneous injection.

The side-effect profile of alpha-interferon is multifarious and includes both acute and chronic reactions. The acute reactions are fever and generalized flu-like symptoms as well as nausea and vomiting. They tend to subside with prolonged therapy. Chronically, interferon can cause growth retardation in children, elevated liver enzymes, alterations in the central nervous system (leukopenia spastic diplegia), febrile seizures, and thrombocytopenia. Rashes, dry skin, alopecia, pruritis, and fatigue are also possible. Most side effects are short term and do not necessitate cancellation of therapy (77,78).

Long-term efficacy of interferon therapy was recently evaluated in a multicenter, nonrandomized prospective series by Gerein (78). The authors found that 63% of patients (with active disease and surgery-free interval less than 3 months) had macroscopic remission at the end of long-term interferon therapy. Even in the group of nonresponders, the majority of patients had an increased surgery-free interval. However, after long-term follow-up of 172 months, only 42% of patients were in complete remission. Gerein also noted a statistically significant difference in responses based upon HPV subtype, with 68% of patients with HPV 6 remaining in remission at the end of the follow-up in contrast to only 18% of patients with HPV 18.

Antireflux Therapy

The relationship of RRP and GERD has been discussed in the literature for well over a decade (23,79,80). It is known that recurrent or chronic exposure to acid and gastric enzymes can cause inflammatory changes to the epithelial lining of the aerodigestive tract. This local inflammatory change may play a role in determining the outcome for an individual patient whose larynx has been exposed to HPV. A recent case series demonstrated treatment of GERD in RRP patients with resistant disease resulted in improved outcomes (79). The authors showed either complete or partial response of RRP in four children when reflux was controlled with either medical management (medication and diet) or in one case, fundoplication. Furthermore, when compliance with reflux therapy waned in three of the patients, the RRP returned. Restarting medical management again resulted in improved RRP disease control. Other authors have reported similar findings. Holland et al. (23), in a retrospective review of JORRP patients, found that "high-risk patients" (defined as higher chance of developing complications due to increased trips to the OR for disease control) who were treated with antireflux therapy were significantly less likely to form laryngeal webs than those without reflux therapy.

Indole-3-Carbinol

Indole-3-carbinol is an over-the-counter nutritional supplement found in high concentrations in cruciferous vegetables like broccoli, cabbage, brussels sprouts, and cauliflower. It is a potent inducer of cytochrome P450-regulated metabolism of estrogen. Estrogen is important in RRP because it increases HPV gene expression allowing for epithelial proliferation (81,82). A study on immune-compromised mice receiving transplanted HPV-infected laryngeal tissue demonstrated nearly a 75% reduction in the formation of papilloma tumors when given indole-3-carbinol (83). Rosen et al. (84) performed a long-term (mean 56.7 months), open-label, prospective study using indole-3-carbinol for the treatment of RRP in adults and children. The authors found either complete or partial response in 70% of the patients. In the trial, pediatric patients did not respond as well to indole-3-carbinol as adults. Larger studies are necessary to further elucidate questions regarding this therapy.

Therapeutic Vaccination—HSPE7

Preliminary research into the development of therapeutic HPV vaccines is focusing on utilizing early viral proteins such as E6 and E7 as the target antigen. One such drug is HspE7, a recombinant fusion protein consisting of 638 amino acids derived from *Mycobacterium bovis* bacilli Calmette-Guerin heat shock protein 65 (Hsp65) covalently linked at its C terminus to the E7 protein of HPV type 16 (HPV 16). The HspE7 protein is produced in *Escherichia coli* expression strain BLR (DE3). Injection of HspE7 in animal studies results in specific humoral and cell-mediated immune responses leading to regression of epithelial cell-derived tumor. Administered subcutaneously in clinical trials, it has been shown to be effective against genital warts in women and girls, not only with HPV 16 but also in non–HPV-16 strains suggesting cross-reactivity. Phase II study results in an open-labeled trial demonstrated that over a 14-month period, the intersurgical interval doubled in almost half the patients and the absolute number of surgeries decreased significantly (85). As a systemic immune modulator, HspE7 has a low side-effect profile, and its

administration can be done in the outpatient setting making it an attractive choice. Larger, placebo-controlled, blinded, phase III trials will be needed to confirm the effectiveness of HspE7. However, manufacturing concerns are currently delaying the regulatory process.

Bevacizumab (Avastin)

Avastin is an angiogenesis inhibitor drug that, when combined with the 532 nm flash-dye laser, may have a significant effect on recurrent respiratory papillomas. In an open-label study involving 10 adult patients, Zeitels demonstrated a 90% reduction in recurrence after five treatments (injections followed by KTP laser) (86). A phase I single center open-labeled study to assess safety and tolerability in 20 adult RRP patients is currently recruiting subjects. Researchers are also contemplating a clinical trial in pediatric RRP patients involving systemic propranolol (inderal) because of its antiangiogenesis properties.

Artemisinin and its related compound artesunate are antimalarial drugs that have shown a therapeutic benefit on canine papillomavirus. These drugs induce apoptosis and have antiangiogenic activity. Limited data are currently available regarding its benefits in RRP patients.

Preventative Vaccination—Quadrivalent HPV Vaccine

The most interesting and promising recent development in the prevention of RRP is the quadrivalent HPV vaccine (GARDASIL, Merck and Co., Inc.). This vaccine is currently licensed by the FDA for the prevention of cervical cancer, adenocarcinoma *in situ*, and intraepithelial neoplasia grades 1 to 3; vulvar and vaginal intraepithelial neoplasias grades 2 to 3; and genital warts associated with HPV 6, 11, 16, and 18 (87). HPV types 16 and 18 cause approximately 70% of cervical cancers worldwide, while HPV types 6 and 11 cause more than 95% of genital warts. The future II study group performed a randomized, double-blind trial in 12,167 women between 15 and 26 years to receive either three doses of a quadrivalent vaccine against HPV 6, 11, 16, and 18 or placebo to evaluate prevention of high-grade cervical lesions (87). The women were followed for 3 years after receiving their first vaccine dose and achieved a 98% efficacy for prevention of high-grade cervical lesions. Based upon this phase III study and several well-designed phase II studies the United States Center for Disease Control (CDC) Advisory Committee on Immunization Practices has recommended vaccination for all girls aged 11 to 12, girls and women aged 13 to 26 who have not yet been vaccinated, and girls as young as age 9, where the physician feels it would be appropriate (88,89). Recently, the FDA has also approved its use in boys aged 9 through 25. The vaccine is predicted to reduce the incidence, morbidity, and mortality of cervicovaginal HPV disease. Based on the above recommendations, numerous countries have passed laws to educate the public and encourage use of the vaccine, but few states in the United States have mandated vaccination (90).

Unfortunately, Hildesheim found that the bivalent vaccine had a lack of efficacy as a therapeutic vaccine (91). In a trial involving 7,000 18- to 25-year-old Costa Rican women, the authors demonstrated no effect of the vaccine on viral clearance. In an editorial published in the same issue of *JAMA*, Markowitz highlights the implications of this study (92). Specifically, she emphasized the need for continued Pap screening and post-licensure safety monitoring. Additionally, she discussed the potential for the vaccine to still benefit women with existing HPV infection with one virus type by boosting the antibody response and increased protection from infection by other HPV vaccine types. An added, and often overlooked, benefit of near universal vaccination may be a concomitant decrease in thwe incidence of RRP in all age groups.

There is also a large body of evidence surrounding the role of HPV infection in the development of head and neck SCC. The overall HPV prevalence in head and neck SCC is estimated at 26% with higher prevalence in oropharyngeal SCC (36%) than in oral (24%) or laryngeal (24%) SCC. Tonsillar SCC has the highest rate of HPV detection at 51%, which makes this anatomic location the highest of any extragenital malignancy (93). D'Souza et al. (94) performed a case-controlled epidemiologic study, which showed a strong association of oropharyngeal cancer and HPV. They found HPV 16 DNA in 72% of the tumor specimens from their enrolled oropharyngeal cancer patients. Nearly 30,000 new cases of oral and oropharyngeal squamous cell cancers are reported annually in the United States. If a third is related to HPV infection, then potentially 10,000 cases could be annually prevented. With a 55% 5-year overall survival and an increased incidence noted in younger, nonsmokers and nondrinkers, a vaccine that could confer long-term immunity could have a huge impact (95).

Theoretically universal vaccination with the quadrivalent vaccine could lead to the elimination of the maternal and paternal reservoir of HPV and thus to a near eradication of RRP caused by HPV 6 and 11 (96). While moral objections to requiring HPV vaccinations are largely emotional, public health officials may have more justifiable concerns about the merits of HPV vaccination based upon the financial and logistic burdens that may be imposed on families and schools. Another legitimate concern is the adverse-event rates in mass scale programs. It is estimated that the cost to fully immunize all 11-year-old girls will exceed $850 million per year (97). Several cost–benefit analyses have shown the vaccine to be greatly cost-efficient, with 13 cents spent on vaccination resulting in the savings of $1 of health care (Fig. 94.5). This is anticipated to improve when the 9-valent HPV vaccine becomes commercially available, covering more of the HPV subtypes responsible for cervical and head and neck cancers. It has been estimated that herd immunity can be achieved if 80% or greater of girls are vaccinated (*JAMA* article). However, the currently recommended three dose regimen of the quadrivalent vaccine is only being given to about 27% of girls

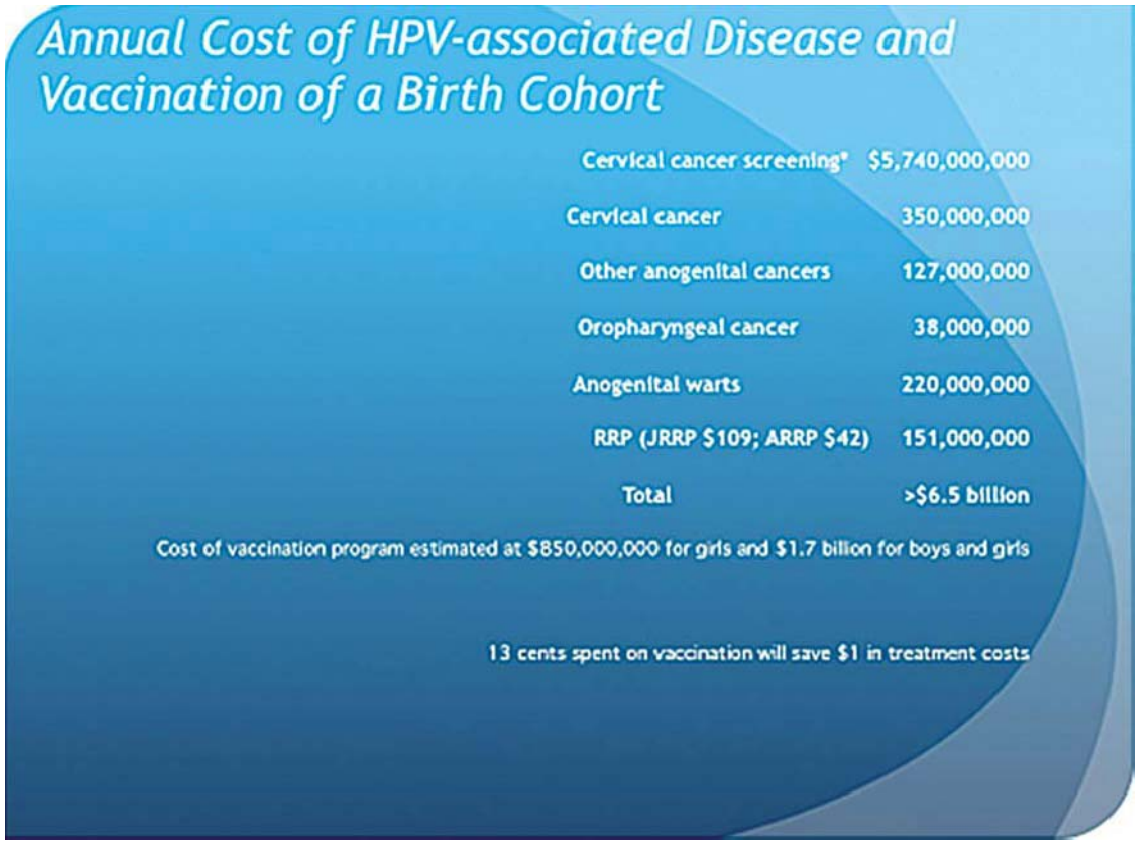


Figure 94.5 Cost of HPV preventative vaccination.

(44% are receiving at least one dose). With the added indication of the vaccine for prevention of anal cancer in boys, the FDA may consider in the near future changing its guidance from a permissive administration to a recommended vaccine. Given the rarity of RRP, multi-institutional studies will have to be continued for many years in order to observe any decrease in the incidence of RRP secondary to widespread vaccination.

It should be stressed that participation in national and regional protocols of adjuvant treatment modalities is essential for the scientific community to learn more about RRP. A national registry of patients with RRP has been formed through the cooperation of the ASPO and the CDC (8). The registry has tracked over 600 children at 22 sites with data on over 11,000 surgical procedures. It is hoped that the national registry will aid in the identification of patients suitable for enrollment in multi-institutional studies of adjuvant therapies and will help better define the risk factors for transmission of HPV and the cofactors that may determine the aggressiveness of RRP. Despite the progress that has been made in RRP research in the past decade, there are still numerous areas that require further investigation (Table 94.4).

A multicenter initiative organized through the RRP task force is currently ongoing to attempt to identify the host genes that govern susceptibility to RRP (98). It is hoped that by determining the host genes that govern susceptibility, we will enhance our understanding not only of RRP but also of host–viral interaction in general. Ultimately, this may lead to additional innovative treatment modalities.

TABLE 94.4 NEW HORIZONS UNDER INVESTIGATION FOR RRP

Role of interleukins, cytokines, and tumor necrosis factor
HPV preventative vaccination and the incidence of RRP
Multidrug chemotherapy for pulmonary cavitary disease
Role of cesarean section and gynecologic surgery during pregnancy in prevention of RRP
Effect of choice of surgical modality on RRP outcomes
Identification of host genes that govern susceptibility to RRP

RRP, recurrent respiratory papillomatosis; HPV, human papillomavirus

HIGHLIGHTS

- RRP is a frustrating, capricious disease with the potential for morbid consequences due to its involvement of the airway and the risk of malignant degeneration.
- No single modality of therapy has been consistently shown effective in eradicating RRP.
- The goals of surgical therapy are to maintain a safe airway with a serviceable voice while avoiding excessive scarring.
- Many adjuvant therapies have been investigated to supplement surgical therapy. Although several of these modalities have shown promise, no adjuvant therapy to date has cured RRP.
- Strides are being made in learning more about the natural history of the disease through the establishment of a registry of RRP patients at the CDC and in Canada and to help clinicians share information on and accurately follow their RRP patients over time.
- Future research is needed regarding prevention of transmission of HPV from mother to child. Specifically, the roles of cesarean section and gynecologic surgery during pregnancy need to be elucidated.
- Development of an HPV vaccine may ultimately prevent transmission of this disease eliminating it from the common practice of pediatric otolaryngologists in a similar fashion that acute epiglottitis has declined with the introduction of the HiB vaccine.
- Surgical therapy for RRP requires a skilled team consisting of otolaryngologists, anesthesia providers, and OR personnel working together in a facility properly equipped to manage difficult pediatric airways.
- Due to the recurrent nature of papilloma disease and the potential for airway obstruction, parental support and education can be invaluable to the safety of the child with RRP.

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95 Adenotonsillar Disease in Children

Anita Jeyakumar *Sean Miller* *Ron B. Mitchell*

Adenotonsillar disease usually presents in children with either recurrent throat infections or sleep-disordered breathing (SDB). Twenty years ago, recurrent tonsillitis was the most common indication for tonsillectomy. Presently, the most common indication for tonsillectomy and adenoidectomy (T&A) is SDB. This shift comes as a result of an evolving understanding of the impact of SDB on childhood health and well-being and a renewed focus on ensuring evidence-based indications for surgical intervention.

Untreated SDB can negatively impact a child's quality of life, behavior, and school performance (1–3). Similarly, children with recurrent throat infections have more bodily pain and poorer general health and physical functioning compared to healthy children (4). In the appropriately selected child, T&A can eliminate or improve the morbidity of SDB and recurrent tonsillitis.

This chapter reviews the current knowledge of the clinical presentation and management of adenotonsillar disease in children.

EPIDEMIOLOGY

In 2006, the most recent data available, 530,000 tonsillectomies were performed in children younger than 15 years of age in the United States (5). The only procedure performed with greater frequency was myringotomy with tube insertion, estimated at about 667,000 in the same year (5).

In the early and midportion of the 20th century, T&A was the most common surgical procedure in the United States, with the indication primarily being recurrent throat infections (6). Secondary to a public backlash and scrutiny of tonsillectomy for unscrupulous indications and unproven efficacy in the late 1970s and early 1980s, there was a decline by about 50% to 75% in the number of T&A procedures performed. However, since then, the frequency of T&A has almost doubled, with the most common indication at present being SDB as opposed to recurrent throat infections (6–8). The incidence of SDB is known to peak during early childhood and to affect 1% to 4% of children (9). In addition, older children and young adults are more frequently being treated for SDB with T&A (10,11).

EMBRYOLOGY

Tonsils are lymphoid organs that develop from components of surface epithelium enveloped by mesenchymal stroma and subsequently populated by lymphocytes and immunologic mediators. Adenoids, also known as the pharyngeal tonsils, develop in close approximation to mucous glands along the posterior surface of the nasopharynx.

The basic structure of the adenoids is characterized by multiple shallow sagittal folds and plicae covered by respiratory epithelium. Invaginations and ingrowth of endoderm followed by programmed cell death creates the characteristic crypts of tonsillar tissue. Lymphoid follicles develop around these crypts and adjacent glandular ducts. Crypts begin to develop at 3 months of gestation and are fully developed by the seventh month. Immunoglobulin populations have been found present in embryonal adenoid tissue. The adenoids will often increase in size until the sixth to seventh year of life at which point they begin to diminish and subsequently atrophy by early puberty. The opening of the Eustachian tube is also variably lined by lymphoid tissue, the tubal tonsils (12).

The palatine tonsils derive from the endoderm of the ventral portion of the second pharyngeal pouch. This epithelium, in a similar manner to the adenoids, invaginates and branches within the surrounding mesenchyme and ultimately undergoes apoptosis to produce characteristic crypts. The capsule of the tonsil develops from a condensation of mesenchyme. Unlike the adenoids, the palatine tonsils are covered by squamous epithelium. Lymphocytes appear in the reticulum by the third month of gestation and become arranged as lymphatic nodules. Lymphocyte

proliferation and maturation then takes place within the surrounding mesenchyme. Definitive lymphoid organization around these crypts can be recognized by the final trimester of development (12).

The lingual tonsils develop along the posterior region of the base of tongue. This area is covered by mucous glands, which are subsequently infiltrated with lymphoid cells during the fifth month of development. Crypts of the lingual tonsils appear at birth and are more shallow and less complicated than their palatine counterparts (12).

Taken as a whole, the adenoids and tubal, palatine, and lingual tonsils form an anatomic arrangement, which is collectively known as Waldeyer ring (Fig. 95.1). The adenoids and tubal tonsils form the posterosuperior extent of the ring, the palatine tonsils provide the lateral portion, and the lingual tonsils at the base of the tongue provide the anteroinferior segment. The tissue of each portion has similar histologic appearance and function. Waldeyer ring serves as a component of the mucosa-associated lymphoid tissue for the upper aerodigestive tract. Table 95.1 summarized the distinctive properties of each component of Waldeyer ring.

The adenoid tissue lies at the superior aspect of the nasopharynx, extending laterally to the Eustachian tubes and the walls of the pharyngeal recess and lying in general approximation to the tubal tonsils, which may be present and surround the opening of the Eustachian tube. The blood supply of the adenoids is from the pharyngeal branch of the external carotid artery with some minor supply from the internal maxillary and facial arteries. Sensory innervation is provided by the glossopharyngeal and vagus nerves. The general shape of the adenoid tissue is that of a loosely defined pyramid with the adenoid apex pointed toward the nasal septum and base toward the posterior wall of the nasopharynx (12).

The palatine tonsils lie at the entrance to the oropharynx between the palatoglossus muscle, also known as the anterior pillar, and the palatopharyngeus muscle, or posterior pillar. The superior constrictor fascia serves as the lateral margin of the tonsillar fossa. The palatine tonsils are the only portion of Waldeyer ring with a discrete capsule and are the largest tonsils within the ring. The tonsillar capsule is a specialized portion of the pharyngobasilar fascia that covers the surface of the tonsil and extends into it to form septa that conduct the nerves and vessels. This capsule adheres to the surrounding fascia by loose connective tissue, forming a relatively avascular plane which is taken advantage of during tonsillectomy. During times of hypertrophy, the palatine tonsils may extend in a more caudal direction to become nearly confluent with the base of tongue and lingual tonsil tissue. Immediately lateral to the superior constrictor is the glossopharyngeal nerve, which may be injured during tonsillectomy. In cadaveric studies (13), the lingual branch of the nerve was shown to be just lateral and in about a quarter of cases adherent to the tonsillar capsule itself. Pain and dysgeusia are potential sequelae from injury to this nerve.

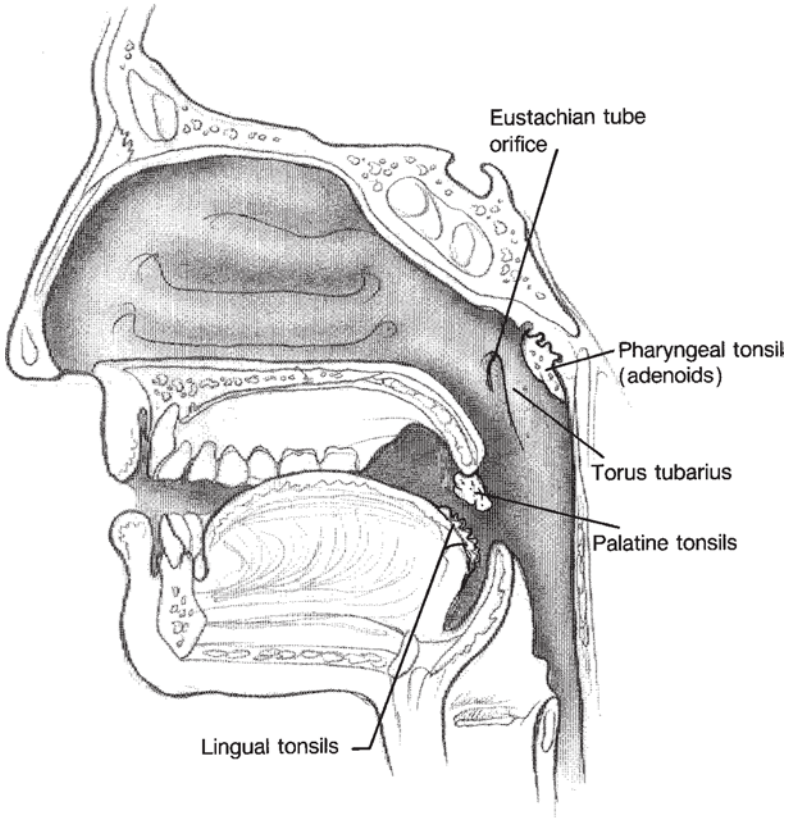


Figure 95.1 Lateral view of Waldeyer ring.

TABLE 95.1 COMPONENTS AND PROPERTIES OF WALDEYER RING

Type	Location	Capsule	Epithelium	Crypts
Adenoid	Superior aspect of nasopharynx	Incomplete	Predominantly: Ciliated pseudostratified columnar	Minimal
Tubal tonsil	Lateral aspect of nasopharynx, at Eustachian tube	None	Ciliated pseudostratified columnar	Minimal
Palatine tonsil	Lateral aspect of oropharynx between palatoglossus and palatopharyngeus	Incomplete	Nonkeratinized stratified squamous epithelium	Long, Branched
Lingual tonsil	Posterior to sulcus terminalis of the tongue	Incomplete	Nonkeratinized stratified squamous epithelium	Long, Unbranched

The blood supply to the palatine tonsils is variable, but in general, they are supplied by several branches of the external carotid artery: ascending pharyngeal, ascending palatine, and branches of the lingual and facial arteries. The blood supply enters from the lower portion of the palatine tonsil pole. The internal carotid artery (ICA) lies approximately 2 to 2.5 cm deep and posterolateral to the palatine tonsil; however, case reports (14) exist of aberrant ICA courses which come within 1 cm of the inferior pole. The ICA may have a tortuous and convoluted course of which the surgeon must be cognizant. Venous drainage is by way of a peritonsillar venous plexus, which surrounds the capsule and drains into the lingual and pharyngeal veins (12).

The lymphatic drainage of the tonsils is primarily to the superior deep cervical and jugular lymph nodes, which may become tender and inflamed during times of infection. The sensory innervation is from the glossopharyngeal nerve and some branches of the lesser palatine nerve via the sphenopalatine ganglion.

The histologic structure of the tonsils is closely related to its function as an immunologic organ. The epithelium of the crypt system acts as the immune system access route for inhaled and ingested antigens. These crypts are lined by a system of antigen-presenting cells that deliver the antigen to the immunologically active lymphoid cells in the tonsillar stroma.

IMMUNOPHYSIOLOGY

The tonsils and adenoids play an integral role in host defense, local immunity, and immune surveillance against invading antigens of the aerodigestive tract. Because the tonsils and adenoids do not have afferent lymphatic channels like other secondary lymph tissues, they are fed by surface epithelia. The aforementioned crypts serve to increase the surface area and effectively trap foreign material, both ingested and inhaled. These crypts are surrounded by numerous aggregates of cellular mediators of the immunologic system. Aggregates of B lymphocytes with more sparsely intervening zones of T lymphocytes and a diverse population of antigen presenting cells (macrophages, B cells, dendritic cells) are found in abundance within the subepithelial tissue of the tonsils (15).

These tissues survey the locally presented antigenic stimuli, destroy them, and generate effector and memory lymphocytes to be disseminated to other mucosal sites. They serve as an inductive site for local and distant antibody responses and generate immunologic memory independent of the systemic immune system. This function is most active during childhood and declines with age (16,17).

Microscopically, the adenoids have three types of surface epithelium: ciliated pseudostratified columnar, stratified squamous, and transitional epithelium. Chronically infected adenoids tend to have a predominance of squamous epithelium. One study demonstrated a significant transition trend to squamous metaplasia in chronically affected adenoid tissue (18).

Given the role in immunologic surveillance, some have questioned the impact of T&A on immunologic integrity. The results of several studies indicate that such interventions do not compromise the immune functions of children. The immunity of children after T&A has been shown to recover compared to their preoperative immune status, and to be similar to their age-matched healthy controls when the surgery is performed in young children and in late adolescence (19). Other studies have concluded that the effect of removal is essentially "clinically insignificant" and argue that no increase in the frequency of immunomodulated diseases is to be expected (20).

CLINICAL PRESENTATION

Adenotonsillar disease is characterized by either infections involving the lymphoid tissue, or hypertrophy or a combination of both. The disease processes can, and often will, affect the adenoids, tonsils, or both. Less often, adenotonsillar disease can be neoplastic. Table 95.2 provides a broad overview of adenotonsillar disease.

Infections

Viruses

Viruses play an important role as initiators of mucosal inflammation, crypt obstruction, and ulceration leading to bacterial superinfection. The clinical presentation of viral tonsillopharyngitis is similar to that of bacterial infection, but often with less severe symptoms, including sore throat, odynophagia, otalgia, headache, and fever. There is often tonsillar erythema and enlargement with or without exudates. The implicated viruses are the same as those involved in a variety of upper respiratory illness: rhinovirus, coronavirus, adenovirus, herpes simplex virus, parainfluenza virus, Epstein-Barr virus, and cytomegalovirus (21).

Of special note is herpangina caused by coxsackievirus. Often affecting young children, this disease may present as small vesicles with erythematous bases that eventually ulcerate and are typically present on the anterior tonsillar pillars, palate, and posterior pharyngeal wall.

Acute infections with Epstein-Barr virus may present as tonsillopharyngitis with dramatic tonsillar hypertrophy, sore throat, fever, cervical and diffuse lymphadenopathy, palatal petechiae, and malaise (21). The diagnosis is confirmed on the basis of clinical presentation, greater than 10% atypical lymphocytes on a peripheral blood smear, and a positive monospot (heterophile antibody) test (22). Care should be taken to not inadvertently prescribe amoxicillin or ampicillin as the risk of morbilliform rashes can approach 95% with this treatment (22).

TABLE 95.2 DIFFERENTIAL OF ADENOTONSILLAR DISEASE

Infection and/or inflammation
- Adenoids
  - Acute adenoiditis
  - Recurrent acute adenoiditis
  - Chronic adenoiditis
- Tonsils
  - Acute tonsillitis
  - Recurrent acute tonsillitis
  - Chronic tonsillitis
  - Tonsillolithiasis

Obstruction
- Nasopharyngeal
- Oropharyngeal
- Nasopharyngeal and oropharyngeal

Neoplasm
- Benign
- Lymphoproliferative
- Lymphoid hyperplasia
- Malignancy

Bacteriology/Microbiology

Any discussion of adenotonsillar infectious disease has to include several important observations. First, most infections can be linked to the presence of beta-lactamase producing organisms that distort the normal aerodigestive bacterial milieu and can cause commensal organisms to become pathogenic. Second, infections are often polymicrobial in nature and often include anaerobic pathogens. Third, obstruction of tonsillar crypts can serve as a nidus for bacterial stasis and can further perpetuate a condition of chronic infection, suppuration, and fistulae (23).

Studies of the bacteriology of adenoid tissue obtained from pathologic postoperative specimens demonstrate the presence of several aerobic species: alpha- and gamma-hemolytic streptococci, *Haemophilus influenzae*, *Staphylococcus aureus*, group A beta-hemolytic streptococci (GABA), and *Moraxella catarrhalis*. Anaerobic species noted include members of *Peptostreptococcus*, *Prevotella*, and *Fusobacterium*. Similar findings have been confirmed in tonsil isolates as well (24,25). Due to these findings and the previously mentioned premises, one must conclude that surface cultures have limited utility for identifying the causative organism, especially in chronic inflammation.

Generally, most authors attribute 15% to 30% of bacterial cases of acute tonsillopharyngitis to GABA, with a varying contribution from other pathogens, including group C beta-hemolytic streptococci, *Neisseria gonorrhoeae*, *Corynebacterium diphtheria*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* (21). Studies have shown that the presence of tonsillopharyngeal exudate and anterior cervical lymphadenitis increase the likelihood that the infectious agent is group A streptococcus (26).

The chronicity of adenotonsillar disease may be attributed to multiple overlapping infections caused by different pathogens within fistula and purulent pockets of the tonsil parenchyma even in the absence of clinical symptoms (23).

Hypertrophy

Although we distinguish between hypertrophy and infectious clinical presentations, it is true that most adenotonsillar hypertrophy is a result of low grade or chronic infectious disease of the involved tissues. Studies support a bacterial etiology for tonsillar hypertrophy (27). Some authors have argued for an etiologic role for *H. influenzae* in the pathogenesis of tonsillar hypertrophy in children (28). Adenoid hyperplasia has been demonstrated to be directly proportional to the number of lymphocytes and the bacterial load of the tissue (28). For the purposes of

this discussion, we will consider hypertrophy as a separate clinical entity, one which does not present with the signs and symptoms of acute or chronic infection—erythema, tenderness, lymphadenopathy, or fever. In practice, many children may have components of both infectious and hyperplastic morbidity.

Adenoid hypertrophy is a common cause of nasal obstruction in children. It can present as chronic or recurrent nasal discharge, snoring, SDB, recurrent otitis media, or Eustachian tube dysfunction (18). Physical examination often elicits a history of mouth breathing, hyponasal voice, and the classic "adenoid facies," characterized by an incompetent lip seal, a narrow upper dental arch, increased anterior face height, a steep mandibular plane angle, and a retrognathic mandible. This development occurs as the result in the changes in head and tongue position and muscular balance secondary to the open mouth breathing that accompanies nasopharyngeal obstruction (29). Recent studies confirm that there are changes in facial growth and development among children with adenoid hypertrophy. These changes are characterized by increased total and inferior anterior heights of the face, as well as more anterior and inferior position of the hyoid bone (30).

Tonsillar hypertrophy can present with dysphagia, SDB at night with gasping for breath, voice changes, and dental malocclusion. Children may even provide a subjective experience of having difficulty "getting food down" or the sensation of oropharyngeal fullness.

The presentation of new onset unilateral tonsillar hypertrophy is most likely due to infection, but the differential should include malignancy. Sudden enlargement of Waldeyer ring should raise suspicion for lymphoma, but actual use of asymmetric hypertrophy without concomitant symptomatology is often of poor predictive value (31). Unusual infections such as atypical mycobacteria, actinomycosis, and lymphoproliferative disease in solid organ transplant children need to be considered with asymmetric enlargement.

CLINICAL EVALUATION

Adenoids

Obstructive adenoid hyperplasia is diagnosed by clinical evaluation. Mouth breathing, snoring, and hyponasal speech are common presenting complaints. Rhinorrhea, postnasal drip, and chronic cough are common and nonspecific findings. The aforementioned adenoid facies may be present. Assessment of hyponasality is accomplished by having the child repeat words that emphasize nasal emission, which are phonemes using the "m," "n," or "ng" sound, such as milkman or mickey mouse and comparing them to words that do not, such as baseball or phrases such as "patty ate apple pie" (32).

Differentiating acute and chronic infections from sinonasal disease can be challenging. Often, acute and chronic adenoiditis can be confused and misdiagnosed as "sinusitis." Most children under the age of 6 will have effective resolution of these symptoms with adenoidectomy (33). Parents should be made aware that if symptoms persist after adenoidectomy, further investigation and treatment of sinonasal disease may be necessary to fully address the appropriate etiology.

A thorough physical exam includes at a minimum anterior rhinoscopy, which is easily facilitated in the cooperative child, with the use of an otoscope and large ear speculum. This allows the clinician to distinguish possible sources of nasal obstruction within the anterior nasal cavity, such as turbinate hypertrophy, edematous mucosa, or foreign body and to differentiate these from sources within the nasopharynx.

Palatal evaluation should also be undertaken, to ascertain the presence of submucous clefting, bifid uvula, or history of nasal regurgitation. This diminishes the possible complication of postoperative velopharyngeal insufficiency. Children with neuromuscular and central nervous system problems are also at increased risk for velopharyngeal insufficiency following adenoidectomy (32,34).

Evaluation of the adenoids in an uncooperative child can be difficult and can be accomplished using lateral neck radiographs, although these are often superfluous compliments to physical exam and history. More recently, an increasing number of children have been evaluated using office nasopharyngoscopy. This technique allows for direct visualization without radiation exposure. Nasopharyngoscopy offers an excellent view of the adenoids and adjacent structures. Parikh et al. (35) have proposed a grading system for endoscopic examination of adenoid hypertrophy that is validated and user-friendly. Other methods such as video fluoroscopy have been shown to be effective at assessing adenoid size but are less commonly used and carry unnecessary radiation exposure (36).

Tonsils

Physical examination should be performed with the child's mouth open and the tongue on the floor of the mouth, within the oral cavity. A tongue depressor should be used to depress the tongue with gentle and firm pressure along the oral tongue. Gagging and tongue extrusion will cause the tonsils to medialize and can produce the appearance of false enlargement. Having the child say "aah" will allow assessment of palatal integrity and motion. Tonsillar size may be measured on a scale of 1 to 4 with 1 (0% to 25% airway obstruction), 2 (25% to 50% airway obstruction), 3 (50% to 75% airway obstruction), and 4 (75% to 100% airway obstruction) (37). By convention, this grading scale is denoted as 1+ to 4+ (Fig. 95.2). Tonsillar hypertrophy is usually defined as falling within the 3+ to 4+ range.

The otolaryngologist must be cognizant of signs of chronic disease, such as peritonsillar erythema, tender

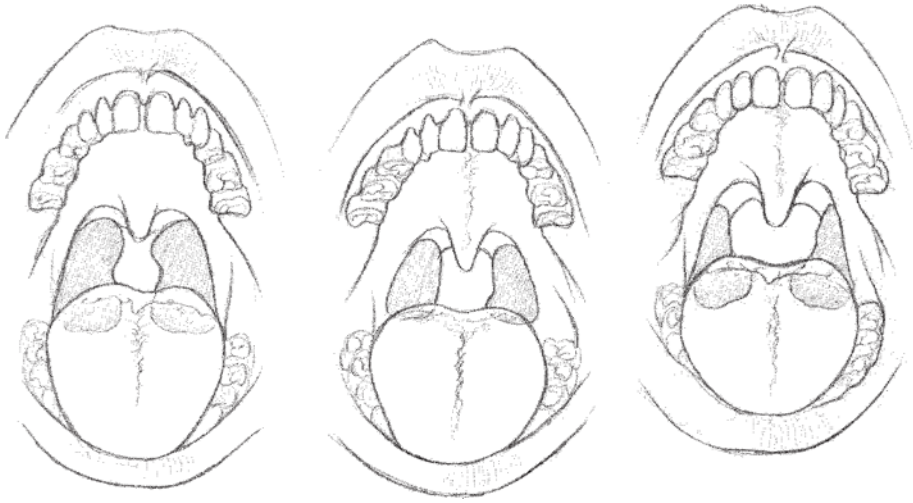


Figure 95. 2 Tonsil grading scale. (Adapted from Brodsky L, Poje C. Tonsillitis, tonsillectomy and adenoidectomy. In: Bailey BJ, ed. *Head and neck surgery-otolaryngology*, 4th ed., Vol. 84. Philadelphia, PA: Lippincott Williams & Wilkins, 2002:1185.).

cervical lymphadenopathy, tonsilloliths, smooth glistening tonsils, or excessively cryptic tonsils.

Of note, children at particular risk for the development of SDB secondary to tonsillar hypertrophy include those with craniofacial anomalies, Down syndrome, obesity, and neuromuscular or CNS abnormalities. These children may have symptoms not necessarily predicted by clinical presentation or tonsillar size.

MANAGEMENT

Infection/Inflammation

Management of a child with adenotonsillar disease depends on the underlying etiology and can include medical and surgical approaches. Acute infections need appropriate antibiotic therapy and symptom control. However, the majority of persistent adenotonsillar disease is considered a surgical problem.

Recurrent or chronic adenoiditis due to infection should be treated with an antimicrobial agent effective against beta-lactamase producing microorganisms. In terms of a durable response from other medical therapies, including inhaled nasal steroids for adenoidal hypertrophy, a Cochrane review (38) has shown only limited short-term benefit.

Acute tonsillitis should be managed with a rapid strep antigen screen and culture swab for definitive diagnosis. Rapid strep antigen screens have a reported sensitivity of 72% to 92%, specificity of 89% to 96%, and a positive predictive value of 68% to 89% (39). The most common bacterial pathogen in acute tonsillopharyngitis is GABA, with a recent meta-analysis attributing nearly 37% of all cases of acute pharyngitis to this pathogen (40). Fortunately, group A strep maintains almost universal sensitivity to penicillin. However, given the preponderance of beta-lactamase producing pathogens and their known influence in the development of tonsillar hypertrophy, the clinician may include a clavulanic acid scavenger as well to ensure appropriate antibiotic therapy and response.

Antibiotics have been demonstrated to offer modest benefits to the treatment of sore throat by shortening duration of symptoms by approximately 1 day (41). As previously discussed, a caveat to antibiotic therapy is the management of infectious mononucleosis. Children known to or suspected of having infectious mononucleosis should not be given amoxicillin or ampicillin containing antibiotics, in order to avoid the development of a rash.

When enlarged tonsils and adenoids cause an acute upper airway obstruction, a nasopharyngeal airway with intravenous steroids may be the most effective way to achieve immediate relief. When bacterial infection is suspected, antimicrobial therapy is initiated. Rarely is there an indication for immediate T&A in the acute setting.

Indications for tonsillectomy have been well discussed and examined throughout the otolaryngologic literature. Multiple studies and consensus statements from national panels have been undertaken to attempt to clarify an appropriate treatment algorithm for the clinician when addressing adenotonsillar disease and to advise appropriate interventions. In 2011, The American Academy of Otolaryngology–Head and Neck Surgery published a Clinical Practice Guidelines on the indications for tonsillectomy based on an extensive literature review and an expert panel that included both otolaryngologists and nonotolaryngologists. They made recommendations to address the two most common indications for tonsillectomy: recurrent tonsillitis and SDB (42), which are summarized at the end of the chapter.

In regards to recurrent tonsillitis, the recommendations endorse the more stringent Paradise criteria as a means for determining which children meet criteria to benefit from tonsillectomy (43). They endorse watchful waiting and close monitoring of episodes of tonsillitis for children who do not have a history of seven episodes in the past year or five episodes per year in the past 2 years or three episodes

TABLE 95.3 PARADISE CRITERIA FOR TONSILLECTOMY (43)

Criteria	Definition
Minimum frequency of sore throats	Seven or more episodes in the preceding year, OR Five or more episodes in each of the preceding 2 years, OR Three or more episodes in each of the preceding 3 years
Clinical features (sore throat plus the presence of one or more qualifiers)	Temperature > 38.3°C, OR Cervical lymphadenopathy (tender or size > 2 cm), OR Tonsillar exudate, OR Positive culture for group A β-hemolytic streptococcus
Treatement	Antibiotics administered in Conventional Doses
Documentation	Each episode and qualifying features noted in a clinical record, OR *If not fully documented*, subsequent observation of two episodes of throat infection and frequency and clinical features consistent with initial history (observation usually recommended for 12-month period)

per year in the past 3 years. This recommendation is made on a thorough examination of the available literature and while weighing the risk and benefits of intervention against watchful waiting. This is based on studies that show that a high proportion of children may experience resolution of symptoms without tonsillectomy (44).

The Paradise paper and subsequent studies demonstrate that the most benefit is achieved in children who are significantly and not just moderately affected by tonsillitis (Table 95.3) (43). A Cochrane review also notes a modest improvement in sore throat for less severely affected children (41). However, even those meeting the criteria should be advised of the modest anticipated benefits of tonsillectomy weighted against the natural history of resolution and the risk of surgical morbidity and complications. The panel suggested that there was not a clear preponderance of benefit over harm for tonsillectomy for the indication of tonsillitis.

In addition, the recommendations further delineate the conditions that should be met to be considered a discrete episode of tonsillitis and not merely pharyngitis or upper respiratory tract infection. The criteria include temperature greater than 38.3°C, cervical adenopathy, tonsillar exudates, or a positive test for GABA.

The recommendations do allow for other compelling indications for tonsillectomy for infectious etiology, including modifying factors such as antibiotic allergy or intolerance, PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis), or history of peritonsillar abscess (PTA). Histories of rheumatic heart disease or glomerulonephritis are additional compelling indications.

The decisions to pursue tonsillectomy for previously described indications including halitosis, chronic tonsillitis, malocclusion, cryptic tonsils, chronic GABA carriage, tonsillitis, and illness, which is impacting school attendance or performance, have not been vetted with sufficient rigor to be recommended as necessitating or benefiting from tonsillectomy based on the present literature. The panel allows for child and clinician discussion and evaluation of these relative indications. They recommend that intervention or watchful waiting be made on a case-by-case basis.

Sleep Disorders/Breathing

In contrast to these weaker indications, what has demonstrated clear benefit and health improvement is the use of tonsillectomy in the management of SDB and its associated morbidity.

SDB is characterized by recurrent partial or complete upper airway obstruction during sleep, resulting in disruption of normal ventilation and sleep patterns (45). Snoring neither indicates nor excludes SDB, but is known to affect many children. SDB is multifactorial disease, which develops in the presence of a combination of anatomy, neuromuscular tone, and adenotonsillar hypertrophy. Therefore, children with special considerations may have SDB in the absence of adenotonsillar hypertrophy. Additionally, it is known that tonsil size does not correlate to SDB (46).

Hypertrophy of the adenoids, tonsils, or both can obstruct the upper airway and result in SDB, alveolar hypoventilation and cor pulmonale, and these conditions respond well to T&A (47). In addition, SDB is known to increase the risk for hyperactivity and symptoms of attention deficit hyperactivity disorder (ADHD) (48,49). Children with SDB may have enuresis (50), behavior problems, poor school performance, reduced quality of life, and growth problems. It is important to note that the severity of SDB does not correlate with the severity of behavioral or quality of life scores.

Although polysomnography is the "gold standard" for diagnosing SDB in children, it is unnecessary in every child. For healthy children with the common presentation

of SDB: somnolence, behavioral problems, poor cognitive performance, nocturnal enuresis, and a physical exam consistent with adenotonsillar hypertrophy, with or without witnessed apneas, it is reasonable to proceed with T&A without prior polysomnogram. There is a 25% to 75% success rate in predicting obstructive sleep apnea clinically, and this number is not improved with the use of questionnaires or nocturnal home video recordings (51). In most instances, preoperative polysomnography is only necessary when the child has medical comorbidities that make them a poor candidate for elective tonsillectomy, age less than 3 years, absence of adenotonsillar hypertrophy, or physical exam findings that are not consistent with airway obstruction (52).

SDB may persist or recur after tonsillectomy and may require other interventions, including the use of continuous positive airway pressure. Parents must be made aware of the limitations and possible outcomes prior to surgical intervention.

In cases of unilateral tonsillar hyperplasia, chronic bacterial infection or infection with atypical pathogens such as actinomycoses or fungi is implicated. Often, asymmetry is explained by asymmetric location within the tonsillar fossa. Tonsillar asymmetry in isolation is not an indication for tonsillectomy (53). Tonsillar asymmetry in the absence of other associated symptoms of malignancy may be most appropriately managed by a period of watchful waiting (31). If there is clinical suspicion of lymphoma, the surgeon should consult preoperatively with pathologist or oncologist to determine the appropriate medium in which to transmit the surgical specimen.

Careful medical history should be taken with specific reference to any bleeding history in the child or family or the use of medication that may lead to increased bleeding. Studies have shown that routine use of coagulation studies is of little utility and is of little prognostic significance for predicting posttonsillectomy hemorrhage, even in children with history of mild bleeding episodes (54). Some authors have advocated for the use of coagulation studies for children presenting with posttonsillectomy hemorrhage in order to identify occult coagulopathy, although a cost–benefit analysis has not been performed (55).

SURGICAL TECHNIQUES

Tonsillectomy

The earliest description of tonsillectomy is credited to Cornelius Celsus, a Roman encyclopedist, around 30 AD. The procedure has been practiced and improved upon tirelessly throughout the intervening millennia. Surgical techniques have evolved considerably to include instruments such as knives, fingers, guillotines, wires, and strings. However, despite the evolution of the techniques and its near ubiquitous use as a medical therapy, physicians have been unable to eliminate the incumbent morbidity and mortality of this common procedure. Over the last two decades, in order to reduce some of the morbidity and expedite recovery time, clinicians have expressed renewed interest and research in different surgical approaches and technology for tonsillectomy.

The complete removal of the tonsil and its capsule had its origin in the early 20th century in the United States (56). Complete removal of the tonsil, however, leaves the musculature of the pharynx exposed to heal by secondary intention, which is thought to be the source of much of the morbidity of the procedure. This aspect of this common surgical procedure, namely healing, by secondary intention is unique and not routinely practiced in nearly any other surgical location within the body.

Since 1980, electrocautery has become the instrument of choice for tonsillectomy due to its familiarity to surgeons, ease of use, and limited intraoperative blood loss. According to the latest survey of members of the American Academy of Otolaryngology and the American Society of Pediatric Otolaryngology, electrocautery is the preferred method for tonsillectomy by 55% of otolaryngologists, coblation tonsillectomy by 20% to 25%, cold steel techniques by 10%, and other techniques including microdebrider partial tonsillotomy in about 10% (57). Other techniques include the use of laser, microscopic bipolar cautery, temperature radiofrequency reduction, and ultrasonic scalpel.

Recently, there has been increasing interest in performing a partial tonsillectomy, or tonsillotomy, to maintain the tonsillar capsule and reduce postoperative pain and bleeding. Most of the literature on tonsillotomy has been published from European centers (58). Large case series have shown that tonsillar regrowth occurs in about 0.5% to 6% of children with a smaller percentage requiring completion tonsillectomy. The operation takes several minutes longer than electrocautery tonsillectomy and the intraoperative blood loss is marginally greater. The role of intracapsular techniques for managing children with recurrent tonsillitis is still unproven (43,59,60).

All methods include an identification of tonsil boundaries, preservation of normal anatomic architecture, and observance of meticulous hemostasis. The surgeon must be aware at all times of the possibility of cautery injury, which can lead to devastating burns of the oral commissure, skin, or ignition of inhalational anesthetics.

Adenoidectomy

Adenoidectomy techniques in the past have employed the use of adenoid curettes or adenotomes with hemostasis achieved with packing; topical hemostatic agents like bismuth, tannic acid, Neosynephrine, or oxymetazoline; or the use of suction electrocautery. Concerns and complications with these techniques centered on excessive bleeding, difficulty in teaching the technique to inexperienced surgeons, and the almost certainty of residual tissue around

the Eustachian tube and posterior choana. Suction Bovie cautery, microdebrider, and coblation are currently widely used for removal of adenoids and have been shown to be effective, efficient, and associated with better hemostasis (61). A known disadvantage of these techniques is the increased expense as compared to traditional methods.

OUTCOMES

Infections

With the exception of management of PTA, the benefit of tonsillectomy for infections continues to be contentious. Most clinical trials about this topic are biased because of poorly defined criteria, nonrandom child selection, exclusion of severely affected children, and reliance on caregivers for data collection. Two studies by van Staaij et al. (62) and Burton and Glasziou (44) suggested a statistically significant reduction in the frequency of infections in severely affected children, but a less substantial benefit in mildly affected children. Paradise et al. had strict inclusion criteria (Table 95.3), and showed that children randomized to two groups had little difference in sore throat symptoms after 3 years of follow-up (43). In fact, in a follow-up study by Paradise et al. (63) where they used less stringent criteria for tonsillectomy, they noted that there was no difference in sore throats for moderate to severe disease after 12 months of follow-up. Data from several studies were pooled in a Cochrane review that showed that children undergoing tonsillectomy experience 1.4 fewer episodes of sore throat in the first year versus the control group (after eliminating the postoperative throat pain) (44). In cases of moderate to severe preoperative sore throats, surgery was associated with 0.2 fewer episodes of sore throats in the postoperative period.

Approximately 30% of children with a PTA satisfy criteria for a tonsillectomy and approximately 10% will subsequently develop a second abscess. To avoid the associated morbidity, expense, and possible deep neck space infectious complications, a tonsillectomy is indicated for children experiencing their second PTA. The tonsillectomy is usually performed as a routine procedure after the PTA has resolved (64).

Sleep-Disordered Breathing

Pediatric SDB is associated with behavioral problems that include hyperactivity, aggression, anxiety, depression, and somatization (1). Mitchell and Kelly (1) reported a significant improvement after T&A for SDB in a high proportion of children with externalizing and internalizing behavioral problems. The improvement was dramatic; was maintained for up to 18 months after surgery; and was seen regardless of gender, age, ethnicity, parental education, or parental income. The degree and severity of behavioral problems in children with SDB as well as improvements after T&A were similar regardless of the severity of the sleep disorder (1).

Health care costs are higher in children with SDB. Tarasiuk et al. (21) compared health care costs in children with SDB who had a T&A to children with untreated SDB and to healthy controls. Children with SDB demonstrated a significantly higher rate of antibiotic use, more hospital visits, and an overall 215% elevation in health care usage. They reported that total health care costs were reduced by one-third in children with SDB following T&A (as opposed to the control or untreated group). The reduction in health care costs was a result of a reduction in outpatient and emergency room visits, hospitalizations, and pharmacy costs.

In a recent meta-analysis, Friedman corroborated a successful outcome for children with polysomnographic documentation of SDB with improvement in polysomnography scores for 66% of children and cure, defined as an apnea–hypopnea index of less than 1, in 60% of children (65). Obese and overweight children do not incur as significant improvement in their SDB as their normal-weight counterparts. Further management strategies may be indicated for successful treatment (66).

Quality of Life

Studies have demonstrated that SDB imparts a quality of life burden, which is similar to children afflicted by juvenile rheumatoid arthritis (47). Dramatic improvements in quality of life scores after T&A for SDB have been shown in a number of studies (1,67,68) and meta-analysis review (47). The improvements were seen both within 6 and 18 months after surgery. The dramatic improvements in quality of life occurred regardless of the severity of SDB. In a similar manner to findings in outcomes in SDB severity, obese children experience less dramatic improvement in quality of life following T&A as compared to nonobese counterparts (68).

Studies of quality of life show an improvement in children who undergo T&A for recurrent tonsillitis. However, studies to date have had significant limitations. Only two studies exclusively enrolled children (69,70), but neither study clearly defined recurrent tonsillitis, both lacked control groups and had low response rates with poor follow-up. Both studies were also limited by poor postoperative data collection. There is a definite need for clearly defined quality of life studies for infectious pathologies and tonsillectomy.

CONTRAINDICATIONS

Contraindications to T&A include coagulation abnormalities that should be addressed prior to surgery, and often require a multidisciplinary approach including hematology involvement and coordination (71). A child with a cleft palate and other craniofacial abnormalities may be predisposed to velopharyngeal insufficiency. These children will rarely undergo complete adenoidectomy. Children with

acute illnesses that might impair the ability to maintain adequate postoperative hydration or safely undergo general anesthesia should defer elective surgery.

COMPLICATIONS

Although lightly considered by the general public and many within the medical profession, tonsillectomy is a major surgical procedure that has the potential for hospitalization, anesthesia risks, prolonged postoperative pain, and ongoing health care costs. The most common major complication after surgery is postoperative hemorrhage. Hemorrhage can be primary (within 24 hours of surgery) or secondary (more than 24 hours after surgery). The incidence of primary hemorrhage ranges from 0.2% to 2.2%, while the incidence of secondary hemorrhage ranges from 0.1% to 3% (72). The management of postoperative hemorrhage may include another operation to control the bleeding or readmission for observation.

In a recent review of a large population (17,000) experiencing posttonsillectomy hemorrhage in Wales, risk factors identified included child age greater than 12, male sex, and surgical techniques (73). The risk for secondary hemorrhage was greater for techniques involving heat, with coblation experiencing a nearly 13-fold increased risk. This finding was in accord with other large studies, which demonstrated the superiority of cold technique in reducing secondary hemorrhage (74). A previous review of nearly 16,000 children in Germany, including both children and adults, identified male sex, infectious mononucleosis, and a history of recurrent tonsillitis as risk factors for hemorrhage (72).

Other complications of T&A include postoperative dehydration secondary to pain, nausea, vomiting, otalgia, postoperative pulmonary edema, nasopharyngeal stenosis, velopharyngeal insufficiency, and intraoperative complications (trauma to teeth, larynx, pharynx, soft palate, laryngospasm, aspiration, endotracheal tube fire, cardiac arrest, lip burn, eye injury, mandible dislocation, or fracture). Clearly, complications are more common in children with other comorbidities such as craniofacial disorders, heart disease, bleeding disorders, and children younger than 3 years (75–77). It is estimated about 1.3% of children have a delayed discharge from the hospital immediately postoperatively, and up to 3.9% children have a secondary complication requiring readmission.

Airway complications are a major cause of medical malpractice after tonsillectomy (78). A recent study identified children with respiratory complications following T&A. Complications ranged from oxygen desaturation requiring supplementation to pulmonary edema. The study found that predictors of postoperative complication could be surmised from preoperative polysomnography and included apnea–hypopnea index, hypopnea index, body mass index, and oxygen saturation nadir (79). Although most children will not have this data available, the clinician is wise to be aware of potential adverse predictors and to tailor postoperative care, including admission for observation in high-risk children, accordingly. In addition, children experiencing recalcitrant postoperative emesis, children with craniofacial syndromes, those who live a great distance from the hospital and those with other serious medical comorbidities, such as diabetes mellitus, seizure disorders, and sickle cell disease, are better served by postoperative admission for observation.

Rare complications of surgery have been reported, including vascular injury, subcutaneous emphysema, jugular vein thrombosis, atlantoaxial subluxation, taste disorders, persistent neck pain, and death. Grisel syndrome is a rare complication following operative procedures or infections in the upper aerodigestive tract. The hypothesized pathogenesis is due to the higher flexibility of the ligaments during inflammation, which leads to increased laxity and subluxation between the axis and atlas of the cervical spine and skull base. When the inflammation heals, the child may experience neck fixation in a rotated position (80).

Mortality has been estimated to be 1 in 16,000 to 1 in 35,000, although these numbers were produced during the 1970s and there is an absence of more recent estimates (80). About one-third of mortality were related to bleeding. In many cases, mortality was associated with other medical comorbidities or impediments to proper health care access (81,82). Another review of posttonsillectomy hemorrhage noted that repeated episodes of hemorrhage could portend a higher risk for mortality (83).

Adenoidectomy has its own attendant risks. Postoperative hemorrhages, velopharyngeal insufficiency, persistent Eustachian tube dysfunction from iatrogenic manipulation, nasopharyngeal stenosis, c-spine subluxation from hyperextension during surgery are all known risks for children undergoing adenoidectomy. Special attention must be given to children with Down syndrome because of the risk of atlantoaxial subluxation. The most common complaint in children undergoing adenoidectomy is persistent postoperative malodorous breath, which may persist for up to 2 weeks. Although postoperative hemorrhage is not as common in children undergoing adenoidectomy alone, other rates of complications are encountered with frequency similar to that of tonsillectomy.

PERITONSILLAR ABSCESS

PTA is the most common deep space infection of the neck. It may be due to contiguous spread from the tonsil parenchyma or as secondary to infection of the minor salivary gland (Weber gland) located at the superior pole of the tonsil. The abscess itself will form in the potential space between the tonsil capsule and the muscles of the superior constrictor, the lateral extent of the tonsillar fossa. In some cases, the infection may violate this fascia and lead to a parapharyngeal abscess by direct extension.

Exact incidence has been estimated at 30 per 100,000 people per year. It occurs more often in children older than 12 years of age, but it has been reported at any age. The incidence of PTAs is coincident with that of streptococcal tonsillopharyngitis—early winter and spring. The classic presentation is that of a prolonged sore throat, which may sometimes improve but then remits. The child will present with the so-called hot potato muffled voice, fever, trismus, malaise, and dysphagia. Tender cervical lymphadenopathy and otalgia may also be present. Physical exam will reveal medial and inferior displacement of the involved tonsil, effacement of the tonsil, and uvular deviation away from the involved tonsil. The diagnosis is clinical. Some authors have advocated the use of intraoral ultrasound to aid in diagnosis, but most rely on physical exam alone. CT scan is the best choice for diagnosing suspected PTA in young uncooperative children (84). Children younger than 5 years who present with poor oral intake, high fever, drooling, and trismus should be suspected of having a PTA (85).

Treatment is incision and drainage. Some authors advocate that needle aspiration is the best initial treatment, with incision and drainage performed if needle aspiration fails (86). In a cooperative child of appropriate age, the procedure can be done at the bedside with a topical anesthetic. Even in a noncooperative child, studies have shown that intravenous sedation provided by emergency room staff may eliminate the need for surgical drainage in the operative room (87). In one series, children of ages 4 to 18 years were treated successfully in this manner without untold complication or adverse effects (88). If the child is able to tolerate Oral intake following the procedure, he or she may be discharged. Treatment should also include the use of intravenous hydration, and appropriate analgesia as well as antibiotic coverage for staphylococcal organisms.

Conversely, if available staffing for conscious sedation is not available or the decision is made to proceed with general anesthetic, immediate tonsillectomy appears to be a safe and effective surgical technique for the management of PTA and parapharyngeal abscess. One study demonstrated that it markedly reduced hospital stay (when performed early in the course of the disease) and duration of antibiotic therapy (89). Another study concluded that so-called quinsy tonsillectomy may be the treatment of choice for any child undergoing general anesthesia for treatment (84).

CONTROVERSIES

There continues to be controversy concerning the superior technique for tonsillectomy, one which minimizes hemorrhage, cost, and operative time. Randomized controlled trials and large prospective cohort studies demonstrated a higher risk of postoperative hemorrhage after hot tonsillectomy compared with cold dissection (90–92). In a systematic review of hot (monopolar electrosurgery) versus cold knife tonsillectomy, only 6 of 815 prospective trials met the necessary inclusion criteria and revealed that postoperative hemorrhage rates were not significantly different when comparing the two methods (93). A Cochrane review showed no significant difference in coblation versus electrocautery (73,94).

Antibiotics are commonly used in the routine, perioperative care of children undergoing tonsillectomy, despite convincing evidence of no beneficial impact on recovery (except for possibly reduced fever). In a review of this practice, there was no demonstrable impact on pain, return to normal activity, or the need for use of analgesics. The authors also note the adverse consequences of known increase in bacterial resistance with the use of antibiotics and risk of allergic reactions (95). The cessation of routine perioperative antibiotic use is recommended.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used infrequently for pain control based on unfounded concerns about increased postoperative hemorrhage, which are not supported by systematic reviews of randomized trials (96). A meta-analysis demonstrated an increased risk of posttonsillectomy hemorrhage with the use of aspirin after tonsillectomy but not for nonaspirin NSAIDs such as diclofenac and ibuprofen (97). Conversely, codeine is often used after tonsillectomy despite no benefit over acetaminophen in randomized controlled trials plus a known adverse event profile that includes nausea and vomiting, and genetic polymorphisms in codeine metabolism may eliminate any analgesic efficacy (98).

In a related consideration, a review of local anesthetic use in both adults and children undergoing tonsillectomy, either infiltrated submucosally or topically, pre- or postexcision offered no improvement in postoperative pain (99).

For several decades, evidence has accumulated that the administration of a single intraoperative dose of dexamethasone in children undergoing tonsillectomy results in decreased postoperative nausea and vomiting, a major source of morbidity (100). Although initial studies demonstrated an increased risk of hemorrhage (100), subsequent reviews have countered that finding (101). In addition, a Cochrane review demonstrated a more rapid advancement to full diet for children receiving dexamethasone (102). Therefore, when considering the balance of the literature, the most recent clinical practice guidelines endorsed the use of intravenous dexamethasone for children undergoing T&A.

CLINICAL PRACTICE GUIDELINES

In 2010, Clinical Practice Guidelines were published for tonsillectomy in children aged 1 to 18 without complicating comorbidities (including diabetes, cardiopulmonary disease, craniofacial disorders, congenital head and neck abnormalities, coagulopathies, or hemoglobinopathies). The intent was to guide clinicians into selecting children who would benefit from tonsillectomy and to optimize their perioperative care. Tables 95.4 and 95.5 are excerpts from the guidelines document summarizing some of the pertinent comments (102).

TABLE 95.4 SUMMARY STATEMENTS OF THE 2010 CLINICAL PRACTICE GUIDELINES (42)

Statement	Summary
1	Watchful waiting for recurrent throat infections if: • <7 episodes in the last year OR • <5 episodes in the last 2 years OR • <3 episodes in the last 3 years
2	Tonsillectomy for infections recommended for the following: • ≥7 episodes in the last year OR ≥ 5 episodes in the last 2 years OR ≥ 3 episodes in the last 3 years • WITH medical documentation of each sore throat, AND one or more of the following: ◦ Temperature >38.3°C ◦ Cervical Adenopathy ◦ Tonsillar Exudate ◦ Positive test for Group A β-hemolytic streptococcus
3	Tonsillectomy may be considered for the following children who do not meet criteria according to statement 2—children with: • Multiple antibiotics intolerance/allergy • PFAPA • History of PTA
4	In consideration for tonsillectomy for sleep disordered breathing, caregivers should be asked about comorbidities such as growth retardation, poor school performance, enuresis, and behavioral problems
5	In children with abnormal polysomnography and hypertrophic tonsils, tonsillectomy can provide a means to improve the health in the children
6	Sleep disordered breathing may persist after an T&A, requiring further management (see Table 95.5)
7	A single dose on intraoperative intravenous dexamethasone during tonsillectomy can significantly reduce postoperative nausea and vomiting
8	Children undergoing tonsillectomy do not need perioperative antibiotics
9	The clinician needs to advocate for pain management, and educate the guardians about the importance of assessing and managing pain
10	Clinicians should evaluate their rates of primary and secondary postoperative hemorrhage annually

TABLE 95.5 2010 CLINICAL PRACTICE GUIDELINES (42)

Tonsillectomy and sleep disordered breathing: counseling

1	Hypertrophic Tonsils may contribute to SDB in children
2	SDB is often multifactorial
3	Obesity plays a key role in SDB in some children
4	Polysomnography is considered the gold standard for the diagnosis of SDB. It is not necessary in all cases, and access may be limited by availability of a sleep laboratory or willingness of third party payers to cover the cost
5	Tonsillectomy is effective in the treatment of SDB in 60%–70% children with tonsillar hypertrophy
6	Tonsillectomy is effective in ONLY 10%–25% of obese children with SDB
7	Caregivers need to be counseled that tonsillectomy is not curative in all cases of SDB especially in children with obesity

NEOPLASIA

As stated in Table 95.2, neoplasia, while uncommon in children, is certainly a consideration in adults. In children, sudden rapid growth of adenotonsillar tissue, with persistent adenopathy should merit consideration of lymphoma. In adults, the tonsil is frequently a site for squamous cell carcinoma. Unusual presentation of adenotonsillar disease should get further evaluation, often with a biopsy and multidisciplinary work up. Further discussion is beyond the scope of this chapter.

CONCLUSIONS

Adenotonsillar disease and its management has enjoyed a long and, at times, contentious existence within the medical field and within otolaryngology. In the properly selected child, T&A can decrease the incidence of infection, correct or improve SDB and its sequelae, and improve quality of life. Although questions remain and controversies persist, this chapter provides a foundation and framework for approaching this critically important topic.

HIGHLIGHTS

- Adenotonsillar disease usually presents in children with either recurrent throat infections or SDB. Presently, the most common indication for T&A is SDB.
- The blood supply to the palatine tonsils is from branches of the external carotid artery: ascending pharyngeal, ascending palatine, and branches of the lingual and facial arteries.
- Approximately 30% of bacterial cases of acute tonsillopharyngitis are caused by GABA, with a varying contribution from other pathogens, including group C beta-hemolytic streptococci, *N. gonorrhoeae, C. diphtheria, C. pneumoniae,* and *M. pneumoniae.*
- Acute tonsillitis should be managed with a rapid strep antigen screen and culture swab for definitive diagnosis. Fortunately, group A strep maintains almost universal sensitivity to penicillin which is the first line treatment.
- Although polysomnography is the "gold standard" for diagnosing SDB in children, it is unnecessary in every child. For healthy children with the common presentation of SDB it is reasonable to proceed with T&A without prior PSG.
- The American Academy of Otolaryngology–Head and Neck Surgery published a Clinical Practice Guidelines on the indications for tonsillectomy based on an extensive literature review and an expert panel that included both otolaryngologists and nonotolaryngologists. They made recommendations to address the two most common indications for tonsillectomy: recurrent tonsillitis and SDB.
- Although lightly considered by the general public and many within the medical profession, tonsillectomy is a major surgical procedure that has the potential for hospitalization, anesthesia risks, prolonged postoperative pain, and ongoing health care costs. In the properly selected child, T&A can decrease the incidence of infection, correct or improve SDB and its sequelae, and improve quality of life.

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Congenital Anomalies of the Nose

96

John P. Bent *David E. Conrad*

Midline congenital nasal lesions are rare, occurring in one out of every 20,000 to 40,000 births (1). Whenever an infant presents with a midline nasal mass, the diagnostic considerations include nasal dermoid, glioma, and encephalocele. These congenital and relatively uncommon lesions share aberrant skull base development, namely, errors in formation of the anterior neuropore. Consequently, the nasal mass often maintains a central nervous system (CNS) connection. As a result, workup must proceed judiciously but promptly, because both reckless and delayed intervention carries risks.

Radiologic advances have tremendously facilitated the management of congenital nasal anomalies. Magnetic resonance imaging (MRI) and/or computed tomography (CT) allows detailed evaluation of the pathology and any associated defects at the skull base. As a result, surgical planning, including the potential role, if any, for the neurosurgeon can be carefully scripted. A variety of approaches gives the surgeon added flexibility, and despite the sensitive location of these defects, most affected children carry an excellent prognosis.

EMBRYOLOGY

To understand the intricacies of congenital midline nasal masses, one must comprehend the normal development of the anterior neuropore (primitive frontonasal region). The two important steps of this process are the formation of the neural tube from ectoderm and the subsequent migration of neural crest cells into mesenchyme to form the skull base and face (Fig. 96.1).

A midline neural groove appears along the dorsal surface of the embryo by the third week of gestation. Shortly thereafter, the ectodermal plate thickens, ultimately forming a neural tube. This precursor to the CNS fuses during the fourth week, with closure beginning in the midportion of the embryo before progressing both anteriorly and posteriorly. Neuropores at the caudal and cranial ends of the neurotube close last. The anterior neuropore, composed of a midline funnel-shaped dural diverticulum, forms at the optic recess of the sphenoid sinus, while the area immediately proximal to the anterior neuropore forms the frontal, nasal, and ethmoid structures.

As neural tube closure progresses, neural crest cells in the lateral portions of the neural tube migrate between the tube and the surface ectoderm into the mesenchyme that will eventually form bone and cartilage. The anterior neuropore is the most distal point of neural crest cell migration; the lack of neural crest cells and the relatively late tube closure predispose this region to developmental defects.

Once neural crest cells migrate into position, underlying mesenchyma organizes into skeletal structures, forming several important spaces (Fig. 96.2):

- Fonticulus nasofrontalis—the fontanelle between the inferior frontal and nasal bones
- Nasal capsule—the precursor to the nasal cartilages and septum, which is continuous with the ethmoid labyrinth
- Prenasal space—between the nasal bones and nasal capsule
- Foramen cecum—the region between the ethmoid and frontal bones, which connects with the prenasal space and the location where the cribriform plate condenses

Under normal conditions, these spaces involute during fetal growth.

Whether congenital anomalies of the nose are related to genetic or environmental factors, or both, remains unknown. Laboratory research suggests that extracellular proteins guide the adhesive and migration properties of the neural crest cells (1). Failure of normal neural crest cell embryology may lead to one of the following congenital lesions.

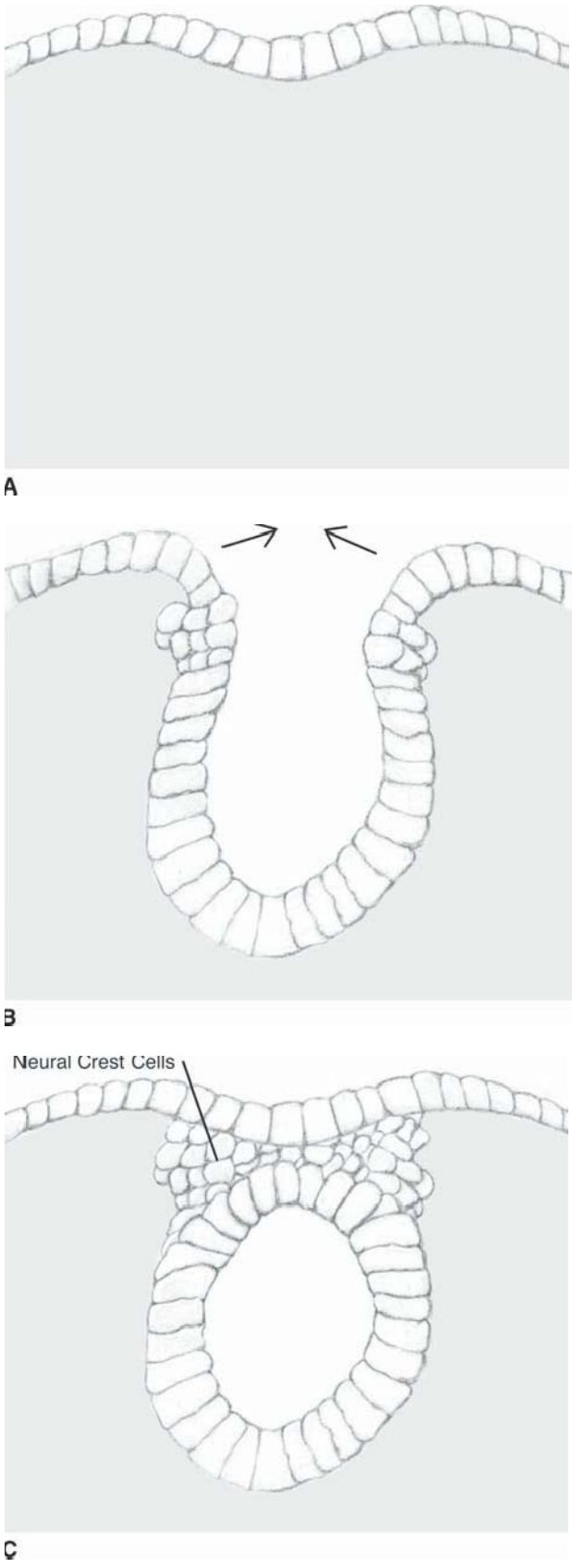


Figure 96.1 Neural tube formation. Dorsal view of embryo with developing neural groove. Note closure in midline first. **A:** Neural groove. **B:** Deepening groove. **C:** Neural tube separated from surface ectoderm; neural crest cells interspersed between surface and neural tube.

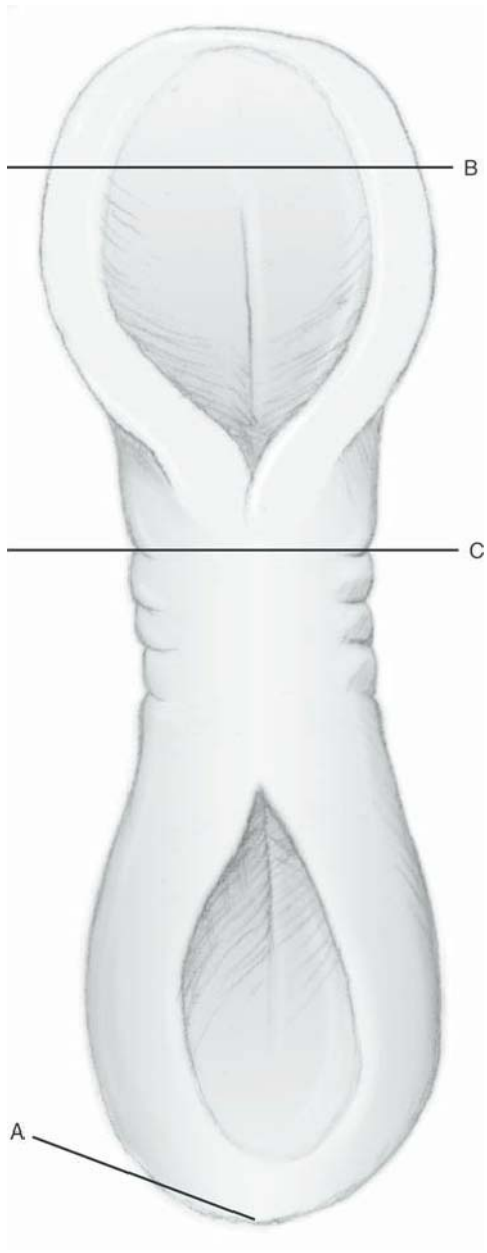


Figure 96.1 (*Continued*) A. Posterior neuropore, B. Anterior neuropore, C. Surface ectoderm covering neural groove.

Dermoid

Surface ectoderm and neuroectoderm lie in direct contact before mesenchymal infiltration, particularly at the junction of bone plates. If developing skin adheres to fibrous tissues of the nasal capsule in the prenasal space or fonticulus, it may be drawn posteriorly and superiorly, forming a squamous epithelial lined tract toward the anterior skull base. Animal models suggest that the failure of separation between neuroectoderm and surface ectoderm may involve insufficient apoptotic cell death during the ventrodorsal patterning of the neural tube (2). Aberrant dural attachments could allow a tract connecting skin to the dura via the foramen cecum, surrounded by condensing bone

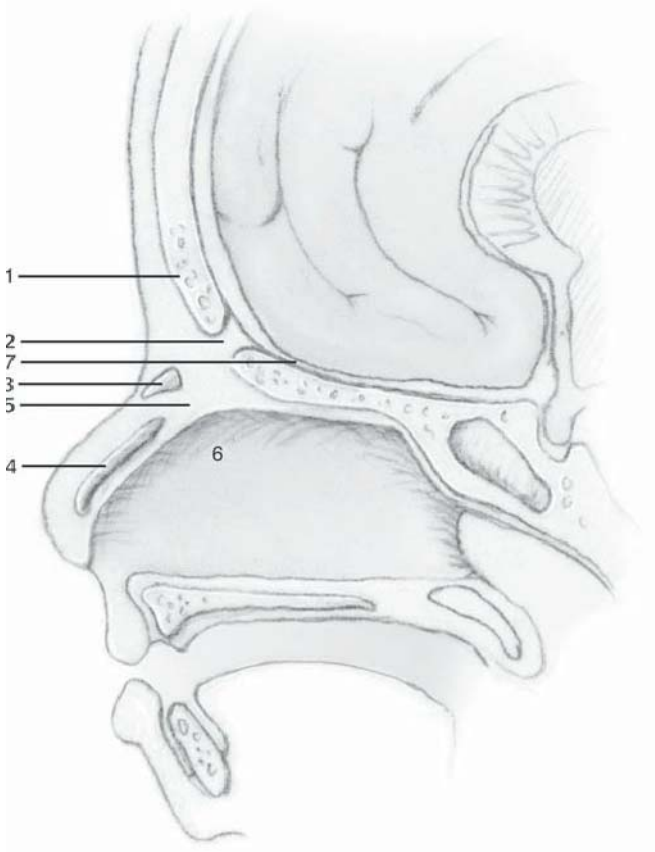


Figure 96.2 Normal embryonic anatomy of nose and anterior skull base. *1*, frontal cartilage; *2*, fonticulus nasofrontalis; *3*, nasal bone; *4*, nasal cartilage; *5*, prenasal space; *6*, nasal capsule; *7*, dura.

(Fig. 96.3). Once the tract forms, dermoid cysts may appear anywhere along the pathway. Alternative simplistic theories have suggested that dura becomes entrapped in the fetal septum, or pockets of epithelium become entrapped below the fusing ectoderm (3).

Glioma

Several theories also exist as to glioma embryogenesis. According to Gorenstein et al. (4), gliomas most likely form when cranial suture closure isolates brain tissue from the intracranial cavity. The fibrous stalk some gliomas maintain to the CNS supports this theory and suggests a developmental relationship between gliomas and encephaloceles. Less prominent theories of glioma formation include a nidus of ectopic neuroepithelia or an outgrowth of olfactory tissue through the cribriform plate (1).

Encephalocele

Like gliomas, encephaloceles probably originate from faulty closure of the skull; unlike gliomas, with encephaloceles the bone never closes, leaving a persistent intracranial–extracranial defect. As with dermoids and gliomas, the precise cause of this dysmorphism remains elusive. Speculation holds that anywhere along the line of neural tube closure, there may be a barrier or delay in neural crest cell migration. Subsequently, mesenchyme forms improperly, leaving the skull base open and allowing herniation of neural tissue (5). Because the midline is the furthest point of migration, this region naturally comprises the site of such defects. Figure 96.4 depicts the parallel between glioma and encephalocele formation.

CLINICAL AND PATHOLOGIC FEATURES

Dermoids contain both mesodermal and ectodermal components and, consequently, may have hair follicles, sweat gland, smooth muscle, and sebaceous tissue, in addition to their squamous epithelial lining. Nasal dermoid cysts represent approximately 8% to 10% of head and neck dermoids and 1% of all dermoids (6). Most dermoids have a sinus tract exiting via a minute skin opening along the nasal midline (Fig. 96.5). This feature distinguishes it from epidermal inclusion cysts, which also lack mesodermal components. The tract usually contains one, but occasionally

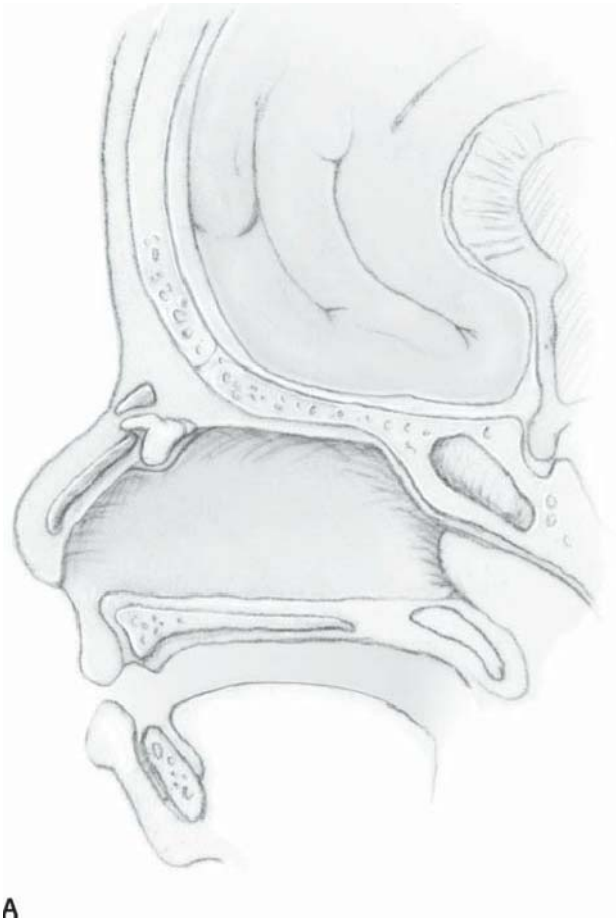


Figure 96.3 Congenital nasal dermoid development. **A:** Normal closure of fonticulus, foramen cecum, with a sinus tract extending to the beginning of the prenasal space.

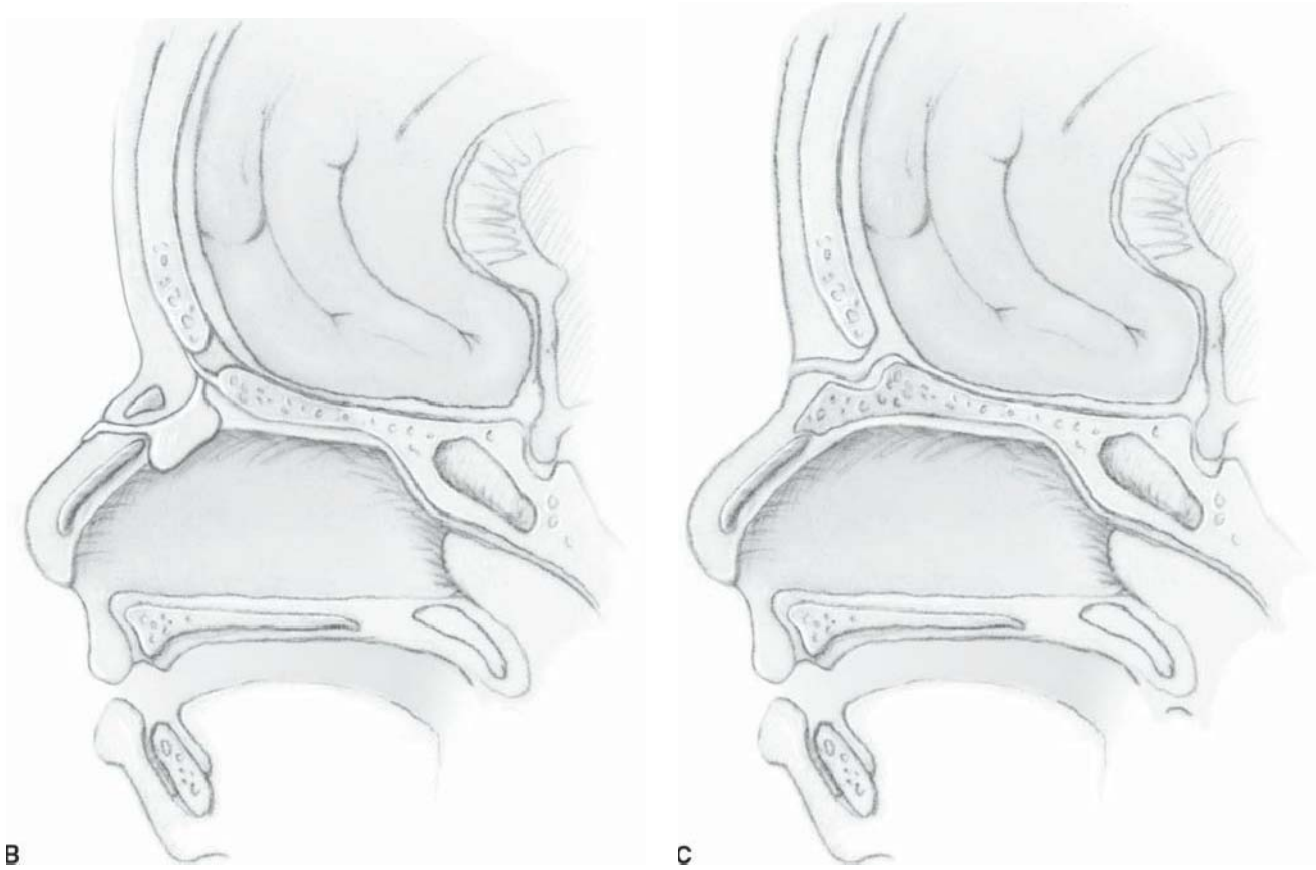


Figure 96.3 (*Continued*) **B:** Patent foramen cecum with fistula from the nasal dorsum through prenasal space. **C:** Patent fonticulus and sinus tract to glabellar skin.

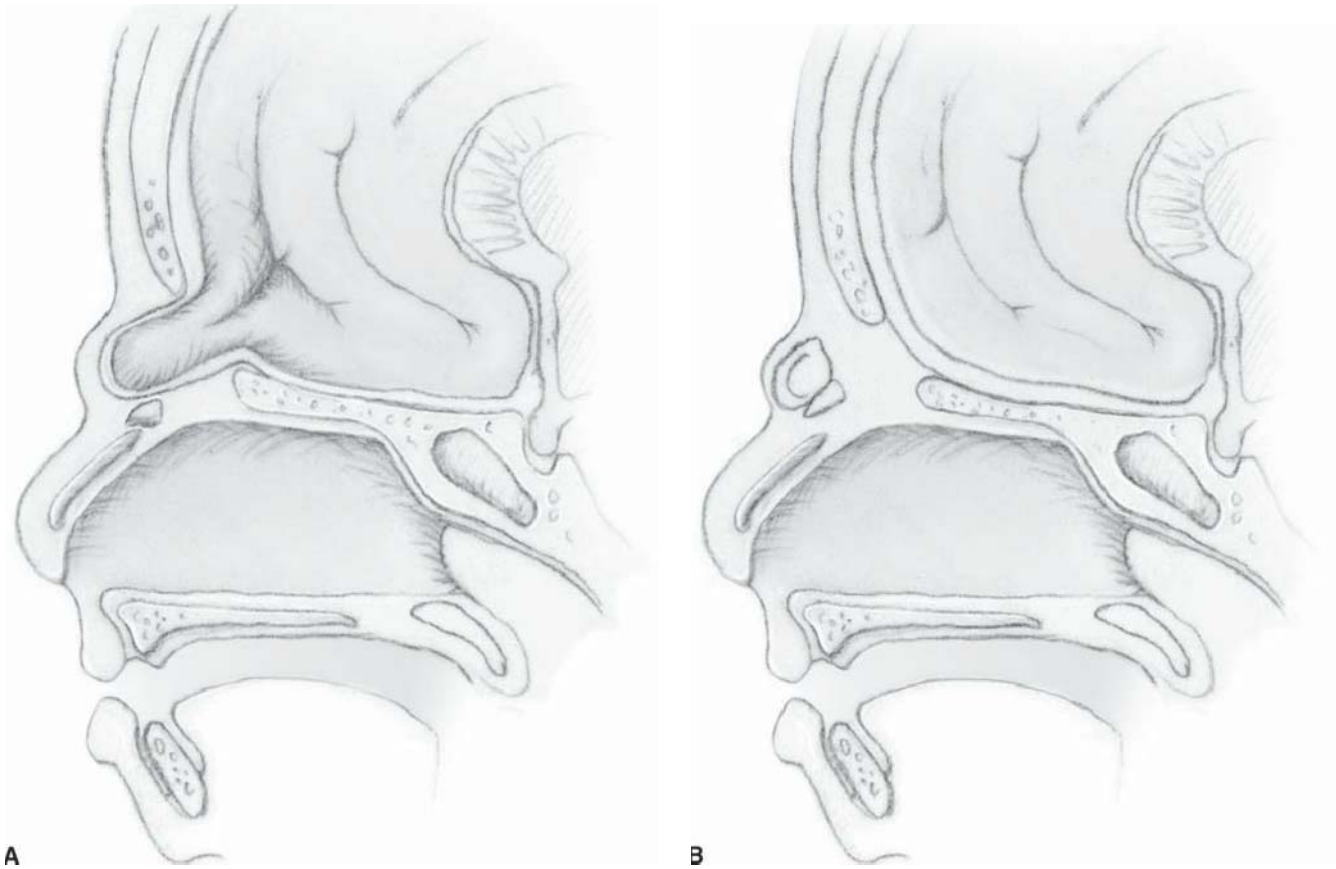


Figure 96.4 Glioma and congenital encephalocele development. **A:** Herniation of dura and glial tissue (encephalocele) through fonticulus. **B:** Intranasal glioma with connection to CNS.

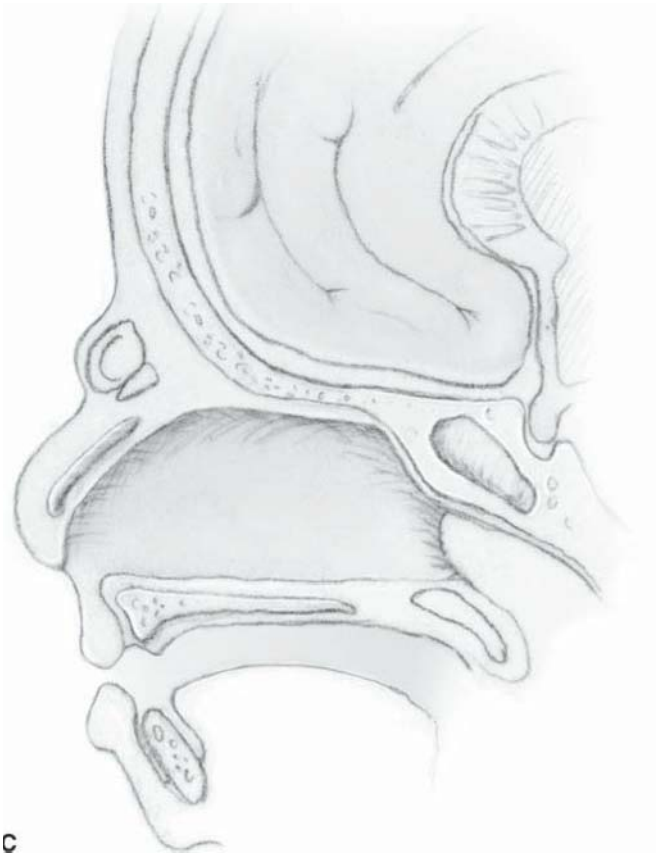


Figure 96.4 (*Continued*) **C:** Closure of bones to form glioma.

there are multiple cysts along its pathway. It may manifest cutaneously anywhere from the glabella to the columella but most typically exits over the dorsum at the osteocartilaginous junction. Craniofacial abnormalities, such as craniosynostosis, cleft lip and palate, and hemifacial microsomia, may also be present (7). Presenting symptoms may include a localized mass lesion over the nasal dorsum, erythema and tenderness, sebaceous or purulent discharge, or simply parental anxiety about cosmesis. Approximately 50% of patients will have a widened nasal dorsum and hypertelorism (8). The sinus tract may be short and the cyst small, but it may extend to the intracranial cavity through the foramen cecum. Cases with an intracranial connection pose an increased risk of meningitis.

Gliomas usually present early in life with symptoms of nasal obstruction. They have a 6:3:1 ratio of extranasal:intranasal:combined lesions (4). The masses are usually not midline, associated with a sinus tract, compressible, expandable with crying, or transilluminating. These qualities help distinguish gliomas from dermoid cysts and encephaloceles. Approximately 15% maintain a connection with dura; this phenomenon applies more to intranasal than extranasal gliomas (9). Such connections will occur through either the foramen cecum or the nasofrontal suture and place affected children at risk for developing meningitis.



Figure 96.5 Sinus tract opening on nasal dorsum.

Encephaloceles contain both meningeal and brain tissue. They tend to be more medially based than gliomas. For purposes of this discussion, meningoceles, which contain meningeal but not glial tissue, are also referred to as encephaloceles. Unlike gliomas, encephaloceles always occur through a significant skull base defect, and as a result, they carry a graver prognosis. Furthermore, these patients are more likely to have associated syndromic features or comorbidities such as Beckwith-Wiedemann syndrome (10). Encephaloceles are classified as occipital, basal, or sincipital, based on the location of the skull base defect. Occipital encephaloceles represent 75% of these defects but are not covered herein due to their lack of proximity to the nose.

Sincipital encephaloceles, also known as frontoethmoidal encephaloceles, comprise 15% of encephaloceles. They occur between the frontal and ethmoid bones at the foramen cecum, immediately anterior to the cribriform plate. Sincipital encephaloceles may be further subdivided as follows (Fig. 96.6):

1. Nasofrontal—These defects are located at the glabella between the nasal and frontal bones (Fig. 96.7). Commonly, these patients have lateral displacement of the medial orbital walls and inferior displacement of the nose.
2. Nasoethmoidal—The sac exits through the foramen cecum, passing under the nasal bones and above the upper lateral cartilages, creating a lateral nasal mass. Consequently, the upper lateral cartilages and septum are distorted and displaced inferiorly.
3. Nasoorbital—Like the nasoethmoidal encephalocele, the nasoorbital encephalocele transverses the foramen cecum before extending into the orbit via a defect in its medial wall.

These lesions are usually pulsatile and classically show expansion with crying, straining, or jugular vein compression (Furstenberg sign).

Basal encephaloceles generally manifest no craniofacial disfigurement, except occasional widening of the nasal root or hypertelorism. They are less common than

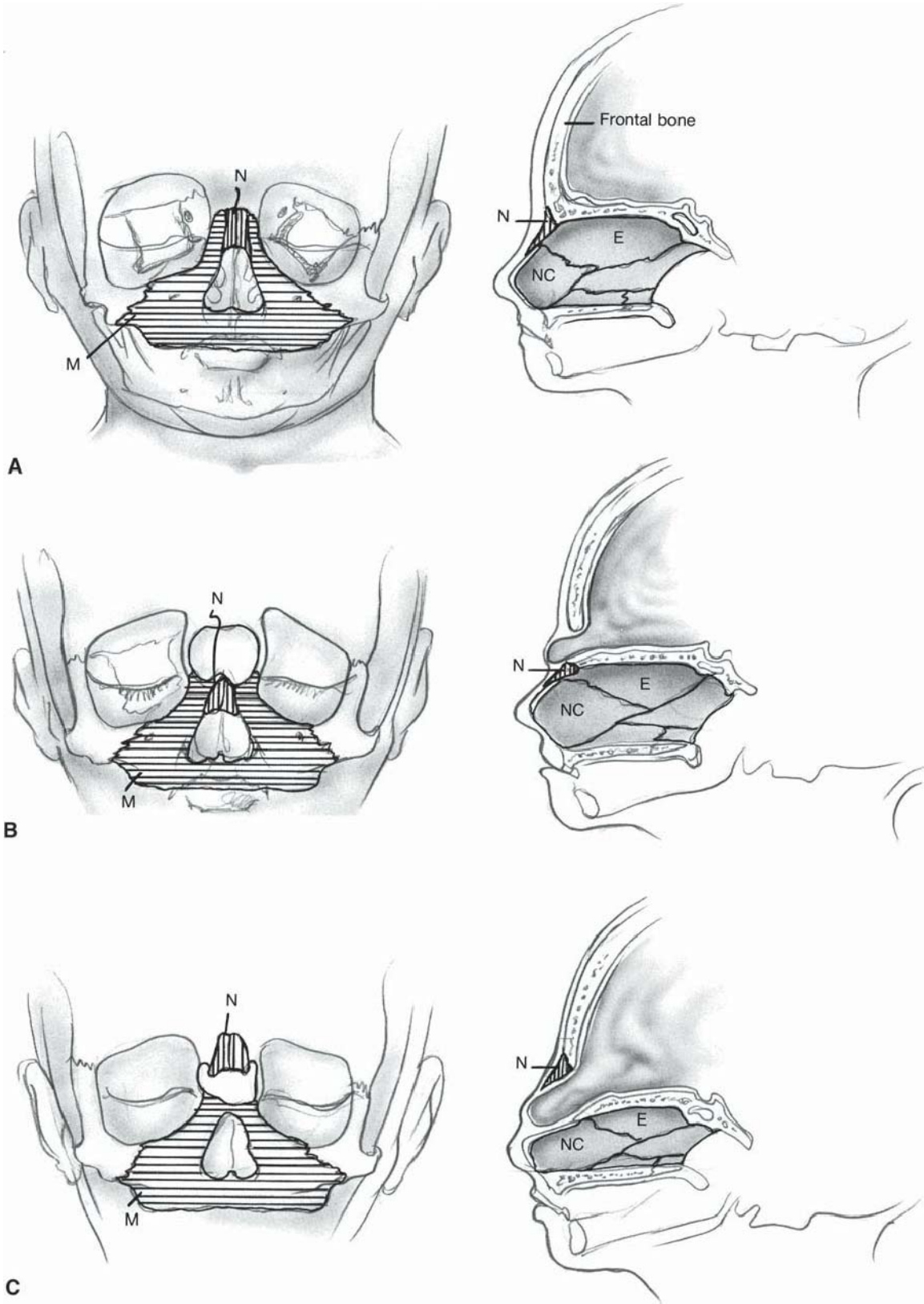


Figure 96.6 Sincipital encephaloceles. E, ethmoid bone; M, maxilla; N, nasal bones; NC, nasal cartilage. **A:** Normal. **B:** Nasofrontal encephalocele, with bony defect superior to nasal bones. **C:** Nasoethmoidal encephalocele, with bony defect inferior to nasal bones.



Figure 96.7 Sagittal MRI of nasofrontal encephalocele.

sincipital or occipital encephaloceles; four subtypes have been described (11):

1. Transethmoidal—The most common variant extends medial to the superior turbinate via a cribriform plate defect.
2. Sphenoethmoidal—The sac protrudes into the nasopharynx via a defect between the posterior ethmoid and the anterior sphenoid wall.
3. Transsphenoidal—The sac also presents in the nasopharynx, exiting intracranially through an open craniopharyngeal canal.
4. Sphenomaxillary—This encephalocele crosses the orbit via the superior and then inferior, orbital fissure to reach the sphenomaxillary fossa.

Basal encephaloceles cause nasal obstruction. Typically, intranasal encephaloceles can be differentiated from polyps via their location medial, not lateral, to the turbinates. Since these lesions may not present with any external facial abnormalities (namely Sphenoethmoidal, Transsphenoidal subtypes), the Otololaryngologist must perform a thorough intranasal exam to differentiate more benign causes of nasal obstruction from a congenital anomaly.

Typical features of nasal dermoids as well as gliomas and encephaloceles are depicted in Table 96.1.

EVALUATION

The differential diagnosis for a congenital midline lesion of the nose includes epidermoid cyst, hemangioma, teratoma, neurofibroma, lipoma, and lymphangioma. In some instances, midline nasal lesions can be detected on routine prenatal sonography (12). Therefore, the physician must supplement physical examination findings with a pointed radiographic workup to assess the anatomic pathway of the lesion. In some cases, pathways that appear to connect a mass to the intracranial cavity on MRI or CT may only represent a fibrous stalk that does not pose a risk to the patient. In instances in which a child presents with an external midline mass without a sinus tract, differential diagnosis includes glioma and encephalocele. Cephaloceles classically enlarge with crying and with jugular compression (positive Furstenberg sign). Because of the small but real possibility of meningitis from an intracranial connection, or the less threatening but still legitimate complication of gradual bony destruction and nasal deformity, a radiologic workup must also be initiated for lesions without a sinus tract. In an infant, these imaging studies can usually be obtained during routine sleep; preschool children older than 6 months usually require sedation. Despite the likely need for patient sedation, the otolaryngologist should promptly obtain an imaging study, because the risk from delayed treatment of an intracranial defect outweighs any concerns regarding anesthesia in the radiology suite.

MRI is the favored imaging modality for suspected anterior neuropore anomalies (7,8,13). For the infrequent circumstance of an anticipated large skull base defect, as with encephaloceles, three-dimensional CT has proven benefit (14). In general, CT tends to give better bone detail, whereas MRI best illustrates soft tissue. The presence of a bifid crista galli and enlarged foramen cecum is highly suggestive of intracranial involvement and implores the need for neurosurgical consultation (13). Although CT best displays the crista and anterior skull base, MRI can adequately image these structures. MRI also has the advantage of providing direct sagittal images, as well as a clear outline of the lesion in contrast to surrounding tissue (Fig. 96.8). Furthermore, MRI poses no risk of radiation. Huisman et al. (15) reported two patients with MRIs showing possible intracranial components that were not detected by CT or surgery. Therefore, MRI should be supplemented with a CT as needed for detailing the anterior skull base or nasal bones, or for clarifying ambiguous intracranial irregularities. Imaging should include the nasal tip to the anterior cranial fossa, including the entire nasal ethmoid and orbital regions.

SURGICAL TREATMENT

Controversy exists regarding both the timing and method of surgery. By delaying intervention, the physician risks growth of the lesion and infection. In 1951, Matson and Ingraham (16) showed that patients treated after an intracranial complication fared worse than those treated prophylactically. For this reason, lesions with confirmed intracranial connections should be treated without delay. On the other hand, if MRI clearly demonstrates no intracranial connection, delays of 2 to 5 years may be contemplated prior to surgery, as long as no infection develops within the cyst. Postponing surgery allows the child time for growth, facilitating the surgical

TABLE 96.1 CLINICAL FEATURES OF CONGENITAL NASAL MASSES

	Associated Anomalies	Midline	Cosmetic Defect	Infection Risk (Soft Tissue)	Meningitis Risk
Dermoid	N	U	Y	Y	Y
Glioma	N	S	S	N	Y
Encephalocele	S	S	S	N	Y

Y, yes; N, no; S, sometimes; U, usually; R, rarely.

dissection and diminishing the risks of altered nasal growth from tissue disruption. The physician must consider these benefits as well as the family's concerns before making recommendations about surgical timing.

Authorities favor a variety of surgical approaches for nasal dermoid cysts, including vertical or horizontal midline incision, lateral rhinotomy, transglabellar incision, or an external rhinoplasty approach. Those placed over or parallel to the nasal dorsum have been the mainstay of surgical exposure over the years (Fig. 96.9), and resulting scars are usually very subtle. However, alternatives that minimize scarring over the dermis must be considered, particularly in this era of enlightened, "minimally invasive" surgery. Pollock (17) suggested a transverse rhinotomy or a vertical zigzag rhinotomy to minimize wound contracture. Mankarious and Smith (18) described the external rhinoplasty incision, using a dermoid punch to release the skin pit from adjacent dermis. Because the dermal sinus tract tends to penetrate the nasal bones inferiorly, the open rhinoplasty provides excellent exposure (Fig. 96.10). Combining this with a vertical midline osteotomy, as necessary, to separate the nasal bones, provides virtually unimpeded exposure to the anterior skull base. Although the midface degloving approach prides excellent exposure to the midface and eliminates the need for a transcolumellar incision, it does not allow for the degree of midline, cephalad exposure afforded by the open rhinoplasty approach. The open rhinoplasty also allows simple reconstruction of the nasal dorsum, as needed, to minimize resulting dorsal depression. It must be noted, however, that an external incision over the nasal dorsum is always required to free the tract from its exterior attachment to nasal dorsal skin regardless of adequate exposure achieved through an external rhinoplasty approach. Parents should be educated appropriately on the inevitability of an exterior scar over the nasal dorsum. In the infrequent case of a dermoid sinus tract located superiorly over the glabella, an external rhinoplasty approach would be insufficient, and the patient would probably be best served with a transglabellar approach (19).

Regardless of the incision made, once the surgeon has followed the sinus tract through the nasal bones, magnification and otologic instruments greatly facilitate the

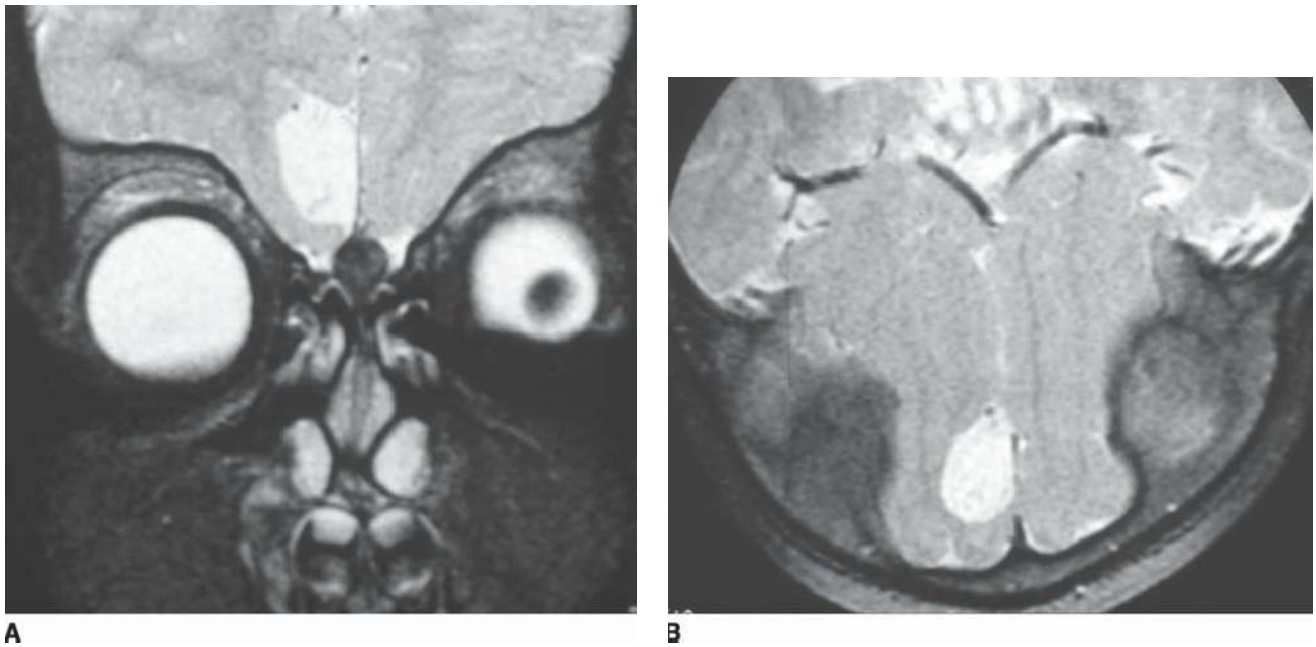


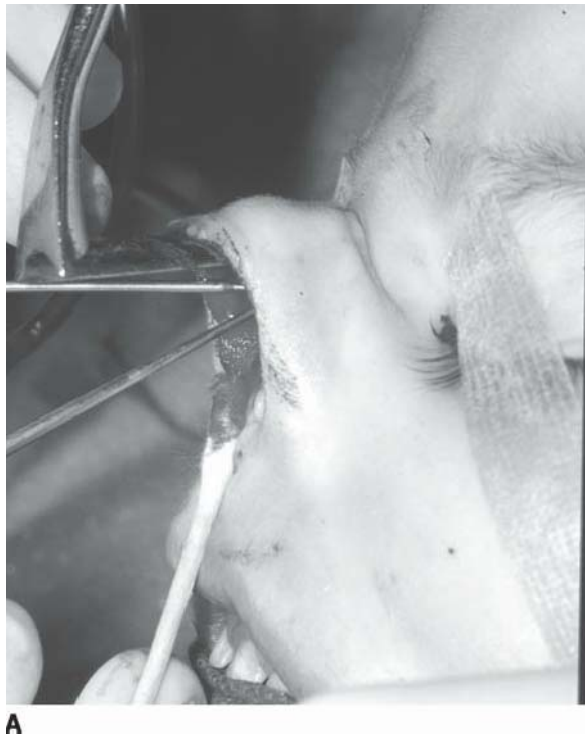
Figure 96.8 **A,B:** Coronal and axial MRI showing frontal lobe dermoid cyst.

Sinus Tract	Intracranial Communications	Intranasal Presentation	Compressible/ Expandable	Skull Base Dehiscence	Low Ethmoid Roof
U	S	N	N	S	N
N	R	S	N	N	N
N	Y	S	Y	Y	S

procedure. The cyst wall should be kept intact and carefully dissected free of the adjacent bone and soft cavity within which it is contained. A neurosurgeon should be consulted in advance to be available for unexpected intracranial communication. On approaching the skull base, the lesion should come free or terminate in a fibrous stalk. If there is any question about the stalk representing an epithelial lined tract penetrating the skull base, a frozen section may be taken of its most superior, extracranial extent. Many authors advocate the residual tract can be ligated (20). One author advocates full removal of the tract due to the scattering of adnexal structures throughout the tract, which may contribute to recurrence (20). Histologic evidence of an epithelial lined tract would require a craniotomy to complete the excision. Without histologic or radiographic proof of intracranial extension, a craniotomy should *not* be commenced. Recurrence ranges from 6% to 12% and can generally be managed in a straightforward fashion (1,21).



Figure 96.9 Vertical midline incision.



A



B

Figure 96.10 **A:** Open rhinoplasty incision with retractor in place, demonstrating wide exposure. **B:** Specimen removed easily via open rhinoplasty.

Gliomas may be excised intranasally. Ideally, the surgeon can identify the stalk and amputate it so that no gross tissue remains *in situ*. Depending on the lesion's location, an external skin incision may be required. Rahbar et al. (1) recently reported a series of 10 gliomas excised without complication or recurrence. Naturally, a neurosurgeon should be available to help with unexpected skull base defects.

Lesions with a potential or known intracranial component must be managed jointly by otolaryngology and neurosurgery. Generally, the otolaryngologist will initiate a midface approach, after which the neurosurgeon will gain intracranial access via a separate, sterile field, using a bicoronal flap and frontal craniotomy. After delivering the specimen, the neurosurgeon typically repairs the skull base defect with a periosteal flap, and then the otolaryngologist returns to close midface incisions with cosmetic techniques. In the case of encephaloceles, the entire procedure may be performed by the neurosurgeon, with the otolaryngologist available to provide intranasal exposure as needed.

Because encephaloceles have the broadest skull base defects of the three congenital abnormalities discussed in this chapter, they have the highest potential for complications. Cerebrospinal fluid (CSF) leaks pose the most common problem. Although encephaloceles fall within the purview of neurosurgeons, otolaryngologists may play a supportive role in closing the defects via endoscopic exposure from below or in helping manage and repair postoperative CSF rhinorrhea. The addition of fibrin glue and an array of absorbable nasal packing increase the rhinologist's armamentarium for these functions.

HIGHLIGHTS

- Nasal dermoids, gliomas, and encephaloceles share embryogenesis but usually can be differentiated based on clinical features.
- Potential or actual CNS communications pose the most challenging aspect of managing these three lesions.
- Once a congenital nasal mass is suspected, MRI should be obtained. CT should be used if MRI leaves any doubts as to bone anatomy or intracranial extent.
- Approximately 25% of dermoids and 15% of gliomas have intracranial extension, which carries the risk of meningitis and therefore warrants prompt surgical treatment. Surgery for lesions without proven intracranial extension may be deferred temporarily.
- Well-planned surgical treatment with neurosurgical consultation usually leads to successful outcomes. Encephaloceles carry the worst prognosis because of the size of the associated skull base defects and associated morbidities.

ACKNOWLEDGEMENTS

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Pediatric Rhinosinusitis

97

Rodney P. Lusk

The goal of this chapter is to review the etiology, diagnosis, and medical and surgical management of acute and chronic pediatric sinusitis. The diseases associated with rhinosinusitis (or sinusitis) are varied and difficult to differentiate (Table 97.1). It is now recognized that prolonged purulent rhinorrhea is not the norm. Children have an immature immune system and, if they attend day care, have an increased exposure to upper respiratory tract infections and possible recurrent sinusitis. Not infrequently, parents are asked to remove their children from the day care center if purulent rhinorrhea is present. This in turn can result in absenteeism from work and lost revenue for the employee and the employer. Sinuses are present in even the youngest children and can be infected. Chronic sinusitis usually involves both the maxillary and the anterior ethmoid sinuses with almost equal frequency.

SIGNS AND SYMPTOMS

Differentiating recurrent acute and chronic sinusitis is difficult because of a lack of specificity of the signs and symptoms. In addition the symptoms are frequently suppressed with antibiotic therapy, further confusing the diagnosis. Upper respiratory tract infections are frequently confused with sinusitis, and the primary delineation between the two appears to be the chronicity of the infection. Wald (1) noted that symptoms of the common cold improve in 5 to 7 days, and if the symptoms persist longer than 10 days, the symptoms are likely to be secondary to either an acute sinusitis or to persistent symptoms of chronic sinusitis. Acute sinusitis will take as long as 3 weeks to resolve symptoms. Historical documentation becomes confusing when antibiotics are prescribed as they suppress symptoms. Dr. Wald called the two types of sinusitis: persistent and severe, which occur secondary to an upper respiratory tract infection, and more severe infections, which are associated with a temperature of above 103°F rectally and thick, purulent nasal discharge. She argues that most nonsevere sinus infections resolve spontaneously, whereas more severe sinusitis requires treatment with antibiotics (1). Signs and symptoms and their severity may vary with the patient's age (Table 97.2). The young patient often has nasal congestion and anterior purulent rhinorrhea. The older patient may not be as symptomatic but complains of nasal congestion, postnasal drip, or sore throat secondary to the chronic drainage. Cough is a frequent complaint and is usually more severe at night. Daytime cough is more significant, however, as it is more likely to be associated with sinusitis. The relation between cough and chronic sinusitis is not clear. The symptom of chronic cough is most dramatic in the asthmatic patient, whose asthma attacks are frequently exacerbated by acute infections. Fever is much more common in the younger patient and is a frequent complaint, although rarely documented in the office.

Pain may manifest itself in a variety of ways. Younger children are irritable and may manifest head banging. The older patient complains of headaches and may be able to localize the area of pain. Unrelenting pain isolated over the vertex or back of the head without other symptoms may be associated with sphenoid sinusitis and needs to be ruled out with a CT scan (2,3). A significant problem with symptom assessment in chronic sinusitis is inadequate documentation. Two good validated instruments, SN5 (4) and S5 (5), are available but not frequently used.

PHYSICAL EXAMINATION

Signs of sinus infections include nasal congestion with dilatation of the mucosa, giving it a bluish appearance. Nasal discharge is often present with a variety of viscosities and may be clear, yellowish, or greenish; the clear drainage is generally thought to be associated with allergies, whereas yellow or greenish drainage is thought to be associated with a viral or bacterial infection. Another common but

TABLE 97.1 DIFFERENTIAL DIAGNOSIS OF DISEASES COMPATIBLE WITH PEDIATRIC CHRONIC SINUSITIS

Chronic sinusitis
Adenoid hypertrophy
Recurrent upper respiratory (viral) infections
Allergies
Immune deficiencies
Ciliary dyskinesia

TABLE 97.3 DIAGNOSIS PHYSICAL EXAMINATION IN CHRONIC SINUSITIS

1. Only anterior rhinoscopy can be performed in most children.
2. Visualize the septum then middle turbinate and then the middle meatus laterally.
3. A clear middle meatus does not ensure that no sinus disease is present.
4. Look for purulent discharge at the middle meatus.
5. Polyps are unusual in children. Think of cystic fibrosis, fungal sinusitis, and NARES syndrome.

nonspecific sign is dark inferior eyelids with puffiness over the maxilla. The physical examination of the child is difficult primarily because of poor compliance (Table 97.3). The approach to the child must be slow and nonthreatening. Head movements from side to side and the narrowing of the nasal vestibule brought on by crying make the examination virtually impossible. If the child refuses examination, little can be gained by trying to force the examination. The tools used to examine the nasal vault may include a nasal speculum and head mirror, microscope and nasal speculum, otoscope, flexible nasal pharyngoscope, or rigid telescope. The Viroscope, by Welch Allyn, offers a unique method of performing anterior nasal examinations. The light headlight is quite bright, and the anterior nasal airway can be viewed through lenses that narrow the parallax of the observer. This allows good visualization of the anterior nasal airway and middle meatus. Regardless of the method used, anterior rhinoscopy is all that can be accomplished, except for nasal pharyngoscopy, which can be performed with the flexible nasopharyngoscope. The flexible scope is most advantageous in the older postoperative patient.

It is best to examine the ears first with an otoscope. If the child tolerates otoscopy, the physician has gained the child's confidence, and anterior rhinoscopy can then be attempted with the otoscope. If all goes well, then vasoconstriction can be best accomplished with 0.05% oxymetazoline. A mixture of 1:1 0.05% oxymetazoline and 4% lidocaine will effectively anesthetize and vasoconstrict the nose for nasopharyngoscopy. After several minutes, the nose is reexamined to evaluate for possible purulence that has flowed into the anterior nasal vault. In children, polyps usually signal cystic fibrosis or allergic fungal sinusitis. It is encouraging if the middle meatus is clear and without edema, but this does not assure a disease-free sinus. Examination with a rigid telescope can be performed in the unusually cooperative child with local anesthesia. Rolling a 2.7-mm telescope into the middle meatus, as is frequently recommended in adults, is virtually impossible in children.

The physical examination, therefore, gives clues to the diagnosis of possible sinusitis but is not diagnostic.

OTHER DIAGNOSTIC AIDS

Table 97.4 lists other diagnostic modalities useful in the evaluation. Transillumination in children is useless as the sinuses are quite small, do not transilluminate, and offer no diagnostic advantages. Ultrasound can be used only in the maxillary sinus and has been found to be inconsistent with plain radiography. Plain films have been found to be inaccurate when compared to computed tomography (CT) scans (Fig. 97.1). McAlister et al. (6) at St. Louis Children's Hospital prospectively studied 70 children with symptoms of chronic sinusitis and compared the plain films with the coronal CT scans. They found a discrepancy between CT scans and plain films of 29% to 23% and concluded that the plain films both over- and underestimate the amount of sinus disease noted on CT scans. Similar findings have been reported by Lazar et al. (7) and Goldstein and Phillips (8). CT scan has become the gold standard for the

TABLE 97.2 SIGNS AND SYMPTOMS OF CHRONIC SINUSITIS

Purulent nasal discharge
Day and night cough
Nasal airway obstruction
Headache, irritability, or facial pain
Fever
Postnasal drip

TABLE 97.4 OTHER DIAGNOSTIC AIDS FOR PEDIATRIC CHRONIC SINUSITIS

Transillumination: No help in children
Ultrasound: Not a viable option
Plain films: Inaccurate assessment of ethmoid sinuses
CT scan: Most accurate assessment of the sinuses
MRI applicable for acute disease extending beyond sinuses; into the orbit and brain

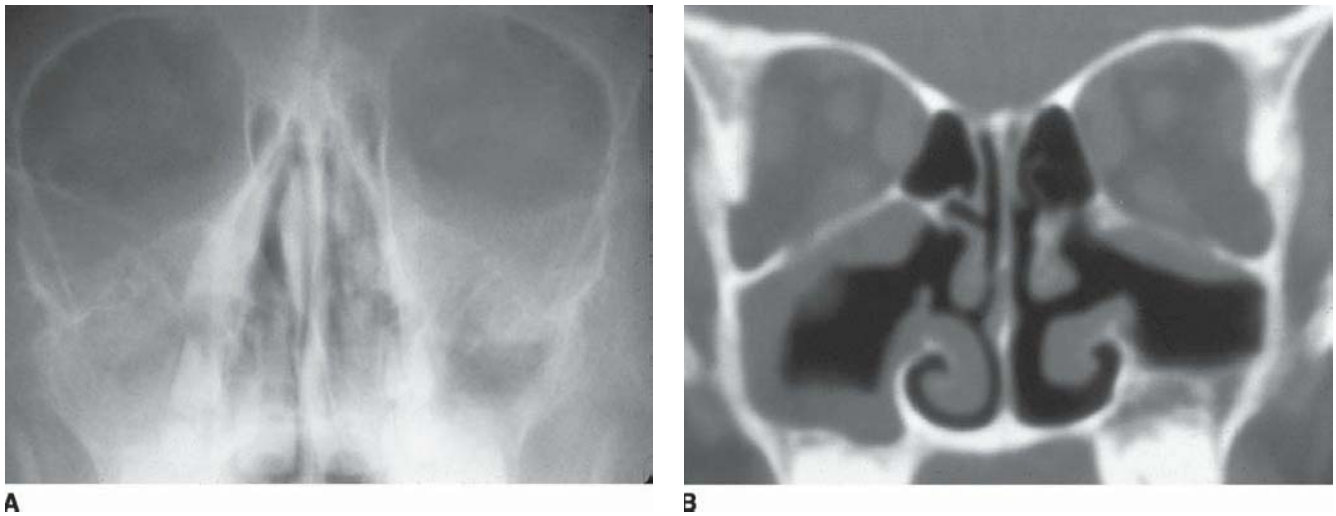


Figure 97.1 **A:** Plain radiograph of a child who has had endoscopic sinus surgery. Notice the opacification of the right maxillary sinus and significant mucous membrane thickening of the left maxillary sinus. The ethmoid sinuses are difficult to assess on this film. **B:** Computed tomography scan of the same patient, taken about 20 minutes later. No disease is seen in the ethmoid cells, and true mucous membrane thickening of the right maxillary sinus was represented as opacification on the plain films. The right maxillary sinus is clear, except for thickening along the roof of the sinus. Note that the maxillary antrostomies are widely patent.

evaluation of chronic sinusitis in children. There is increasing concern that children are receiving significant doses of radiation from CT scans. Brenner et al. (9) raised the concern that radiation in infants increased the risk of cancer later in life. This was highly controversial; however, Rogers (10) noted that children were getting doses similar to adults and the smaller heads were associated with greater doses of radiation (11). This is particularly important when it is understood that 25% to 30% of a child's bone marrow is located in the skull. Pediatric radiologists are acutely aware of this issue and now practice ALARA or "as low as reasonably achievable" to obtain the desired results.

ETIOLOGY

Our understanding of the etiology of chronic sinusitis continues to evolve. A principle that is now a cornerstone in our understanding of chronic sinusitis is that initially an inflammatory obstruction occurs in the natural ostium of the sinuses. The cause of the inflammation may be multifactorial but is usually secondary to a viral or bacterial infection. An area that appears particularly prone to obstruction is the ostiomeatal complex. This narrow channel, the infundibulum, drains the frontal, anterior ethmoid, and maxillary sinuses. The infundibulum is bordered by the uncinate process anteriorly and arches posteriorly where it is bordered by the ethmoid bulla. The frontal sinuses drain most frequently into the superior portion, and the maxillary sinuses drain into the posterior half of the infundibulum. Edema from any cause can narrow the infundibulum or the ostium and cause obstruction, which could result in a secondary infection. The viruses most frequently encountered are in patients with acute sinusitis: rhinovirus, parainfluenza, influenza, and adenovirus. The obstruction may be secondary to anatomic abnormalities or inflammation secondary to upper respiratory tract infections, allergies, or barotrauma. It was thought for many years that an anatomic variation of the anatomy around the ostiomeatal complex is associated with a higher incidence of chronic sinusitis. Children with septal deviations, paradoxical turbinates, and infraorbital cells do not have a higher incidence of chronic sinusitis (12–14).

We know that normal ciliary function is necessary for healthy sinuses; we also know that chronic sinusitis is associated with abnormal cilia. The cilia beat more slowly and less efficiently in patients with mucosal infections. When two ciliated surfaces come together, a localized disruption of the ciliary clearance and a secondary pooling of secretions occur. In the area of the ostium, the secretions may become secondarily infected and cause an acute or chronic sinusitis. Ciliary function is important because the ostia are often small and located in positions that are not conducive to spontaneous drainage. The best example of this is the maxillary sinus, where the ostium is located at the superior medial border. Kartagener syndrome is an example of significant ciliary dysfunction, and virtually all of these patients have evidence of chronic sinusitis. Some investigators believe that gastroesophageal reflux disease (GERD) plays a vital role in the etiology of chronic sinusitis. Barbero (15) noted that the parallel existence of upper airway inflammation, intractable sinusitis, and gastroesophageal reflux suggests a causal relation. Another possible explanation is GERD causes interruption of the normal mucosa over the adenoid pad allowing the formation of

biofilms deep within the crypts of adenoid tissue. This in turn could be associated with a nidus for seeding of the nose with pathologic bacteria. It is likely that a relation exists between GERD and sinusitis in some patients, but the overall frequency is not understood. The presumed etiology for this association is once again inflammation followed by ostial obstruction and subsequent infection. Gastric secretions are very caustic to nasal mucosa, and only occasional, once every few days, regurgitation may be enough to result in a diseased state. Infrequent exposure will not be noted with our current methods of diagnosis.

Most episodes of sinusitis occur during the winter when viral upper respiratory tract infections are at their greatest. This lack of correlation with the incidence of peak allergy calls into question the overall role of allergies in sinusitis. In some patients, seasonal allergy plays a role. Environmental and food allergies, which are not seasonal, may also play a significant role in some patients. A variety of immune deficiencies and ciliary dysfunction also may be associated with chronic sinusitis.

BACTERIOLOGY

Despite the importance of sinusitis, relatively few studies investigated the microbiology of chronic sinusitis in children. This is probably because of the inaccessibility of the sinuses except the maxillary, which is accessible through a puncture but requires a general anesthetic in younger patients.

The literature focusing on chronic versus acute sinusitis is inadequate, but some useful information can be ascertained from studies performed on acute sinusitis. Investigations of acute sinusitis found that *Streptococcus pneumoniae* was the most common organism (30%), followed closely by *Moraxella catarrhalis* and *Haemophilus influenzae* (20%). *H. influenzae* is usually nontypeable. Both *M. catarrhalis and H. influenzae* have a high incidence of β-lactamase–producing enzymes and are therefore resistant to many antibiotics. Anaerobes were infrequently found (only one in 79 sinus aspirates), and *Staphylococcus* also was rare. One-fourth of patients with bilateral maxillary sinusitis had discordant bacterial cultures. Because the cultures were taken about 10 days after the onset of symptoms, viruses were not often found. The bacteria involved with subacute infections (i.e., infections lasting between 10 and 21 days) are similar to those of acute sinusitis, with *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae* being the most common (Table 97.5).

The bacteria of chronic sinusitis are similar, with notable exceptions. Brooks et al. (16) found a high incidence (~50%) of anaerobic bacteria in the culture of maxillary sinus contents. Most of the anaerobes were anaerobic cocci and *Bacteroides* sp. Nord (17) also cultured only the maxillary sinus and found a high incidence of anaerobic bacteria. The use of broad-spectrum antibiotics has resulted in an increase in the incidence of resistant bacteria of the upper respiratory tract. There is evidence that *H. influenzae* is now much more resistant to ampicillin in pediatric rhinosinusitis (18). There is also an increase in the incidence of *S. pneumoniae* serotype 19A, which has an unusually high resistance rate (19). There are also multiple studies reporting an increased incidence of MRSA-positive cultures (20–22). PCV7 vaccinations have resulted in vaccine-specific serotype eradication of bacteria, but there has been a shift to other resistant *H. influenzae*–resistant strains (23).

TABLE 97.5 MOST COMMON BACTERIA OF CHRONIC PEDIATRIC SINUSITIS

Aerobic Bacteria
Streptococcus pneumoniae
Moraxella catarrhalis
Haemophilus influenzae
Staphylococcus aureus, increasing incidence of MRSA
α-Hemolytic streptococci
Pseudomonas aeruginosa
Anaerobic bacteria
Peptococci
Peptostreptococci
Bacteroides

MEDICAL MANAGEMENT

Mechanical cleaning of the nasal airway with saline irrigation is increasingly recognized as a valuable factor in treatment of chronic sinusitis (24,25). The problem is patient compliance in the pediatric age group. Kassel et al. (26) reported, in a metaanalysis report, a 40% incidence of noncompliance. Studies however have failed to show that it helps with acute sinusitis (27). There is a general consensus that buffered normal saline is better for ciliary function and therefore is preferable to hypertonic solutions. Treatment for other possible causes of sinusitis, including allergies and immune deficiencies, should also be instituted before endoscopic sinus surgery. In a recent questionnaire of pediatric otolaryngologists (28), the cornerstones for the medical management of chronic sinusitis continue to be prolonged broad-spectrum antibiotic therapy, irrigation with normal saline, and topical nasal steroid sprays. Currently, the oral antimicrobial classes used to treat acute rhinosinusitis include b-lactams, fluoroquinolones, macrolides/azalides, lincosamides, and sulfonamides/trimethoprim with one ketolide as a possibility (Table 97.6). A complete discussion of these classes of antibiotics is beyond the scope of this chapter but can be found in the Supplement to *Otolaryngology—Head and Neck Surgery*, Antimicrobial Treatment Guidelines for Acute Bacterial Rhinosinusitis (29). Antibiotics should be reserved for patients with bacterial infection, with the goal of eradicating the pathogen from the site of infection.

TABLE 97.6 MEDICAL MANAGEMENT OF PEDIATRIC SINUSITIS

Antimicrobial Dosage

Amoxicillin (90 mg/kg/d) in three divided doses
Amoxicillin clavulanate (Augmentin), 90 mg/kg/d every 12 h of 600 mg/5 mL suspension
Erythromycin–sulfisoxazole (Pediazole), 50/150 mg/kg/d in four divided doses
Sulfamethoxazole–trimethoprim (Sulfa or Bactrim), 40/8 mg/kg/d in divided doses
Cefuroxime axetil (Ceftin), 30 mg/kg/d in two divided doses
Cefprozil (Cefzil), 30 mg/kg/d in two divided doses
Cefpodoxime proxetil (Vantin), 10 mg/kg/d in two divided doses
Clindamycin (Cleocin), 30 mg/kg/d in four divided doses
Clarithromycin (Biaxin), 15 mg/kg/d in two divided doses
Azithromycin (Zithromax), 10 mg/kg/d in one loaded dose

The current recommendations for treatment of pediatric patients with mild disease and who have not received antibiotics in the previous 4 to 6 weeks would include high-dose amoxicillin (90 mg/kg/day) in three divided doses or amoxicillin/clavulanate (90 mg/kg/day every 12 hours of 600 mg/5 mL suspension), cefpodoxime proxetil, cefuroxime axetil, or cefdinir (29). If the patient has a history of immediate type I hypersensitivity to the b-lactams, then consider trimethoprim/sulfamethoxazole (TMP/SMX), azithromycin, clarithromycin, or erythromycin. If the patient has received antibiotics within the past 4 to 6 weeks, then consider high-dose amoxicillin/clavulanate (90 mg/6.4 mg/kg/day), cefdinir, cefpodoxime proxetil, or cefuroxime axetil. If the patient is type I hypersensitive, then consider the same alternatives. At times, combined therapy is appropriate. Examples of combined therapy include high-dose amoxicillin or clindamycin plus cefixime or rifampin. Rifampin should not be used as monotherapy for longer than 10 to 14 days, as resistance can occur rapidly (29).

The treatment of acute and recurrent sinusitis should cover *S. pneumoniae, M. catarrhalis,* and *H. influenzae*. These three bacteria account for 70% of the bacteria causing sinusitis. One hundred percent of the *M. catarrhalis* and thirty to fifty percent of the *H. influenzae* bacteria are β-lactamase producers; for this reason, the antibiotic selected should cover the β-lactamase producers. The appropriate duration of antibiotic therapy still has not been systematically studied in children and is based on otitis media investigations. Empirically, acute sinusitis is usually treated for 10 to 14 days, if there is improvement of symptoms within 48 to 72 hours. Symptoms may last for up to 3 weeks even if adequately treated. If significant improvement has not occurred by then, an alternative antibiotic should be used. If the patient is not asymptomatic at the end of the first course of treatment, then the antibiotic should be continued for 7 to 10 more days.

No studies have evaluated the efficacy of prophylactic antibiotics in the treatment of recurrent or chronic sinusitis. Our current practice is to use a broad-spectrum antibiotic that would cover the bacteria of acute sinusitis as well as *Streptococcus* and *S. aureus* for 3 weeks (see Table 97.5). It is tempting to use prophylactic antibiotics; however, this should be used very sparingly because it may be a significant cause for emerging resistant bacteria. Rifampin, loracarbef, clindamycin, and TMP/SMX have been found to be effective against the penicillin-resistant strains of *S. pneumoniae*.

The role of anaerobes is unclear but should be considered in patients with chronic sinusitis. Gram-positive anaerobic streptococci and staphylococci are generally penicillin susceptible and therefore present no medical therapeutic problems. Gram-negative *Bacteroides* species producing β-lactamase respond nicely to amoxicillin/ potassium clavulanate (30). As a general rule, very few otolaryngologists are using IV antibiotics to treat chronic sinusitis (28).

Adjunctive medical modalities such as antihistamines, topical or oral decongestants, topical or oral steroids, and anti-inflammatory agents have not been studied in children or adults. Topical nasal steroid sprays are used on a regular basis (28) and are considered to be very safe.

SURGICAL MANAGEMENT

There is now general consensus regarding the surgical management of chronic sinusitis in children. Virtually all pediatric otolaryngologists would recommend adenoidectomy as a first step, and many would perform it prior to embarking on a complete workup for allergies or immune system assessment (28). The following surgical modalities have been used to treat chronic pediatric sinusitis (Table 97.7).

Adenoidectomy

Previous investigations have shown an association between children with diseased tonsils and adenoids and evidence of sinusitis. It is obvious that the removal of a large obstructive adenoid pad would be an appropriate initial mode of therapy to see if the symptoms abate (Fig. 97.2). There

TABLE 97.7 SURGICAL MANAGEMENT OF PEDIATRIC CHRONIC SINUSITIS

Questionable efficacy
Tonsillectomy
Antral lavage
Inferior meatal antrostomy

Probable efficacy
Adenoidectomy (as a first treatment) 70% successful
Middle meatal antrostomy/possibly balloon sinuplasty
Anterior or anterior and posterior ethmoidectomy
Frontal sinuses are not developed and sphenoid is rarely diseased in children.

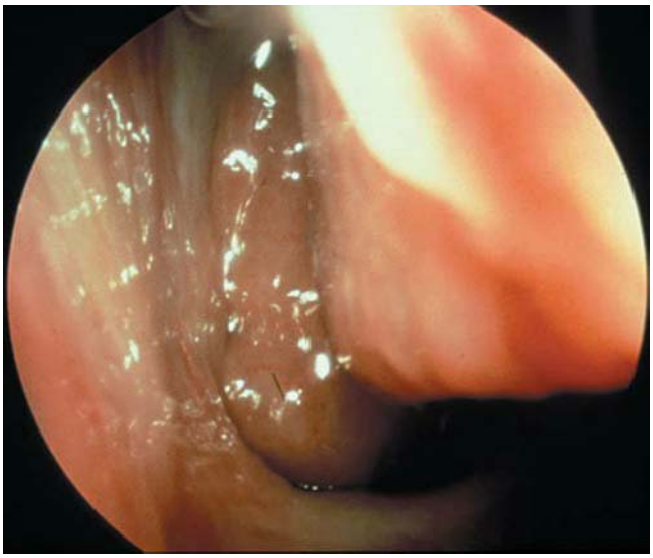


Figure 97.2 Adenoid enlargement.

is now general agreement that removal of even a small adenoid pad will decrease symptoms. The reason was not obvious until biofilms were noted on and in the crypts of the adenoid pad in children with chronic sinusitis (31–34). Brietzke and Brigger (35) in a metaanalysis noted significantly improved symptoms in 69.3% of patients after an adenoidectomy. It would therefore appear to be appropriate to perform an adenoidectomy in children who are not adequately managed with aggressive medical management.

Antral Lavage

Antral lavage has been described as a method to both detect and treat recurrent sinusitis. One of its obvious deficiencies is that it addresses only the maxillary sinus. The lavage can be performed through the natural ostium, the inferior meatus, or the canine fossa. There is now renewed interest in lavage with newer tools to cannulate the natural ostium of the maxillary sinus and provide more aggressive cleaning of the cavity (36). The studies are too few to make any recommendations about the efficacy of these techniques.

Inferior Meatal Antrostomy or Nasal Antral Windows

At one time, nasal antral windows were the mainstay of surgical management of chronic rhinosinusitis. The procedure is now rarely used except in children with underlying immunodeficiency, AIDS, and in some cases of cystic fibrosis. Muntz and Lusk (37) performed a retrospective evaluation in 39 children who were treated with bilateral inferior meatal antrostomies for chronic sinusitis and found that symptoms were not controlled in 60% of patients at 1 month and 73% at 6 months. We therefore abandoned the procedure in children.

Middle Meatal Antrostomy

An alternative mechanism for ventilating the maxillary antrum is to open the natural ostium through a middle meatal antrostomy. Ostrum was cited by Wilkerson (38) as the first investigator in the United States to make a case forcefully for limited middle meatal antrostomy. Hilding (39) did a series of experiments creating maxillary antral windows at different sites in rabbits and concluded that the infection rate would be higher if the natural ostium were opened. On the basis of these findings, it became heresy to open the natural ostium of the maxillary sinus. Wilkerson (38) rekindled interest in the middle meatal antrostomy and showed that it was effective in treating some patients with chronic sinusitis. There is now good evidence that the middle meatal antrostomy can be safely operated on and remains patent. Failure to identify the natural ostium or enlarge it can result in persistent obstruction and persistent disease. A new technique of opening the natural ostium of sinus with a high-pressure balloon has been introduced in adults and is starting to be investigated in children. At this point in time, 55% of pediatric otolaryngologists have been trained in the use of balloons, but only 7% use it occasionally and no one is using it routinely. Ramadan has performed most of the studies to date, and (40–42) the results are encouraging; however, they have not been reproduced at other centers. Randomized studies will be required to assess the efficacy and cost-effectiveness of using the new tool. In children, the only place it would be efficacious would be in the maxillary sinus as the frontals are not developed, the sphenoid sinuses are rarely diseased, and the technology is not applicable in the ethmoid sinuses.

Ethmoidectomy

Ethmoidectomy has gained wide acceptance as an acceptable method for managing medically intractable chronic rhinosinusitis in adults and children. It can be performed through the external, intranasal, or transantral approaches. With the advent of the Hopkins rod-lens system, endoscopic ethmoidectomy has become the standard procedure and allowed ethmoidectomy to be safely performed in children. The role of endoscopic ethmoidectomy in children continues to be clarified but is accepted as a viable option in refractory chronic sinusitis. Gross et al. (43) and Lusk and Muntz (44) established that endoscopic ethmoidectomy could be safely performed and was effective in children. Extensive sphenoethmoidectomy is usually not justified in children unless they have symptomatic polyps secondary to cystic fibrosis, allergic fungal sinusitis, or nonallergic rhinitis with eosinophilia syndrome (NARES). Anterior ethmoidectomy and a small maxillary sinus antrostomy is usually all that is needed in children. The posterior ethmoid and sphenoid sinuses are not usually involved; therefore, a more limited or conservative procedure is appropriate. Most pediatric otolaryngologists will

only do an anterior ethmoidectomy and maxillary antrostomy initially (28). Terris and Davidson (45) reviewed the adult and pediatric literature for endoscopic sinus surgery and found 1,713 patients who had undergone surgery and 91% who were improved. Hebert and Bent (46) did a meta-analysis of endoscopic sinus surgery in children and noted a uniformly high rate of success. Chang (19) found an 86% overall satisfactory rate from surgery when it was assessed by the parents. Individual symptom improvements were as follows: nasal obstruction, 91%; purulent rhinorrhea, 90%; postnasal drip, 90%; headache, 97%; hyposmia, 89%; and chronic cough, 96%. This study was confined to Asian children. The use of absorbable stenting material such as Merogel (Medtronics, Minneapolis, MN) has been felt by some to decreased the need for a secondary look because it is thought to decrease scarring (47,48). It is to be placed into the cavity dry (Fig. 97.3) and then injected with 2 to 4 mL of normal saline to promote absorption within 2 weeks. If the stent is not injected with saline, it will remain in the cavity longer than desired. Sobol et al. (49) reported that only 15% of pediatric endoscopists were using stents in 2005; however, this trend has reversed somewhat and 38% of endoscopists are now using some kind of absorbable stent (28). Thirty-six percent never use absorbable stents in children. Very few endoscopists, 11%, are now doing second looks with a general anesthetic (28).



Figure 97.3 Bioresorbable nasal dressing (MeroGel) placed in the middle meatus.

The ethmoid cavity in children is narrow, and it can be difficult to know exactly where you are. The safety of revision endoscopic sinus surgery and extensive sinus surgery required for cystic fibrosis has been enhanced with the use of guided imaging (Fig. 97.4). Guided imaging is now being used more frequently; however, there is no consensus as to when it is appropriate.

Facial Growth

Animal studies in piglets (50,51) led to the suspicion that endoscopic sinus surgery could lead to an interruption of facial growth. The first study to mention facial growth as an issue in children was Wolf in 1995 and he noted no interruption of facial growth in children (52). Senior (53) compared children with unilateral ethmoidectomy for orbital cellulitis 7 years after their intervention. He compared these patients to normal adults and adults with a history of sinusitis and noted no significant variation in the size of the maxillary or ethmoid sinuses. Bothwell et al. (54) examined facial growth in children who had endoscopic sinus surgery at a mean age of 3.1 years. Sixty-seven children who had endoscopic sinus surgery were examined for interruption of facial growth 10 years later at a mean age of 13.2 years. Forty-six children who had endoscopic sinus surgery were compared with twenty-one children who had chronic sinusitis but did not have surgery. Quantitative anthropomorphic analysis was performed by using 12 standard facial measurements, and a facial plastic surgery expert performed qualitative facial analysis. With these parameters, no evidence was found that endoscopic sinus surgery affected facial growth as compared with children with endoscopic sinus surgery, children with chronic sinusitis, and the normal population.

COMPLICATIONS

Table 97.8 summarizes complications of sinusitis.

Orbital Complications

Complications of acute and chronic sinusitis are best recognized and treated early. Most of the complications arise from acute sinus infections and extend into the adjacent orbit and cranial cavities. A bimodal distribution of orbital and intracranial complications is found. Orbital complications are more common in younger children, have significant morbidity, and are potentially life-threatening. Children younger than 7 years are more readily treated with aggressive medical management, whereas older children are more likely to require surgical intervention and have intracranial complications. For children aged 7 years and older, magnetic resonance imaging (MRI) in addition to CT scans should be performed to assess for intracranial disease (Fig. 97.5). Infections from the sinus can spread to the orbit through the arteries, veins, or lymphatics but most often spread by direct extension through a dehiscence in the lamina papyracea (Fig. 97.6A and B).

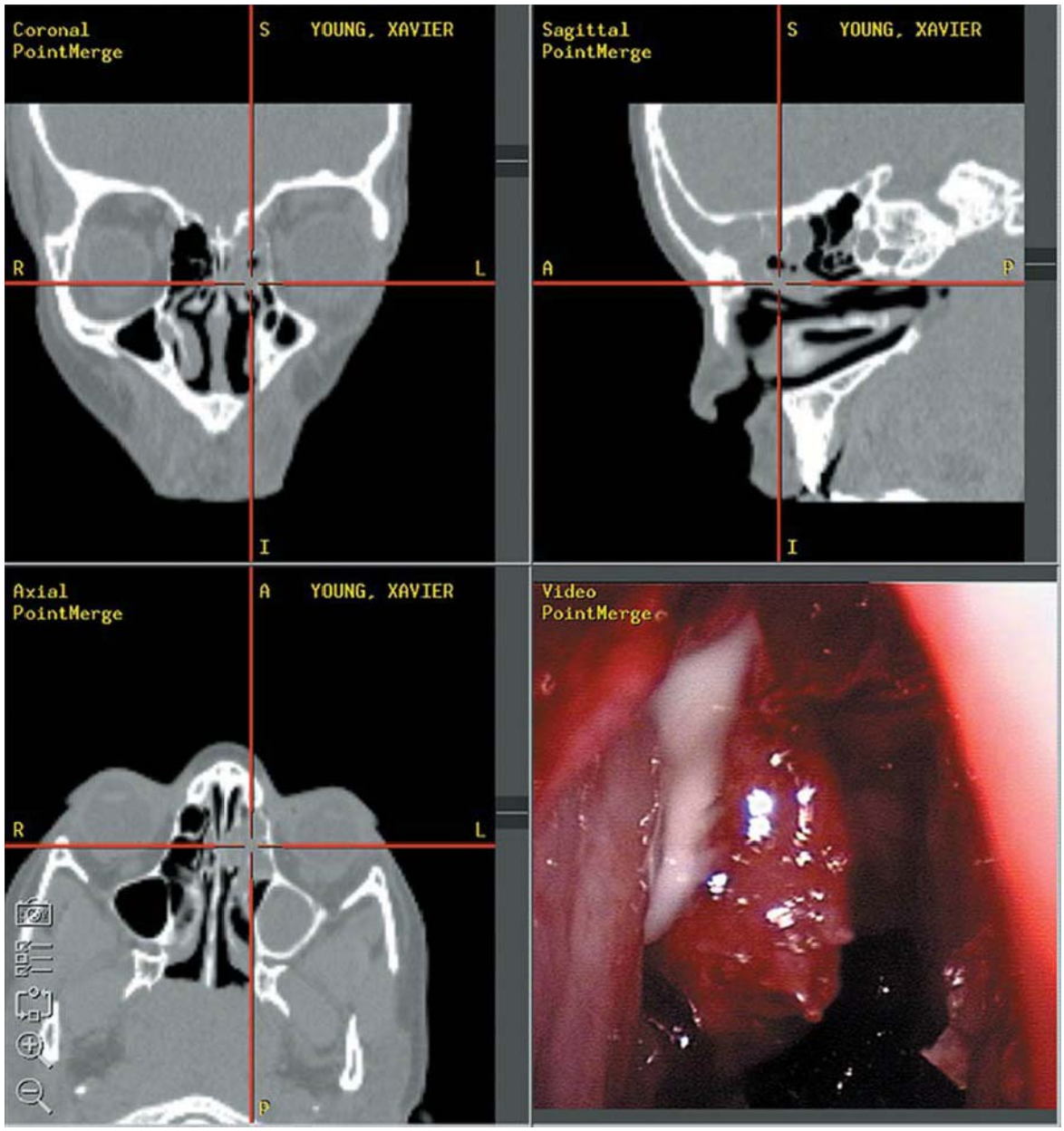


Figure 97.4 Guided imaging in children; probe in the sphenoid sinus.

The signs and symptoms of orbital complications can be used to stage the disease and guide management. The time-honored classification proposed by Chandler and colleagues has gained the widest acceptance.

Group 1: Inflammatory (preseptal) edema of eyelids without tenderness, obstruction of venous drainage, no associated visual loss or limitation of ocular movements

Group 2: Orbital cellulitis with diffuse edema of the adipose tissue in the orbital contents secondary to inflammation and bacterial infections, no abscess formation

Group 3: Subperiosteal abscess; abscess formation between the orbital periosteum and the bony orbital wall. The mass displaces the globe in the opposite direction (usually down and lateral); the proptosis may be severe with decreased ocular mobility and visual acuity. The abscess may rupture into the orbit through the orbital septum.

Group 4: Orbital abscess; a discrete abscess within the orbit. Proptosis is usually severe but is symmetrical and not displaced, as in the subperiosteal abscess. Complete ophthalmoplegia results, and visual loss occurs in 13%.

Group 5: Cavernous sinus thrombosis; progression of the phlebitis into the cavernous sinus and to the opposite side, resulting in bilateral symptoms.

These stages are important because they help specify the treatment and define the prognosis.

TABLE 97.8 PERSISTENT SINUS DISEASE

Orbital complications
- Orbital inflammation (preseptal)
- Orbital cellulitis
- Subperiosteal abscess
- Orbital abscess
- Cavernous sinus thrombosis
- Blindness

Intracranial complications
- Meningitis
- Epidural abscess
- Subdural abscess
- Acute and chronic brain abscess

The physical examination is important. Proptosis can occur with any inflammatory reaction within the orbit. If the proptosis is symmetrical, the entire orbit is likely to be involved, but if it is asymmetrical, a mass in the opposite quadrant is likely to be causing the proptosis. In general, the greater the proptosis, the greater the pressure and the more severe, and therefore, the more dangerous the infection. The axial CT scan is the best method of diagnosing subperiosteal and orbital abscesses. Cavernous sinusitis is rare but does occur in children.

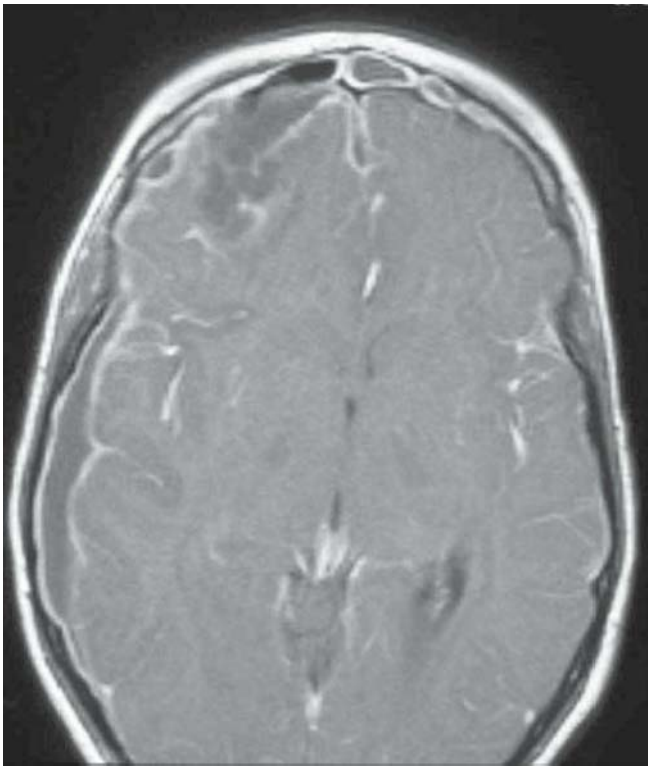


Figure 97.5 MRI scan of patient with frontal sinusitis and epidural abscess.

If the infection originates in the sinuses, the most likely causes are the bacteria that cause acute sinusitis: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *S. pyogenes*. *Staphylococcus aureus* is more likely to occur with chronic infections and in the older child. Intracranial complications are most likely to be associated with *Streptococcus* species and *Staphylococcus*. MRSA is becoming a more significant and resistant cause of the intracranial and intraorbital complications (55).

Progressive loss of visual acuity is a symptom that demands rapid investigation and intervention. The visual loss can be secondary to direct pressure on the optic nerve or secondary to neuritis. Regardless of the cause, when the abscess is drained, the visual loss usually reverses rapidly.

Orbital cellulitis and abscesses are potentially life-threatening infections. Managing these complications requires the expertise of many specialists. Medical management starts with aggressive intravenous antibiotics that cross the blood–brain barrier to prevent intracranial infections. The signs and symptoms of fever, motility, and visual acuity are carefully monitored. If no improvement is seen after 24 hours of intravenous antibiotics or if the patient's clinical status worsens, an axial CT scan is performed to identify a possible abscess. If one is found, it is surgically drained. If a decrease in visual acuity is noted, immediate evaluation and surgical intervention are implemented. Arjmand et al. (56) recommended removing a larger portion of the lamina papyracea for drainage. Manning (57) recommended removing a much smaller portion of the lamina papyracea, with equally good results. It now appears that subperiosteal abscess can be safely drained endoscopically. Children recover quicker with endoscopic drainage, and the hospital stay is approximately half of that with using an external approach (56). The endoscopic approach in an acutely infected sinus is technically more difficult but is associated with a lower incidence of complications than is the external approach. Each surgeon will have to decide which procedure is the most efficacious and safest.

An orbital infection that extends posteriorly into the cavernous sinus is very dangerous and has significant sequelae (58). Most of the patients with this complication secondary to sinusitis have involvement of the sphenoid sinus, which frequently extends into the ethmoid sinuses. The signs and symptoms of cavernous sinus thrombophlebitis are similar to those already mentioned for orbital cellulitis, abscess, or subperiosteal abscess. If cavernous sinus thrombosis or intracranial complications are suspected, an emergency axial CT scan and MRI with contrast are indicated. If cavernous sinus thrombosis is present, the CT scan will show a lack of contrast enhancement in one or both cavernous sinuses. Aggressive intravenous antibiotic therapy should be directed toward gram-positive cocci (*S. aureus*) and gram-negative bacilli with a third-generation cephalosporin such as cefuroxime axetil. If the sphenoid sinus is involved, it should be drained through the ethmoid sinus.

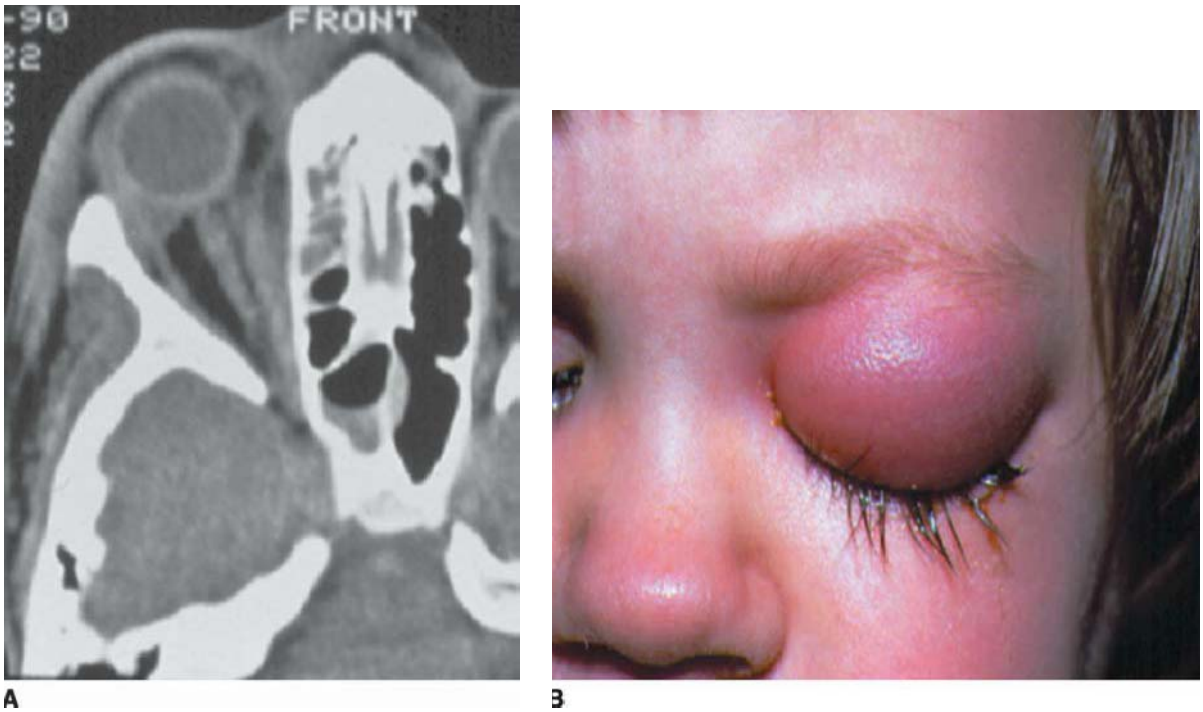


Figure 97.6 **A:** Computed tomography image of same patient with frontal sinusitis and epidural abscess. **B:** Clinical photograph of patient.

Intracranial Complications

Intracranial complications include meningitis and epidural, subdural, and acute or chronic brain abscess. Brain abscesses are the most common intracranial complications with sinusitis and are exceeded in overall frequency only by orbital complications. Patients most frequently present with headaches (92%), fever (85%), and nausea and vomiting (62%) (59). The most common form of abscess is the subdural, followed closely by the frontal lobe abscess or a combination of the two. Intracranial sequelae are most likely to occur in older children or adults, and in male patients (60), the incidence varies with location. Brain abscesses and inflammation are most readily identified with an MRI and are most likely to occur in the frontal lobes (60). These are particularly silent and may be difficult to diagnose on clinical grounds. Many of the patients have no signs of increased intracranial pressure. Symptoms of intracranial pressure include bradycardia, papilledema (this may not be present, as it takes some time to develop), stiff neck, hypertension, nausea, vomiting, and decreased consciousness. A dilated pupil is an ominous sign and suggests transtentorial herniation. Common symptoms of intracranial abscess include fever, headache, behavioral changes, seizures, nuchal rigidity, focal neurologic signs, and occasionally photophobia. Patients with epidural abscess generally are first seen with a continuous dull headache, sudden elevation of temperature, and clear cerebrospinal fluid (CSF). Patients with subdural abscesses are toxic, with changes in mental status, severe headaches, nuchal rigidity, focal neurologic changes, papilledema, and cloudy CSF with leukocytes, but no bacteria or positive cultures. These abscesses are thought to be the most dangerous intracranial complications and require emergency surgery.

Intracranial abscesses involve the same pathogens as ear infections and acute sinusitis (*S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*). Chronic sinusitis is associated with a much higher incidence of *S. aureus* and a-hemolytic streptococci, which also must be covered. Medical therapy must include antibiotics that pass through the blood–brain barrier and cover the most frequently cultured bacteria. Several different regimens have been proposed: cefuroxime and metronidazole, chloramphenicol (75 to 100 mg/kg/day), and oxacillin (150 to 200 mg/kg/day).

The *Pocket Book of Pediatric Antimicrobial Therapy* recommends that until the specific etiology is identified, methicillin (150 to 200 mg/kg/day IV every 6 hours), aminoglycoside or cefotaxime (150 to 200 mg/kg/day IV every 6 hours), *and* metronidazole (30 mg/kg/day IV every 8 hours) should be used. The duration of therapy is individualized.

Medical management alone has met with variable success. Johnson et al. (61) did not cure a single patient with medical therapy, which consisted most frequently of chloramphenicol (75 to 100 mg/kg/day) and oxacillin (150 to 200 mg/kg/day). Antibiotics have the greatest chance of success if the lesion were small and the symptoms were short in duration.

Surgical management is based on the extent and location of the disease. The intracranial approach is dictated by the location of the lesion.

HIGHLIGHTS

- The signs and symptoms vary with the child's age. Purulent nasal discharge, cough, nasal obstruction, and irritability are the most common symptoms.
- The physical examination is frequently limited to anterior rhinoscopy because of the limited cooperation of the child and because of the narrow pediatric nose.
- Plain films do not define the extent of the disease and are particularly deficient in the ethmoid sinuses. Coronal CT scans are required to define the anatomy and the extent of the sinus involvement.
- The bacteria most often associated with chronic pediatric sinusitis are a-hemolytic streptococcus, *S. aureus*, *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae*. MRSA is becoming more frequent and causing more complications.
- The antibiotics most often used for chronic sinusitis are amoxicillin/potassium clavulanate (Augmentin) and second-generation cephalosporins.
- Surgical modalities of questionable value are tonsillectomy, antral lavage, and inferior antral windows. Adenoidectomy is now generally accepted as the first surgical mode of therapy. Most investigators now believe that biofilms along with adenoid hypertrophy are the primary reasons for performing an adenoidectomy. The reported success rate is variable but is 67% as documented with metaanalysis studies.
- Endoscopic ethmoidectomy (anterior or anterior and posterior) and maxillary antrostomy have proven to be successful in a number of different investigators' hands and are 80% to 90% successful in controlling the symptoms of chronic sinusitis.
- Investigators are split on the use of absorbable stents; there is a general swing back toward using them.
- Second look is no longer necessary with pediatric endoscopic sinus surgery.
- Emergencies in sinusitis are usually secondary to acute sinusitis and associated with infections that extend into the orbital and intracranial cavities. These infections are potentially life-threatening and have a high incidence of morbidity.
- Large gaps remain in our knowledge of chronic sinusitis. We have not accurately defined its incidence or natural history. The etiology of sinusitis is multifactorial and complicates clinical trials. The bacterial flora must be further delineated to direct appropriate medical therapy. The duration of antibiotic therapy and the role of prophylactic antibiotics require further study.

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Salivary Gland Disease in Children

98

Matthew K. Whitley *Karen B. Zur*

Pediatric salivary diseases, both benign and malignant, are not as prevalent as those in the adult population. The nonneoplastic disorders include acute and chronic inflammation (bacterial and viral), cysts, granulomatous diseases, Sjögren syndrome, sialolithiasis, and sialorrhea. Neoplastic diseases are subcategorized into mesenchymal versus epithelial and further classified as benign or malignant. This potpourri of disorders can affect the major or minor salivary glands, but predominantly the parotids and submandibular glands.

The evaluation of salivary gland pathology is the same as that done for the adult population, with emphasis placed on a thorough history and physical examination. Each of the topics discussed in this chapter addresses specific diagnostic tools to assist in the evaluation as well as the currently recommended medical or surgical intervention or both.

INFLAMMATORY CONDITIONS

Acute and chronic inflammatory diseases of the major and minor salivary glands are the most common pediatric salivary disorders (Table 98.1).

Acute Sialadenitis

Acute Bacterial Sialadenitis

Acute sialadenitis, as its name implies, is an acute inflammation of the affected gland, characterized by tenderness, localized pain, and overlying edema. Occasionally, purulent drainage may be seen emanating from the duct of the involved gland. Salivary stasis, due to either decreased saliva production or duct obstruction, increases the risk of sialadenitis. Conditions such as sialolithiasis, duct strictures, trauma, congenital sialectasis, autoimmune conditions, and dehydration contribute to stasis. Because of the serous (and therefore less bacteriostatic) composition of the parotid gland, it is more susceptible to acute suppurative sialadenitis than is the mucinous submandibular gland. During the past decade, the use of antibiotics along with fluid hydration and electrolyte management has almost eliminated the development of fulminating acute suppurative parotitis in hospitalized surgical patients. The predominant organisms include aerobic and anaerobic bacteria. Common aerobes include *Staphylococcus aureus* and *Haemophilus influenzae*, whereas the predominant anaerobes are gram-negative bacilli and *Peptostreptococcus* species (1).

The treatment is the same as that in the adult population. Local measures to increase salivary flow such as glandular massage, use of sialogogues, local heat (i.e., warm compress), and hydration complement the use of systemic antibiotics. Initial choice of antimicrobials should include a penicillinase-resistant antistaphylococcal agent that can be adjusted if no clinical improvement is seen within several days or based on culture results.

Episodes of recurrent acute sialadenitis in children often resolve by puberty (2). A conservative approach between episodes includes intermittent dilation of the ducts to avoid stricture (see section on "Recurrent Juvenile Parotitis"). Sialography can be performed in these patients to rule out duct strictures or changes in gland architecture. If chronic changes are seen, sialadenectomy should be considered. When the submandibular gland is involved, excision of the gland is recommended. When the parotid is involved, the decision-making process is complicated by the facial nerve. Various surgical alternatives have been described with limited success (3). The most effective and reliable approach is a total parotidectomy with facial nerve preservation. A superficial parotidectomy alone increases the risk of recurrent infections because of possible sialocele formation.

Neonatal Sialadenitis

Infections of the parotid and submandibular glands are rare but increasingly recognized in the premature neonate.

TABLE 98.1 DIAGNOSIS AND MANAGEMENT: DISEASES OF THE SALIVARY GLAND

Disease	Features	Management
Acute bacterial sialadenitis	Acute onset, prepubescent, purulent saliva from duct, diffuse swelling and tenderness	Hydration, sialogogues, massage, antibiotics
Neonatal sialadenitis	Warm, tender erythematous mass in neonate; expressible purulence from gland duct; *S. aureus* and *P. aeruginosa* most common	Hydration, antibiotics, avoid gland manipulation, incision and drainage if no response to antibiotics
Viral	Acute onset, similar to bacterial sialadenitis but no purulence	Symptomatic
Chronic sialectasis	Unilateral, diffuse, intermittent enlargement related to eating	Antibiotics for acute exacerbation, ductal dilation and incision, parotidectomy if refractory
Sialolithiasis	Rare in pediatric population; intermittent, unilateral pain and swelling associated with eating	Sialogogues, removal of calculus, consider extracorporeal shockwave lithotripsy
Cysts	Mostly seen in sublingual gland (ranula)	Marsupialization or excision
Granulomatous lesions	Chronic enlargement, nodularities	Treat underlying condition
Sjögren syndrome	Bilateral, symmetrical enlargement of glands; xerostomia; uncommon in pediatric population; may occur in association with other autoimmune disorders	Symptomatic, long-term follow-up
Sialorrhea	Abnormal in child older than 4 y, neurologic or mental impairment	Physiotherapy, anticholinergic/antihistamine, surgical, botulinum neurotoxin A (Botox) in some cases

The diagnosis is clinical and confirmed by a warm, tender, erythematous mass with expressible purulence from the gland's duct.

Acute suppurative sialadenitis of infancy is thought to be due to the reduction in salivary flow, immunologic immaturity, and presence of bacteria in the oral cavity of these neonates (4). Dehydration, prolonged orogastric tube feeding, and congenital anomalies of the floor of the mouth have also been associated with suppurative sialadenitis in the neonate (4). *S. aureus* and *Pseudomonas aeruginosa* are the most commonly identified pathogens. The management is similar to that of acute sialadenitis in the child and adult. Hydration and antimicrobial therapy should lead to a response within 48 to 72 hours. Unlike in the older population, it is important to avoid gland manipulation in a preterm child to reduce the risk of systemic septicemia (4). If no satisfactory improvement is seen, incision and drainage is recommended. Recurrences are uncommon.

The differential diagnosis of unilateral gland inflammation in this age group includes submandibular fat necrosis, infected lymphangioma, and cervical lymphadenitis. To confirm the diagnosis, ultrasonography can be performed but is not indicated.

Viral Sialadenitis

Mumps

Worldwide, the most common inflammatory condition affecting the parotid gland is mumps. Mumps is caused by the paramyxovirus, which has a 2- to 3-week incubation period and has been known to inflame the gonads, meninges, and pancreas as well. It is most commonly seen during the winter and spring. The contagious period occurs 2 to 3 days before the development of gland enlargement, with a prodrome characterized by malaise, fever, chills, anorexia, and a sore throat. The clinical findings are similar to those described for bacterial sialadenitis, except for the presence of purulence from the duct orifice. The management is symptomatic.

Salivary Gland Disease in the HIV Patient

Oral manifestations are one of the earliest clinical indicators of human immunodeficiency virus (HIV) infection and progression in children (5). It has been estimated that 4% of the HIV-infected children in the United States have salivary gland disease (6). Salivary gland disease in this population can be classified as enlargement, xerostomia, or both.

Salivary gland enlargement is most commonly seen in the parotid gland, followed by the sublingual and submandibular glands (7). It is characterized by a gradual growth causing facial asymmetry. Parotid enlargement has been associated with generalized lymphadenopathy and lymphoid interstitial pneumonitis, occurring between ages 4 months and 4.5 years (5). Theories abound regarding the etiology of the lymphoepithelial cysts seen in this condition. One of them posits a relation with T-lymphocyte $CD8^+$ cell infiltration in the gland (5). Some have suggested that lymphoepithelial cysts are caused by the obstruction of the salivary ducts from lymph nodes that are entrapped during parotid gland development. These benign lymphoepithelial lesions are seen initially with progressive painless

swelling of the parotid (8). In the HIV population, they are bilateral in up to 80% of cases. Parotid pseudocysts are secondary to viral inflammation and are often the initial manifestation of HIV. Testing for HIV should be done in all children with parotid cysts (8).

Treatment options should be individualized to the patient, with consideration of the risks and benefits of the proposed interventions. Most lymphoepithelial cysts will regress with antiretroviral therapy (5). Only in severe cases of salivary gland dysfunction or disfigurement is surgical intervention appropriate. The approach is cyst aspiration, partial gland excision, or doxycycline sclerotherapy (5). Sclerotherapy may be useful for growth prevention in 75% of cases and for regression of the cyst in only 25% of cases (8).

The diagnostic modality of choice in HIV patients with salivary gland enlargement is computed tomography (CT) or magnetic resonance imaging (MRI). The use of ultrasound in the evaluation of salivary gland enlargement in this population has been proposed as an alternative to conventional imaging and as a good screening tool for malignancy (in lymphoma, which appears solid). Once a malignancy has been ruled out, the management of salivary gland enlargement in the HIV population is watchful waiting (5).

Epstein-Barr Virus (EBV)

Epstein-Barr virus (EBV) infection is a known cause of infectious mononucleosis, which is transmitted through saliva. It also has been implicated in the pathogenesis of certain types of salivary gland tumors in the adult population but not in the pediatric population (9).The adenopathy of mononucleosis can involve periparotid and perisubmandibular lymph nodes.

Chronic Inflammation

The pathogenesis of the chronic salivary inflammatory disease spectrum also has changed with the interplay between sialadenitis, sialectasis, and sialolithiasis. A heterogeneous group of disorders in chronic inflammatory sialadenitis also exist, which include the group of specific and nonspecific granulomatous diseases.

Juvenile Recurrent Parotitis (JRP)

Juvenile recurrent parotitis (JRP), which was formally known as recurrent parotitis of childhood, is the most common inflammatory salivary gland disorder in children in the United States and is second only to mumps worldwide. This condition presents with recurrent inflammation and infection without a definitive etiology. The onset is generally between 3 and 6 years of age, and recurrent episodes continue throughout puberty, when the disease usually resolves. Patients present with pain and edema over the involved gland (often the parotid) and can have systemic symptoms such as fever. On physical exam, patients often have enlarged Stensen's papilla with associated yellowish plaques of protein coagulum around the opening. Treatment is medical, but sialadenoscopic washout and irrigation has also been described with success (10).

Both flexible and rigid sialadenoscopy have been used for both diagnostic and therapeutic treatment of salivary gland disorders. Small rigid scopes with working ports for saline, antibiotic, or steroid irrigation as well as for balloon dilation are available. One study of 36 patients with JRP showed a 92% recurrence-free rate at 36 months after sialadenoscopic irrigation and steroid infusion (11). Another study of six children had 100% success rate in treating recurrent infections (12). Further research is necessary to further delineate the role of this treatment modality in pediatric salivary gland disease.

Chronic Sialectasis

Chronic inflammation of the salivary glands can lead to ductal dilation, chronic salivary stasis, ascending infections, and parenchymal destruction. It is seen mostly in the adult with a history of childhood recurrent sialadenitis, sialolithiasis, and strictures. The presentation is unilateral, diffuse enlargement of the involved gland with swelling related to eating. Sialography can identify a stricture with proximal ductal dilation. The management includes a spectrum of therapies including ductal dilation or duct incision (if the stricture is distal). Conservative therapy is less effective in management of parotid sialectasis. In this situation, a parotidectomy with facial nerve preservation is required.

Because of the morbidity associated with facial nerve dissection in an inflamed field, alternative modes of therapy have been proposed. The use of botulinum toxin A to modulate parasympathetic stimulation and reduce salivary flow has been reported (13). The theory is that chemical denervation leads to atrophy of parotid gland acini.

Sialolithiasis

Relative to adults, sialolithiasis is a rare condition in the pediatric population. Relatively few cases of pediatric calculus formation in the salivary glands have been reported in the literature. In a review done in 1995, in total, 86 cases were cited. The submandibular glands are the most common site for calculus formation, followed in frequency by the parotid gland. The sublingual glands and the minor salivary glands are rarely affected. Physiologic factors such as alkaline pH, high calcium concentration, and mucin content of the saliva contribute to stone formation. Furthermore, it has been speculated that the tortuosity of Wharton duct with passage of secretions against gravity can promote stasis and calculi (14). The most common presenting symptoms include intermittent, unilateral swelling in the affected gland with ipsilateral pain, all associated with eating.

When an obstruction is suspected, radiography is 90% sensitive. In the past, panoramic and anteroposterior films were used; however, because of bony overlap of the facial

skeleton, these studies are not effective at identifying calculi. Axial CT scans are useful in identifying radiopaque sialoliths. The majority of stones can be found along the course of the ducts (Stensen's or Wharton duct) (14) with a rare occurrence of intraparenchymal stones. Most submandibular gland calculi are radiopaque, while a significant majority of parotid stones are radiolucent. Nonopaque sialoliths can be identified with ultrasonography and, in particular, color Doppler ultrasonography (15).

The underlying pathophysiology leading to stone formation is stasis secondary to either duct obstruction, decreased saliva production, or a side effect of pharmacotherapy. The most common etiology of chronic duct obstruction is mucous plugging with deposition of calcium salts. Accidental biting of Stensen's duct also can contribute to duct stricture and stasis. Decreased salivary production due to autoimmune disease is less commonly encountered in the pediatric population.

The aim of management of sialolithiasis is to restore the normal parenchymal architecture of the gland and allow its long-term functional recovery. A conservative and mostly effective mode of therapy includes stimulation of saliva production by instructing the child to suck on acidic sialogogues. In children, submandibular stones have been reported to pass out of the duct spontaneously after this maneuver. Spontaneous passage of parotid stones is less likely because of the pathway of Stensen's duct through the buccinator muscle (15).

If conservative treatment fails, alternative modes of therapy include duct dilation, sialolithotomy, or sialadenectomy. The latter is indicated if the stone is located in the posterior third of the gland or when damage to the parenchyma of the gland results in a nonfunctional gland. To evaluate this, radiographic imaging including sialography, scintigraphy, ultrasonography, and MRI can be used.

Because of the potential morbidity associated with sialolithotomy and sialadenectomy, a less invasive mode of therapy has been recently proposed. Extracorporeal electromagnetic shockwave lithotripsy (EESWL) has improved the nonsurgical approach to treatment of salivary gland calculi (15). In their report of seven patients treated with noninvasive EESWL, Ottaviani and colleagues reported complete stone disintegration in 71% of the patients and 29% partial resolution. EESWL therapy is instituted after resolution of the acute inflammatory state with antibiotics and anti-inflammatory agents. Symptom relief was observed in all patients who were studied. After an average of five sessions, all but one had complete functional recovery of the gland, as observed on scintigraphy (15). McJunkin et al. (16) recently described a case of treatment of a 2-cm parotid sialolith with a single session of lithotripsy with complete resolution.

Cysts

Mucous retention cysts are epithelium-lined cysts that result from duct obstruction. Mostly seen in the sublingual gland and presenting similar to a ranula, these true cysts involve the minor salivary glands. A ranula, in contrast, is not a true epithelium-lined cyst and represents a collection of extravasated mucin. Plunging ranulas extend below the mylohyoid muscle and can be first seen with a cervical or intraoral neck mass or both. Management is by marsupialization or excision, often in association with removal of the sublingual gland (3).

Granulomatous Lesions

Chronic salivary gland enlargement may be due to granulomatous inflammation resulting in a nodularity to the gland that must be differentiated from a neoplastic process. Tuberculosis, sarcoidosis, histoplasmosis, tularemia, cat-scratch disease, and toxoplasmosis have all been reported (3).

SALIVARY GLAND NEOPLASMS

Neoplasms of salivary gland origin are relatively uncommon in the pediatric population. They comprise 8% of all pediatric head and neck tumors, representing the fourth most frequent, after neoplasms of the nasopharynx, skin, and thyroid (17). The histologic pattern of the tumors seen in the pediatric versus adult populations is the same; however, the rate of occurrence of each subtype is different in these groups. Approximately 15% to 25% of all salivary gland tumors are malignant in adults, whereas in the pediatric population, this rate is higher, approaching 50% when vascular neoplasms are excluded (17). When including the vascular tumors in these statistics, about 35% of all salivary gland lesions in children are malignant. Thus, a solid mass identified in a child has a 2.5-fold higher rate of malignancy in comparison to a solid mass identified in an adult. Salivary gland neoplasms can be classified into benign (including the vascular lesions) and malignant tumors. The latter are subclassified into low-grade and high-grade malignancies based on histology.

Benign Mesenchymal Tumors

Benign salivary gland tumors may be of nonepithelial or epithelial origin. The mesenchymal lesions include hemangiomas (73.5% of nonepithelial tumors), lymphatic vascular malformations (18.5%), neurogenic tumors (4.2%), lipomas (1.5%), and the rarer lesions xanthoma and fibromatosis (18).

Hemangiomas account for approximately 50% to 60% of neoplasms seen in the pediatric population (19). These are nonencapsulated, often infiltrating lesions that are composed of solid masses of cells and multiple anastomosing capillaries replacing the acinar structure of the gland, while not affecting the ductal structures or the facial nerve. They appear spongy and lobulated, with a purple blush. The distribution of hemangiomas among the various salivary glands is as follows: 80% occur in parotid, 18% in the submandibular glands, and 2% in minor salivary glands

(19). Two types of hemangiomas are encountered: The capillary form is rapidly growing, present at birth, and often regresses by the age of 1 year. The cavernous form is more aggressive, appears in the older child, and has a tendency to bleed and deform. This hemangioma subtype is more difficult to manage.

The capillary hemangiomas are more commonly seen in girls, either at birth or in the first few months of life. Clinical diagnosis is the rule, and the course of resolution is almost predictable (*albeit* controversial) with conservative management. Cavernous hemangiomas are initially seen later in life. Diagnosis of salivary hemangiomas is mostly based on physical examination. Hemangiomas involving the salivary glands, specifically the parotid area, can be quite deforming. They are usually confined to the intracapsular region and may extend to the overlying skin. Ultrasound imaging may be helpful in differentiating this vascular lesion from a cystic mass but cannot define the extent of the disease. In unusual cases, an MRI may be obtained. This radiographic modality is diagnostic and can help define the limits of the mass.

Treatment of hemangiomas is not necessary if the mass is small and not involving critical organs or affecting function. In general, spontaneous involution occurs by age 4 to 6 years. In certain instances, a trial of prednisone, 3 to 5 mg/kg/day for several weeks, may serve as an effective initial course of treatment (19). A treatment protocol does not exist, but a study examining 1,109 cases of cutaneous hemangiomas (including head and neck lesions) suggested that systemic corticosteroids are effective in 36% of patients, independent of dosage, pharmacologic agents, and duration of therapy (ranging from 7 weeks with conventional-dose prednisolone regimen to 35 days of high-dose methylprednisolone regimen). According to this report, the dimension of the lesion and age at initiation of treatment are important factors affecting response to treatment. Furthermore, the authors cited a 21% rebound growth after discontinuation of systemic therapy (20). It is important to recognize that long-term systemic corticosteroid therapy is not benign. The efficacy of therapy should be questioned if no response is seen within several weeks of therapy, as systemic complications are well recognized. The indications for surgical intervention in young patients with hemangiomas are increase in tumor size, rapid tumor growth, failure of tumor to involute, and hemorrhage into the lesions.

Much interest exists in the recent literature related to the use of propranolol to treat various head and neck hemangiomas. While promising for salivary hemangiomas based on theoretical use, data are somewhat limited. Moralis et al. described a case of a 2 month old with an extensive parotid hemangioma that resolved with oral propranolol for 16 months (21). Another recent report described a large series of head and neck hemangiomas treated with propranolol, including two children with parotid lesions. Both children had good responses, although one had a relapse when treatment was discontinued 7 months into treatment (22). More research is needed to characterize the promising role of this medicine for the treatment of these particular lesions.

Lymphatic vascular malformations are the second most common benign tumors of the salivary gland. These lymphatic malformations do not replace the normal glandular parenchyma seen in the hemangiomas; rather, normal salivary gland tissue is found adjacent to the dilated lymphatic vessels. Like hemangiomas, lymphangiomas are soft, diffuse, nondiscrete lesions that become distended in the dependent position and ballotable and compressible in the upright position. They are present at birth, with about 50% to 60% of the tumors occurring before age 12 months and 90% before age 24 months. Occasionally, rapid enlargement may occur after trauma, infection, or spontaneous hemorrhage into the cyst. The histologic subtypes are macrocystic, microcystic, or mixed venous and lymphatic malformations.

Radiographic diagnosis is definitive with CT or with the classic finding of fluid/fluid levels seen on MRI. These studies can delineate the extent of disease and surrounding organ involvement. Unlike the hemangiomas, lymphatic malformations generally require surgical excision, as these lesions do not spontaneously regress. The timing of intervention is not clearly established. Intuitively, if airway compromise is observed, urgent intervention should be carried out. Otherwise, excision can be planned on a routine basis but should not be postponed later than a few years of age because of the risk that chronic infection and inflammation of the mass, especially if of parotid origin, might damage the facial nerve.

Injection of sclerosing agents has been reported, along with use of radiotherapy and electromagnetic treatment; however, these treatment alternatives have been used without significant success and with a risk of significant morbidity (23) (Table 98.2). More recent reports of the use of intralesional injections of OK-432 in treatment of macrocystic lymphatic vascular malformations of the head and neck show some response after one or two injections. OK-432 has not been approved for use in the United States by the Food and Drug Administration and is used experimentally in select US institutions.

Malignant Mesenchymal Tumors

Rhabdomyosarcoma is the most common sarcoma in children, most commonly occurring in the nasopharynx and orbit (24). It has been reported to occur in 2.1% to 3.5% of malignant salivary gland tumors in children (24,25). Usually the parotid gland is secondarily involved in cases of advanced disease and is rarely seen as a primary parotid tumor.

The classic histologic findings in rhabdomyosarcomas include the "small round blue cells" with scant cytoplasm and primitive-appearing nuclei (26). Radiographic findings on CT demonstrate heterogeneous attenuation and isoattenuation relative to muscle. The MRI findings

TABLE 98.2 DIAGNOSIS AND MANAGEMENT: BENIGN SALIVARY GLAND NEOPLASMS

Histology	Features	Management
Mesenchymal origin		
Hemangiomas	74% of mesenchymal tumors, present at birth	Observation; if symptomatic, steroids; surgical excision for complications
Lymphatic vascular malformations	19%, majority first seen by age 24 mo, distensible in dependent position	Surgical excision, sclerosing agents—not widely accepted
Epithelial origin		
Pleomorphic (mixed) adenoma	Slow growing, painless, freely mobile	Parotidectomy with facial nerve preservation
Warthin tumor	Parotid; unilateral, multifocal, painless mass; often cystic	Parotidectomy with facial nerve preservation
Oncocytoma	Mitochondria rich	Surgical excision
Monomorphic adenoma	Rare; slow growing	Surgical excision

typically reveal a heterogeneous mass with ill-defined borders, isointense to muscle, and diffusely enhancing after contrast administration (26).

The diagnosis of rhabdomyosarcomas is confirmed by fine-needle aspiration (FNA), incisional biopsy, or both. Definitive therapy includes a combination of interventions in variable order based on treatment protocols. The surgical approach includes sialadenectomy, wide local resection of involved tissue (mandible, skin, muscle), and limited lymph node dissection, if indicated (25). Radiation therapy and chemotherapy protocols exist and should be administered based on local practices. They include adjuvant chemotherapy and radiation therapy, induction chemotherapy followed by surgery and postoperative radiation and additional chemotherapy, and induction chemotherapy with additional postoperative chemotherapy (25) (Table 98.3).

Epithelial Neoplasms

After excluding the clinically evident mesenchymal tumors, solid salivary gland masses are difficult to evaluate in children (19). In general, the history, physical findings, radiologic studies, skin tests, serologic results, and FNA biopsy findings may suggest a disease process, but diagnostic certainty is almost always achieved after excision of the tumor (19). It was found that in respect to pediatric salivary neoplasms, the higher or larger the gland, the higher the likelihood of malignancy. This relation is inverse compared with that known in the adult population (17,26). The parotid gland is the predominant location for salivary tumors (65.8%), and the majority of these tumors are malignant (80%) (17).

The presentation most commonly seen in patients with salivary gland tumors is a mass lesion. In a series of pediatric parotid tumors reported by the Massachusetts Eye and Ear Infirmary, 89% of neoplasms were found at the angle of the mandible; none of these were in association with cervical adenopathy (19).

The evaluation of a solitary mass of the salivary gland should include a thorough history and physical examination. Discussion in this chapter is focused on the parotid gland because it is the most likely site of tumor involvement in the child. In many situations, radiographic imaging techniques can provide a high degree of specificity that can be used to guide therapy and to plan a surgical approach. The merits of each diagnostic modality are described in association with the particular pathologic entities described. In general, ultrasonography may be used to assess the size of the parotid gland, distinguish diffuse from focal disease, assess vascularity and adjacent vascular structures, distinguish cystic from solid lesions, and guide FNA.

However, contrast-enhanced CT and MRI provide more accurate and diagnostic information. In most pediatric parotid diseases, especially when an inflammatory condition is suspected, CT is the modality of choice. CT has the ability to detect calcium deposits with tenfold sensitivity over plain films. Solitary or multiple calcifications usually indicate the presence of chronic sialadenitis. If calcification is seen within the gland's parenchyma but not within a mass, then the most likely condition is a chronic inflammatory process. If, conversely, the calcification is within a salivary gland mass, the lesion is most commonly a pleomorphic adenoma (27).

MRI is useful in situations in which a cranial neuropathy (specifically, involving the facial nerve) or a nonpalpable mass is found. This modality often shows the margins of a salivary gland mass more sharply than does the CT scan. Controversy still exists in regard to indications for use of the CT scan versus the MRI in salivary masses (27).

After radiographic evaluation of the solitary salivary gland mass, cytologic examination is useful in distinguishing tumor from inflammation and in recognizing a malignant tumor from a benign one. The sensitivity in detecting the presence of a salivary gland tumor by using FNA is

TABLE 98.3 DIAGNOSIS AND MANAGEMENT: MALIGNANT SALIVARY GLAND NEOPLASMS

Histology	Features	Management
Mesenchymal origin		
Rhabdomyosarcoma	Most common sarcoma in children, "small blue cells," parotid secondarily involved	Combined surgery, radiation, and chemotherapy in any order
Epithelial origin		
Mucoepidermoid carcinoma (MEC)	Majority of salivary gland malignancies; cystic or solid; low, intermediate, high grade	Wide local excision or total parotidectomy with facial nerve preservation; no clear indication for elective neck dissection, modified neck dissection for clinical nodes, no established protocols for postoperative radiation or chemotherapy
Acinic cell carcinoma	Second most common malignancy, 90% 5-yr survival with combined therapy	Wide local excision with facial nerve preservation, adjuvant chemotherapy reported, possible postoperative radiation
Adenocarcinoma	Solid mass	Wide local excision with facial nerve preservation, adjuvant chemotherapy reported
Undifferentiated carcinoma	Poor prognosis	Parotidectomy with facial nerve preservation unless obviously involved
Adenoid cystic carcinoma	Rare in children, neurotrophic	Wide local excision, consider facial nerve resection/biopsy if suggestive, chemotherapy
Squamous cell carcinoma	Extremely rare in children	Wide local excision, consider possible higher rate of lymph node spread than in adult
Carcinoma ex pleomorphic	Extremely rare in children	Wide local excision with facial nerve preservation if possible

reported to be 92% (28). The sensitivity of determining that the tumor is malignant is between 84% and 88%, whereas the specificity of malignancy is between 95% and 100%. Reports of performing FNA in children are encouraging, citing minimal discomfort and no need for general anesthesia (28). Unlike certain cases after open biopsies of malignant neck lesions, performing an FNA confers no risk of tumor seeding and does not potentiate difficulties in subsequent resection, tumor fungation through the skin, and early recurrent tumor in the wound (29).

Therefore, the accepted recommendation is for primary FNA for cytologic verification and classification. In cases in which the aspiration biopsy is inconclusive, the minimal procedure for diagnosis and treatment of a solitary mass should be a superficial parotidectomy (or submandibular gland excision) with facial nerve preservation. Because high-grade malignancies are extremely uncommon in children, preservation of the facial nerve should be the rule unless it is involved with the tumor. With this in mind, the parents should always be counseled regarding the risk of facial nerve injury and the need for sacrifice in the event that the intraoperative findings suggest a high-grade malignancy.

Benign Epithelial Tumors

Benign salivary neoplasms of epithelial origin include the pleomorphic (mixed) adenoma, Warthin tumor, oncocytoma, and adenoma (see Table 98.2). The benign mixed tumor is the most common solid tumor mass seen in children (19). Pleomorphic adenomas comprise a heterogeneous mix of epithelial and connective tissue components that are well encapsulated with occasional interdigitation into surrounding parenchyma. The lesions are slow growing, painless, freely mobile, and do not involve the facial nerve. The most common sites of origin are the tail of the parotid and the hard palate.

The imaging of a benign mixed tumor shows the characteristic appearance of a benign mass. On CT scans, the margins are well defined, and the mass is nonenhancing. Larger tumors tend to lobulate, rendering a characteristic appearance on both CT and MRI. On CT, the lobulation appears to be a conglomerate of masses, whereas the finding on MRI confirms a single mass. Calcifications within the mass are highly characteristic of this tumor.

The Warthin tumor (papillary cystadenoma lymphomatosum) is the next most common benign tumor of the major salivary glands and is found only in the parotid gland (26). Its most common manifestation is a unilateral, multifocal, painless mass that quite often is cystic. Histologically, these tumors consist of a double layer of mitochondria-rich oncocytes that rest on a dense lymphoid stroma lining the papillary projections. On CT and MRI, Warthin tumors are well-encapsulated, homogeneous cystic or solid lesions, often in the tail of the parotid. When multiple lesions are seen either in one parotid gland or bilaterally, the most likely diagnosis is a papillary cystadenoma lymphomatosum. Management is superficial

parotidectomy with facial nerve preservation. Oncocytoma (oxyphilic adenoma) describes a solid tumor that is entirely composed of mitochondria-rich oncocytes. The imaging characteristics are nonspecific, and treatment is surgical excision. Monomorphic adenomas occur rarely. They are benign, slow-growing, encapsulated lesions of the parotid gland (in the majority of cases) with occasional minor salivary gland involvement (upper lip) (27). Histologically, these tumors resemble the adenoid cystic carcinoma but lack the invasion seen in the latter. Treatment is surgical extirpation. Other rare benign neoplasms include neurofibromas, xanthomas, and angiolipomas.

Malignant Epithelial Tumors

Cancers of epithelial origin are common in the adult population; however, pediatric epithelial malignancies are rare. A 1972 review by the Armed Forces Institute of Pathology of 9,993 cases of salivary gland lesions demonstrated 430 (4.3%) lesions occurring in children younger than 15 years. Of these, 3% were malignant. Primary malignancies of the salivary gland include carcinomas, sarcomas, and lymphomas. As in the adult population, the most common malignant tumor is the mucoepidermoid carcinoma (MEC). Other less common malignant epithelial neoplasms include the acinic cell carcinoma (16.8% of malignant salivary gland tumors [24]), adenocarcinoma (8.1%), undifferentiated carcinoma (8.7%), adenoid cystic carcinoma (7.6%), squamous cell carcinoma (1.3%), and carcinoma ex pleomorphic. The most common site of malignant salivary gland tumors is the parotid. In general, malignancies of the salivary glands occur later in childhood, whereas the high-grade malignancies are more predominant in the young child (15 years and younger).

MEC is the most common malignant salivary gland tumor in the pediatric population (46% to 55%) (18,24,30). It is a unique epithelial neoplasm composed of variable proportions of epidermoid, mucous, and intermediate cells. Historically, the clinical behavior of this neoplasm is dependent on its histopathologic appearance; ranging from the low-grade benign-behaving type to an extremely aggressive, high-grade neoplasm with a high mortality rate. The low-grade MECs have a high mucinous content, forming cystic spaces. Conversely, high-grade carcinomas are poorly circumscribed, tend to be solid, and have a predominantly squamous composition. Nuclear pleomorphism, high mitotic rate, and necrosis are seen in the high-grade MEC. The intermediate MECs are less cystic and more solid than the low-grade lesions and do not exhibit the features of high-grade neoplasia previously mentioned.

It has been reported that the majority of MECs appear in major salivary glands, and the rest in the minor salivary glands (17,18). MEC is the most common radiation-induced salivary gland malignancy. A greater percentage of salivary gland malignancies appear as second malignancies after radiation (6%) than as primary salivary gland malignancies (0.08%) in children (18). This emphasizes the importance of long-term follow-up of the salivary glands of children who received multimodality therapy for a variety of pediatric primary tumors. The CT and MRI findings vary with the grade of the tumor. The low-grade MEC appears like a pleomorphic adenoma, whereas the high-grade lesions have indistinct infiltrating margins and are more homogeneous.

Treatment of the salivary gland neoplasms includes total parotidectomy with preservation of the facial nerve. Because high-grade malignancies are uncommon in children, facial nerve preservation is the rule if it is not involved with the tumor (17,19) (see Table 89.3). The indications for elective neck dissection are not defined in the literature, but according to some reports, it does not seem to be necessary in children with salivary gland malignancies (17). In patients with clinically suggestive lymphadenopathy, a modified neck dissection is advocated.

The issue of administration of postoperative radiation therapy in the pediatric population is controversial, in light of the inherent risk of developing a second malignancy. Complications related to radiation therapy are not trivial, with one study reporting a 60% rate of sequelae such as dental caries, prolonged trismus, facial deformity, and osteoradionecrosis. Because of the relative infrequency of pediatric salivary gland malignancies, no established and standardized protocols exist for postoperative radiation or chemotherapy. Some authors advocate postoperative radiation therapy for high-grade malignancy, microscopic residual tumor, perineural invasion, soft tissue extension, or multiple levels of lymphadenopathy; presence of a deep tumor with facial nerve involvement; and after salvage surgery (17).

Few clinical reports are found in the literature with respect to adjuvant chemotherapy for malignant salivary neoplasms. Effective regimens include methotrexate and doxorubicin for MEC and a combination of 5-fluorouracil, doxorubicin, and cyclophosphamide (Cytoxan) for treatment of adenocarcinomas and acinic cell carcinoma. Adenoid cystic carcinoma is reportedly best treated with cisplatin, doxorubicin, and 5-fluorouracil (17) (see Table 98.3).

The prognosis of malignant salivary neoplasms in the pediatric population is dependent on the type and grade of tumor. In the MEC, relapse rates for the high-grade malignancies are relatively high but the overall prognosis is good. A recent study from MD Anderson Cancer Center examined 61 patients with salivary gland malignancies. The overall 5-year survival was 93% and 26% developed a recurrence. Seventeen percent had metastatic disease. High tumor grade, positive surgical margins, and perineural invasion were associated with poorer prognosis and increased rates of locoregional recurrence. Of note, late locoregional recurrence was common with the median age of presentation of recurrence of 8 years. This underscores the need for lifelong surveillance of these patients. Furthermore, several patients developed second primary tumors after irradiation, emphasizing the need for vigilance. Patients had lower incidence of late complications compared to adults (30). Another study from the same institution looked specifically

at 49 children with MEC. 5-year and 10-year survival was 98% and 94%, respectively, and 10% of patients had recurrence (31). Cervical lymph node metastasis occurs in 20% to 37% of cases of MECs. Taken together, current data support aggressive treatment of these tumors with long-term follow-up surveillance (24,30).

AUTOIMMUNE CONDITIONS

Sjögren Syndrome

Sjögren syndrome (SS) is an autoimmune condition characterized by chronic inflammation of the salivary and lacrimal glands, resulting in xerostomia and keratoconjunctivitis sicca, respectively. SS may occur alone (primary SS) or in association with other systemic connective tissue disorders such as rheumatoid arthritis, systemic lupus erythematous, scleroderma, polyarteritis nodosa, or dermatomyositis (secondary SS). The common manifestations of salivary gland involvement include bilateral, symmetrical enlargement of the parotid glands (and occasionally submandibular glands). Occasionally, episodes of unilateral or intermittent parotid enlargement can be observed (32).

In children, unlike in the adult population, this condition is uncommon. Nearly 200 cases have been reported in the pediatric population (32). The differential diagnosis for chronic salivary gland enlargement includes primary tumors, lymphoma, acute bacterial and viral infections, sarcoidosis, tuberculosis, histoplasmosis, lead or copper sensitivity, chronic sialadenitis, liver cirrhosis, diabetes mellitus, and malnutrition.

Pediatric SS is a clinical diagnosis based on findings from physical examination, clinical history, and laboratory data, with histologic findings of lymphocytic or plasmacytic infiltration of the involved glands helping to confirm the suspected diagnosis (32). Clinical suspicion should be raised when a constellation of symptoms includes recurrent salivary gland enlargement, chronic xerostomia, or xerophthalmia (33). The evaluation should include Schirmer testing, rose bengal corneal staining with a slit-lamp examination, laboratory evaluation, scintigraphy, and salivary gland biopsy.

The laboratory panel should include erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor, a complete blood cell count, lupus inhibitor, anti-SS-A/anti-SS-B antibodies, EBV, and quantitative immunoglobulin studies (32,33). These are done to rule out secondary SS. Scintigraphy can be performed to evaluate the functional status of the glands.

A biopsy of the salivary glands should be performed to confirm the suspicion of SS. Minor salivary gland biopsy has become widely used as the diagnostic modality of choice. However, lip biopsies have been shown to be poorly sensitive and often provide inadequate salivary gland samples. Reports in the literature cite a rate of sensitivity of 33% to 58% by using lower-lip biopsy (32). In one of the more recent publications, McGuirt et al. (32) performed biopsies of the tail of the parotid and showed a 100% sensitivity rate in six patients. No complications were reported with this type of biopsy, but it does produce a cutaneous scar. Histopathologically, SS is identical to what has been known as Mikulicz disease.

Treatment is directed at prevention of intraoral and ocular complications due to the sicca syndrome. Chronic xerostomia increases the incidence of dental caries; appropriate methods of prevention of dental caries include reduction of sugar intake, topical fluoride application, and close monitoring of dental plaque. Symptoms of severe xerostomia can be alleviated by frequent mouth rinses with water, over-the-counter artificial saliva, aerosolized water/glycerin combinations, and use of sialogogues. More recently, pharmaceutical agents such as pilocarpine (Salagen) have been recommended for treatment of adult xerostomia. Unfortunately, no studies have been performed in the pediatric population to prove safety and efficacy.

In cases of primary SS, long-term follow-up is necessary to ensure that no systemic disease has developed. In cases of secondary SS, treatment with systemic antiinflammatory agents is necessary. In the short term, systemic antibiotics and corticosteroids are necessary to manage symptomatic parotid swelling (see Table 89.1). Another reason for long-term follow-up of these patients is the occasional association of SS with lymphoma in the adult population. Numerous reports document the increased risk of non-Hodgkin lymphoma 6 months to 13 years after the initial diagnosis of SS in adults. With this in mind, among the 200 reported cases of SS in the pediatric population, lymphoma has developed in none (32,33).

OTHER DISORDERS

Sialorrhea

Excess drooling, or sialorrhea, is the pathologic loss of saliva from the oral cavity. It is most commonly seen in the neurologically or mentally impaired patients. It is an important clinical problem in about 10% to 38% of patients with cerebral palsy (CP) (34).

Drooling is a normal physiologic condition seen in the infant until maturation and social awareness are achieved. Commonly, by age 3 to 4 years, drooling should resolve. Approximately 1.5 to 2 L of saliva per day is produced in the oral cavity and oropharynx. In the nonstimulated state, nearly 80% of the flow is produced by the submandibular glands and the sublingual glands, 10% to 15% by the parotid glands, and 5% to 10% by the minor salivary glands (35,36). Sialorrhea is often a manifestation of a discoordinated swallowing mechanism, most commonly in the oral phase. This deficit may be central, as in CP or mental retardation, or peripheral, as in facial nerve or glossopharyngeal nerve palsy (36). It is not due to an overproduction of saliva, as studies have shown that drooling patients

produce the same amount of saliva as do controls (37). A number of other factors contributing to sialorrhea include poor head control, constant open-mouth posture, poor lip and tongue control, hypoactive gag reflex, diminished intraoral sensation, and constant tongue-thrusting movement. Drooling also can be due to chronic nasal obstruction secondary to adenotonsillar hypertrophy, nasal septal deformity, turbinate hypertrophy, or rhinorrhea. Nasal obstruction may exacerbate sialorrhea by encouraging an open-mouth position. These potential sites of pathology should be addressed before manipulation of salivary flow.

The management and evaluation of sialorrhea should be interdisciplinary, and important issues to consider are dental disease, head positioning, malocclusion, airway obstruction, and the side effects of medical therapy.

The initial treatment of sialorrhea is noninvasive. This approach includes physiotherapy, anticholinergic/antihistamine pharmacotherapy, or both. Physiotherapy has been shown to be effective in higher-functioning children but is effective as an adjunct even in children with less neuromuscular coordination if started early in infancy (36). Even though the results are not overwhelming, it is recommended to undergo a physical therapy consultation before surgical intervention (36) (see Table 98.1).

Depending on the modality of therapy chosen, the treatment of drooling may lead to problems with oral health. Saliva buffers and provides ions for remineralization of the teeth, and so regular dental exams are important to encourage in order to minimize carries and other pathologies such as gingivitis, tooth destruction, cheilitis, crusting of the tongue/palate, and burning sensation intraorally (38).

The aim of pharmacotherapy is to reduce salivary flow by blocking parasympathetic stimulation of the salivary glands. The lack of compliance and success with this route of treatment stems from intolerable side effects such as urinary retention, constipation, blurred vision, xerostomia, and restlessness, making these drugs less desirable for long-term use. The results with oral medications are not consistent and dose dependent and must be used with caution in patients with cardiac disease, pyloric obstruction, ileus, etc.

Radiation therapy for management of sialorrhea is no longer recommended because of the risk of developing a malignancy.

Multiple different surgical options exist for patients with excessive drooling. Surgical management of drooling has been directed at either rerouting the flow of saliva or reducing the salivary output. The goal is to reduce salivary flow significantly while maintaining a moist intraoral environment to avoid dental caries and xerostomia. Submandibular duct rerouting was previously commonly used. The procedure is easy to perform and has reportedly good results; however, the increase in salivary flow to the oropharynx may cause salivary contamination of the lower respiratory tract. Rerouting in a patient with severe spastic esophageal disease or esophageal stricture should be avoided, and a barium swallow is an indicated preoperative study. Complications related to submandibular duct relocation include ranula and lateral neck cyst formation, requiring additional surgery. Some institutions recommend addition of simultaneous sublingual gland excision to complete the procedure (39). In performing this procedure, it is crucial to avoid the large veins in the floor of the mouth as ligation of those veins may result in tongue edema.

Denervation of the parasympathetic stimulus via bilateral tympanic neurectomy or bilateral chorda tympani nerve section has a reported success rate ranging from 47% to 100%. For an approximate success rate of 75%, both nerves must be sectioned bilaterally (40). Disadvantages include short-term success due to late regrowth of preganglionic fibers, loss of taste to the anterior two-thirds of the tongue, production of mucoid saliva, and bilateral otologic procedures. The main contraindication is a history of unilateral sensorineural hearing loss.

Submandibular gland excision also is an option, either alone or in combination with another procedure. The approach to this gland is simple and familiar to the otolaryngologist. Obviously, salivary flow is significantly diminished, potentially promoting dental caries and dysphagia secondary to lack of lubrication. Excision of the parotid glands has not been advocated because of risk of injury to the facial nerves.

Parotid duct ligation is commonly performed in conjunction with submandibular duct excision to control sialorrhea. Ligation of the submandibular ducts is not recommended because of the increased risk of calculus formation in comparison with the parotid. This is hypothesized to be due to the higher alkalinity and viscosity of submandibular saliva, the higher concentration of calcium and phosphate salts, the longer duct system, and the stasis that is associated with the orifice being superior to the gland (41).

At our institution, the recommended approach is bilateral submandibular gland excision with bilateral parotid duct ligation. This targets the resting salivary gland flow as well as the stimulatable salivary production during food intake. A review of 93 patients undergoing this procedure showed a significant improvement in drooling in 65% of patients and elimination of drooling in 21% of the patients (41). Another study of 33 patients examined patient caregiver satisfaction after various surgical interventions. Patients undergoing four duct ligations had markedly lower satisfaction scores and higher recurrence rates when compared to submandibular gland rerouting with sublingual gland excision and submandibular gland excision with parotid duct ligation (42). A recent metaanalysis found overall surgical success to be 81.6% across all studies. The highest rate of success was with bilateral submandibular gland excision and parotid duct rerouting, with rates that were similar to those for submandibular gland excision with parotid duct ligation (43,44).

Recent reports suggested using botulinum neurotoxin type A injections into the major salivary glands as an option for management of sialorrhea. The therapeutic effect is based on the anticholinergic action of the toxin at the level of the salivary gland receptors. Thus, injection

of botulinum toxin can depress the secretory capacity of the glands, which is responsible for secretion of water and electrolytes. It has been shown, too, that the toxin does not affect the adrenergic portion of salivary gland innervation, which is mainly responsible for protein discharge. Thus, the patient retains a sufficient basal secretion, avoiding xerostomia and dental caries. The intraglandular injections should be performed with a 25-gauge needle with ultrasound guidance. According to the protocol reported by Jongerius et al. (34), weight-dependent dosages are injected into each gland: 15 U/gland for children who weigh less than 15 kg, 20 U/gland for children weighing between 15 and 25 kg, and 25 U/gland for children who weigh more than 25 kg. Each dose is fractionated and divided over three sites in the gland. This study also suggested a similar efficacy between the use of Botox and scopolamine, yet without the side effects of the medical form of management.

A recent study by Khan et al. of 45 children injected with Botox for sialorrhea showed that 80% of caregivers reported increases in quality of life associated with decreased drooling. Mean duration of effect was 4.6 months. Side effects were generally mild, but did include several cases of dysphagia and one episode of aspiration pneumonia (45).

Botox B has been used for management of dystonia; however, due to immunogenic effects (by creating autoantibodies) and due to higher autonomic side effects, it is not frequently used for this indication (46).

When persistent or recurrent sialorrhea is observed after surgical intervention, radionuclide scans using a 99m technetium pertechnetate (^{99m}Tc) might be useful in elucidating the need for repeated ligation of the parotid ducts. However, no well-designed studies have reported findings in groups of patients who underwent successful procedures compared with those with poor results to allow useful interpretation of these scans (39).

Trauma

Injury to the salivary glands can be the result of blunt and penetrating trauma as well as secondary to radiation therapy. A systematic evaluation of gland parenchyma, duct integrity, and facial nerve status will ensure proper management. Injury to the gland's substance does not require specific therapy, except for wound irrigation and possible drainage and antibiotics. Facial nerve function evaluation is essential on presentation. Deep penetrating wounds with facial nerve compromise should be surgically managed within 3 days. Injury anterior to Ohngren line (an imaginary vertical line between the lateral canthus and mental foramen) does not require repair of the facial nerve, as regeneration is highly likely. Posterior to this line, primary repair is required. Exploration of the main trunk of the facial nerve and identification of its branches will help identify proximal and distal nerve stumps.

When a penetrating wound is found posterior to the anterior border of the masseter, injury to Stensen's duct should be suspected. This requires wound exploration and primary repair, most often over an inert silicone rubber (Silastic) stent. Probing the duct transorally should help in identifying the site of injury if it is not clearly seen on wound exploration. If primary reanastomosis is not possible because of loss of duct substance, then the duct can be rerouted intraorally. Another option is to ligate the proximal stump, allowing the parotid gland to atrophy. Salivary gland hematomas or pseudocysts may result from blunt trauma. Historic details will usually elucidate the etiology of an acute onset of a parotid mass as a hematoma or a delayed presentation of a cyst. It may be necessary to aspirate or drain these collections. A pressure dressing should be applied to avoid reaccumulation of the fluid. Pretreatment ultrasonography will usually be diagnostic.

Much less common in the pediatric population is the occurrence of pneumoparotitis, which requires no treatment. This is seen in individuals who require increased intraoral/buccal pressure to play a musical instrument or in glassblowers.

The salivary glands are sensitive to radiation trauma. Xerostomia is an expected complication and can be managed with artificial saliva preparations. Increased hydration and use of sialogogues should be encouraged to avoid dental caries. Close surveillance is important as well, as the risk of a secondary malignancy is increased even after low-dose radiation.

HIGHLIGHTS

- The most common pediatric salivary gland disorders are inflammatory.
- All pediatric salivary gland cysts should be evaluated to exclude HIV as an underlying etiology.
- Sialolithiasis is uncommon in the pediatric population. The most commonly affected site is the submandibular gland, followed by the parotid. Ninety percent of the calculi are radiopaque.
- Salivary gland neoplasms represent 8% of pediatric head and neck neoplasms (fourth most common after nasopharyngeal, skin, and thyroid tumors).
- Fifty percent of pediatric salivary neoplasms, excluding vascular neoplasms, are malignant (higher rate than in adults). A solid mass in a child is 2.5 times more likely to be malignant than it is in the adult.
- Seventy-four percent of benign salivary tumors are hemangiomas. The majority occurs in the parotid gland, and diagnosis is clinical. Treatment is conservative unless rapid progression or functional obstruction occurs.
- Lymphangiomas account for 19% of benign salivary neoplasms in the pediatric population. Unlike hemangiomas, lymphangiomas do not replace the glandular parenchyma. Treatment is surgical.

- The parotid gland is the predominant location for salivary tumors (65.8%). The majority of these tumors are malignant (80%) and appear at the angle of the mandible.
- A role for FNA exists in diagnosing salivary gland tumors; however, definitive diagnosis should be based on permanent pathology sections.
- Although the CT scan is the diagnostic modality of choice for evaluating salivary gland diseases, the jury is out with respect to CT versus the use of MRI.

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Otitis Media in the Age of Antimicrobial Resistance

99

Margaretha L. Casselbrant *Ellen M. Mandel*

Otitis media (OM), inflammation of the middle ear, is, next to the common cold, the most common diagnosis made in children. Prior to the antibiotic era, it was a very serious disease with high morbidity and mortality due to intratemporal and intracranial complications. With the introduction of antibiotics, the frequency of sequelae and complications were reduced. However, overuse of antibiotics in the treatment of acute otitis media (AOM) and otitis media with effusion (OME) has led to the development of resistant bacteria. Therefore, judicious use of antibiotics is recommended, and today, watchful waiting without antibiotics may be considered as an option in mild disease, especially in older children.

DIAGNOSIS

Definition/Symptoms and Signs

Although considered to be a continuum, OM can be subclassified into AOM and OME based on signs and symptoms. As the treatment of AOM and OME differs, it is important to accurately diagnose the two conditions. AOM is generally characterized by rapid onset of signs and symptoms of inflammation in the middle ear accompanied by middle-ear effusion (MEE). Signs of inflammation include bulging or fullness of the tympanic membrane (TM), erythema of the TM, and acute perforation of the TM with otorrhea. Symptoms include otalgia, irritability, and fever. OME, on the other hand, is defined as MEE without signs and symptoms of acute inflammation as found in AOM (Fig. 99.1).

Pneumatic Otoscopy

Pneumatic otoscopy is the primary diagnostic tool to evaluate the status of the middle ear as it allows for assessment of the TM and its mobility. The normal TM is translucent, concave, and moves briskly with application of positive and negative pressure. A visible landmark is the handle (manubrium) of the malleus, which is attached to the TM, with the umbo in the center of the TM. To adequately visualize the TM, the external ear canal must be cleared of cerumen and debris. The assessment of the TM should include *position, color, degree of translucency, and mobility*. To ascertain the mobility of the TM, a good airtight seal must be obtained between the speculum and the ear canal. The largest speculum that fits comfortably should be used. A bulb through which air is puffed should be attached to the otoscope, allowing for visualization of TM mobility. Reduced or no mobility of the TM indicates loss of compliance of the TM either as a result of effusion in the middle ear or increased stiffness due to scarring or increased thickness of the TM. Total absence of mobility of the TM may also be due to an opening in the TM either as a perforation or a patent tympanostomy tube. Other features, such as fluid levels or bubbles, may be more easily discerned with movement of the TM. The position of the TM ranges from severely retracted to bulging. Mild to moderate retraction indicates negative pressure, MEE, or both, while a severely retracted TM is usually associated with effusion. Fullness and bulging of the TM is caused by increased pressure, fluid, or both, in the middle ear. Opacification of the TM may be caused by thickening or scarring or middle-ear effusion. A red but translucent TM is usually caused by crying or sneezing due to engorgement of blood vessels in the TM. On the other hand, a "red" opaque TM that is full or bulging is often a sign of AOM. A pink, gray, yellow, or blue retracted TM with reduced or no mobility is usually seen with OME. Myringitis is inflammation of the TM without fluid in the middle ear. Use of an *operating microscope (otomicroscopy)* may clarify features seen on otoscopy, and visualization of scarring and atrophy of the TM may be enhanced. Use of a Siegel otoscope with the otomicroscope to provide the pneumatic component is advised.

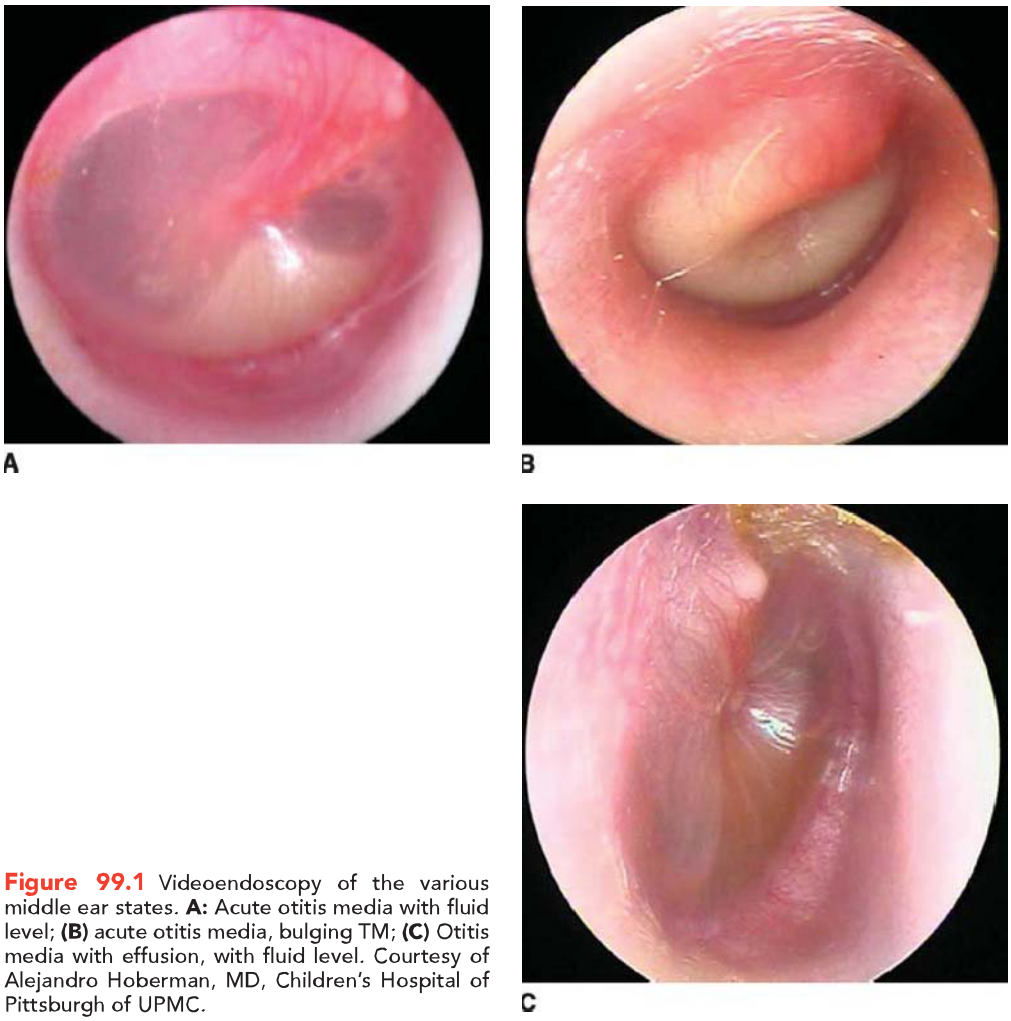


Figure 99.1 Videoendoscopy of the various middle ear states. **A:** Acute otitis media with fluid level; **(B)** acute otitis media, bulging TM; **(C)** Otitis media with effusion, with fluid level. Courtesy of Alejandro Hoberman, MD, Children's Hospital of Pittsburgh of UPMC.

Immittance Testing (Tympanometry)

Immittance testing (tympanometry) is an excellent adjunct to the assessment of middle-ear status and the management of OM. When otoscopic evaluation is uncertain or difficult to perform, tympanometry can be very useful in evaluating ear disease in children. It is easy to perform and most often well accepted by the patient. It has been used for school screening as well as in pediatricians' offices. It is also valuable for documentation of middle-ear status over time with repeat testing. The most commonly used frequency for tympanometric testing is 226 Hz; however, for children less than 6 months of age, a frequency of 1,000 Hz is recommended. A small probe that emits a tone is placed in the ear canal with an airtight seal. The tympanogram is obtained by plotting the immittance (acoustic energy of the reflected tone) of the middle ear as a function of the pressure in the external ear canal, which is varied from −400 to +200 daPa. The instrument provides measures such as peak compensated (static) admittance, tympanometric peak pressure, acoustic reflex, and tympanometric width (TW), a measure of gradient. Algorithms have been developed to determine the presence or absence of MEE, some combining pneumatic otoscopy and tympanometry. The following set of criteria using TW to categorize middle-ear status is used: TW < 150 daPa = no OME, TW > 350 daPa = OME, and TW between 150 and 350 daPa = presence or absence of OME is determined by otoscopy (1). A flat or rounded pattern (TW > 350 daPa) with a small ear canal volume indicates MEE, while a flat pattern with a large ear canal volume suggests a perforation or a patent tympanostomy tube. In a normal air-filled middle ear with equal pressure on both sides of the TM, the peak pressure of the tympanogram is 0 daPa. Other methods of ascertaining middle-ear status have been investigated including spectral gradient acoustic reflectometry (2,3) and ultrasound (4), but they have been found to have limitations, although they may be useful for screening.

Audiometry

MEE usually results in a mild to moderate conductive hearing loss. The assessment of hearing is essential to management, as hearing impairment can predispose to delay in speech and language development and may later affect school performance. Audiometry should be used to help

determine management of the child, with more aggressive management considered if there is significant hearing impairment.

Behavioral audiometry requires cooperation of the child with the examination, and the test is adapted to the age of the child. *Visual reinforcement audiometry* is used for children 6 months to 2 years of age and involves presentation of a sound stimulus in the sound field with observation of the child's conditioned head turn response. This is rewarded with a visual reinforcement such as an animated toy. *Play audiometry*, for children older than 2 years, is similar to *conventional audiometry* (for children over 5 years of age), but the child places toys in a bucket rather than raising a hand to acknowledge they heard the sound. *Conventional* hearing thresholds in the sound field or ear-specific are determined at 0.25, 0.5, 1, 2, 4, and 8 kHz, depending on the age of the child. High frequency testing, from 12 to 20 kHz, can also be obtained in children (see Chapter 100).

Auditory brainstem audiometry (ABR) and *transitory otoacoustic emission (TOAE)* are excellent methods for testing children who do not cooperate with behavioral hearing evaluation because of very young age or developmental delay. Except for infants, sedation or general anesthesia is usually necessary for ABR testing in younger children. Three electrodes are placed (forehead and each mastoid process) to record the response to clicks of 2,000 to 4,000 Hz or pure-tone burst. The ABR consists of five to seven vertex positive waves. Waves I to III presumably reflect activity of the auditory centers in the eighth nerve fibers and pons; waves IV and V presumably reflect activity of the auditory centers in mid- to rostral pons and caudal midbrain, respectively; and activity from waves VI and VII is less certain. The ABR reflects auditory neural electrical responses that are adequately correlated to behavioral hearing thresholds. However, a normal response on the ABR suggests only that the auditory system up to the midbrain level is responsive to the stimulus employed. Thus, it does not guarantee normal hearing.

Transitory otoacoustic emissions measure cochlear function (outer hair cells) and is an objective test of auditory function. It is commonly used for newborn hearing screening as it is fast and easy to perform. It is excellent for testing children who do not cooperate with behavioral testing. MEE may confound the results. Therefore, if the OAEs are absent, immittance testing should be performed to assess the middle ear. For children who fail TOAE testing, follow-up audiologic testing must be done to assess type and degree of hearing loss.

EPIDEMIOLOGY

Incidence and Prevalence

OM is considered a worldwide pediatric health care problem. The Early Childhood Longitudinal Study-Birth Cohort (ECLS-B), a nationally representative longitudinal study of more than 8,000 children born in 2001, showed that OM was diagnosed in 39% of children by 9 months and 62% of children by 2 years of age (5). Although the highest incidence of OM is in young children, it occurs in older children, adolescents, and adults. The Oslo Birth Cohort, enrolling infants born in 1992 to 1993, found that among 10-year-olds 13% had at least one episode of OM in the previous 12 months (6). Approximately 3% to 15% of patients with OM referred to otolaryngology clinics are adults (7). While recent studies from the United States (8), Norway (9), the Netherlands (10), and the United Kingdom (11) have indicated that there is a general decline in OM incidence, studies from developing countries and indigenous populations continue to demonstrate a heavy burden of OM (12,13).

Acute Otitis Media

Most children experience at least one episode of AOM during their childhood. The cumulative incidence of the first episode of AOM based on studies from various countries ranges from 19% to 62% by age 1 year and 50% to 84% by 3 years of age (Fig. 99.2) (14–20). In the majority of these studies, the peak incidence of AOM occurred during 6 to 12 months of life (20). The incidence decreases with age, and by 7 years of age, few children experience episodes of AOM. Recurrent episodes of AOM are common in young children. By 6 months of age, 20% have had two or more episodes (21). Three or more episodes of AOM by ages 1, 3, 5, and 7 years have been documented in 10% to 19%, 50%, 65%, and 75% of children, respectively (20). Six or more episodes of AOM were documented in 39% of children by age of 7 years. It should be noted that these data were obtained prior to the use of pneumococcal vaccine in infants and young children.

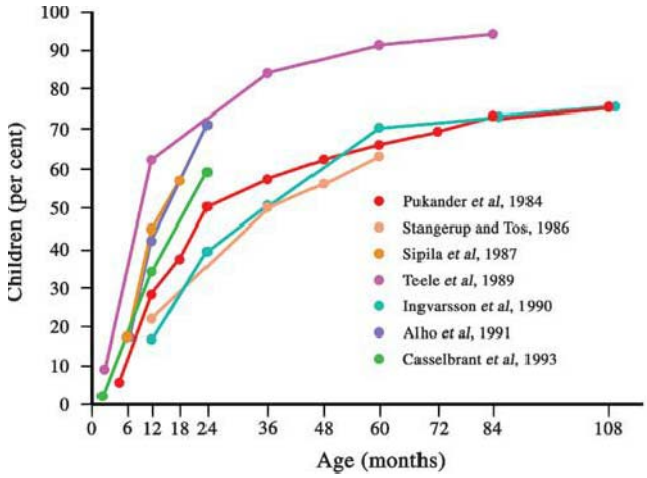


Figure 99.2 Cumulative incidence of first episode of AOM. (Reproduced from Casselbrant ML, Mandel EM. Epidemiology. In: Rosenfeld RM, Bluestone CD, eds. *Evidence-based otitis media*, 2nd ed. Hamilton, ON: BC Decker, 2003:147.)

Otitis Media with Effusion

It may be difficult to determine the "true" incidence of OME as by definition OME is asymptomatic. Therefore, a short time between observations is needed to precisely assess the onset and time to resolution of each new episode of OME as approximately 65% of OME episodes in children 2 to 7 years resolve within 1 month (22). Monthly examinations with otoscopy and tympanometry in 2- to 6-year-old children in a day care center in Pittsburgh revealed MEE at least once in 53% to 61% of the children and a Danish study found an incidence of MEE of 26% in 7-year-old children followed monthly for 1 year using tympanometry (23).

The point prevalence of MEE from different countries shows a wide variation depending on the age of the child, season of the year, as well as type of assessment. Thus, it must be emphasized that when comparing the outcome between studies, there is a need to evaluate study methodology and exercise caution when drawing conclusions. However, nearly all children experience at least one episode by 3 years of age (24).

Risk Factors

Risk factors can be host related (age, gender, race, prematurity, allergy, immunocompetence, cleft palate and craniofacial abnormalities, genetic predisposition) as well as environmental (upper respiratory infections [URIs], seasonality, day care, siblings, tobacco smoke exposure, breast-feeding, socioeconomic status, pacifier use, and obesity) and are considered important in the occurrence, recurrence, and persistence of middle-ear disease.

Host-Related Factors

Age

The highest incidence of AOM occurs between 6 and 11 months of age (20), and onset of the first episode of AOM before 6 months (20) or 12 months of age is a powerful predictor of recurrence (25). The risk of persistent MEE after an episode of AOM is inversely correlated with age (20), and children who experience their first episode of MEE before 2 months of age are at a higher risk for persistent fluid during their first year of life than are children having their first episode later (26).

Sex

Most investigators have reported no apparent sex-based difference in the incidence of OME. Some studies have found a significantly higher incidence of AOM in males as well as more recurrent episodes than in females, but others have not found this (24).

Race

Previous studies have suggested a lower incidence of OM in black children compared to white children. However, more recent studies in which the children were followed prospectively with examinations of the ears every 6 weeks showed no difference between the black and white children in their experience with OM (27,28). One study, part of an American population–based sample survey evaluating school children ages 6 to 10 years with tympanometry, also reported no difference between black and white children. However, the prevalence of OME was significantly higher in Hispanic children compared to white children (29).

Allergy/Immunocompetence

Controversy remains regarding the role of allergy in the pathogenesis of OM as allergy is a common problem in children, occurring at a time when respiratory infections and OM are common. Most, but not all, of the epidemiologic studies have supported an association. Pukander and Karma (30) found, in 707 children with AOM, that in children with atopic manifestations, the persistence of MEE for 2 months or longer was greater than in children without allergy. However, in another study, atopic diathesis was not found to predispose a child to the development of AOM (31). Tomonaga et al. (32) determined that allergic rhinitis was present in 50% of 259 patients (mean age of 6 years) in whom OME had been diagnosed while OME was present in 21% of 605 patients (mean age of 9 years) in whom allergic rhinitis had been diagnosed. Among 108 children (ages 5 to 8 years, mean age of 6 years) in whom neither condition had been diagnosed, the incidences of allergic rhinitis, OME, and both of these conditions were 17%, 6%, and 2%, respectively. Another investigative group (33) compared 76 children with MEE admitted for bilateral myringotomy with tube insertion (M&T) to 76 controls matched by age, gender, and season of admission for a general surgical procedure. Results showed a nearly fourfold increase in the risk of persistent MEE in children who had atopic symptoms for more than 15 days per month. In another study, Bernstein and Reisman (34) determined the allergy status of a group of 200 children who had undergone one or more M&T procedures. They diagnosed allergy in 23% of the entire group but found that the frequency was 35% among the 88 children with multiple myringotomies with tube insertions. The frequency of allergy in these patients was higher than that reported for children of similar age in the general population. The above studies generally found a higher frequency of OME in allergic children compared with age-matched nonallergic children, as well as higher frequencies of allergy in children with OME compared with children without OME. Skoner et al. (35) suggested that if significant allergic rhinitis is diagnosed in a patient with OME, it should be treated aggressively. More studies are needed to evaluate the relationship between these two conditions.

Children with recurrent OM as well as other recurrent infections may have a defect in the immune system such as a defect in phagocyte function, humoral immunity, local

immunity, or other immune defects (36). Immunologic screening is indicated to exclude an immunodeficiency in children with frequent episodes of OM or an abnormal course of disease (37). While agammaglobulinemia and hypogammaglobulinemia are rare, deficient or lowered immunoglobulin (Ig)A or decreased levels of one or more IgG subclasses, in particular IgG2, are more common. The specific antibody response to bacterial capsular polysaccharides is often low. Kaur et al. (38) reported finding that, after an episode of AOM due to *Streptococcus pneumoniae*, otitis-prone children and children who failed treatment for AOM had less of an IgG serum antibody response compared to non-otitis-prone children to proteins of *S. pneumoniae*. Children infected with the human immunodeficiency virus have a significantly higher recurrence rate than normal children or children who have seroconverted (39).

Cleft Palate/Craniofacial Abnormality

To date, no evidence suggests an effect of cleft palate/cleft lip type or laterality on OME prevalence (40), and an equally high OME prevalence was reported in patients with diagnosed submucosal cleft palate (41) but not in patients with bifid uvula (42,43). OM is considered "universal" in infants less than 2 years of age with unrepaired cleft palate (44). After surgical repair of the palate, the occurrence of OM is reduced, which is most likely due to improvement of eustachian tube function. In a prospective study of 150 children with cleft lip and palate, enrolled between 2 and 18 months of age, Robinson et al. (45) reported a 92% prevalence of OME before palate repair, no short-term change after palate repair, but a reduced prevalence to 70% at 4 years of age. Many children continue to have problems up into the teens. A reduction of middle-ear disease by newer palatoplasty procedures has been suggested (46). OM is also common in children with other craniofacial abnormalities also due to anatomical or functional eustachian tube dysfunction (47). Down syndrome children have, in addition to poor active eustachian tube function, low resistance of the eustachian tube, which predisposes to reflux of nasal secretions into the middle ear (48).

Genetic Predisposition

The frequency of the occurrence of one episode of OM is so high that a genetic predisposition cannot be expected. However, a predisposition to recurrent episodes of OM and chronic MEE may have a significant genetic component. The etiology of OM is multifactorial, involving environmental as well as genetic factors. A large number of genes may be involved, each contributing to a particular increase in disease risk.

Twin and triplet studies have been used to assess the heritability of OM. Two retrospective studies using questionnaires have been published. The first study, using 2,750 Norwegian twin pairs, estimated the heritability at 0.74 in females and 0.45 in males (49). In the second study, the estimated heritability was, on average, 0.57 at ages 2, 3, and 4 years (50). In a prospective twin/triplet study from Pittsburgh with monthly assessments of middle-ear status, the heritability estimate for OM at age 2 years was 0.79 in females and 0.64 in males (51). Heritability is a population statistic to ascertain if a trait is heritable, while linkage and association studies may identify genetic regions or specific genes influencing the particular trait or disease. Daly et al. (52), using genome-wide linkage analysis, have suggested that regions of chromosomes 19q and 10q contain genes contributing to the susceptibility to chronic OME/recurrent AOM. Subsequent fine mapping of both regions further strengthened the evidence for this linkage (53). A second genome-wide linkage analysis demonstrated linkage regions with plausible candidate genes in 17q12 (AP2B1, CCL5, and a cluster of other CCL genes) and in 10q22.3 (SFTPA2) (54). Polymorphisms in mannose binding proteins (55), surfactant protein (56), mucin expression (57), and cytokines (58,59) have been associated with mucosal immunity and development of disease. In addition, polymorphisms in three genes (FBXIIO, TLR4, and PAII) originally identified in mouse models of OM have shown evidence of susceptibility to childhood OM in cohort studies (60–62).

Environmental Factors

The main risk factors for OM are day care, number of siblings, tobacco smoke exposure, breast-feeding, birth weight, socioeconomic status, and air pollution. Environmental risk factors for OM across Western countries, including European countries, the United States, Canada, and Australia, have shown large variations in rates across the various countries: day care at ages 1 to 3 years (Sweden 75% vs. Italy 6%), breast-fed at 6 months (Norway 80% vs. Poland 6%), and women smoking (Germany, France, and Norway 30% to 40% vs. Portugal less than 10%) (63).

Upper Respiratory Infection/Seasonality

Both epidemiologic evidence and clinical experience strongly suggest that OM is frequently a complication of an URI. The incidence of AOM is highest during the fall and winter months and lowest during spring and summer months, which parallels the incidence of URI (22). This supports the hypothesis that an episode of URI plays an important role in the etiology of OM. Rhinovirus, RSV, adenovirus, and coronavirus have been detected in MEE during episodes of AOM (64,65). Winther et al. (66) reported that the OM complication rate of a cold-like illness was 33%. The predominant virus in this population was the rhinovirus.

Day Care/Home Care/Siblings

Almost universally, day care center attendance remains a very important risk factor for development of OM. For example, prevalence of high negative middle-ear pressure

and flat tympanograms (type B), indicative of MEE, have been shown to be highest in children cared for in day care centers with many children, intermediate in children in family day care with fewer children, and lowest in children cared for at home (67). Data from the United States ECLS-B, including more than 8,000 children studied at 9 months and 2 years of age, showed a significant increased risk for recurrent AOM and tube insertion for children attending day care (5).

Birth order has been shown to be associated with episodes of OM and percentage of time with MEE (22). Firstborn children had a lower rate of episodes of AOM and less time with MEE during the first two years of life than children with older siblings. Also, having more than one sibling was significantly related to early onset of OM (30), and the presence of more children in the household was related to more time with MEE (28).

The reason for the higher morbidity in children in day care centers and in children with older siblings may be related to the greater opportunity for exposure to viral URI, which may cause eustachian tube dysfunction leading to the development of OM.

Tobacco Smoke Exposure

An association between OM and passive exposure to smoking has been reported by many investigators, while others have not been able to demonstrate such an association. In most studies, the information regarding smoke exposure has been obtained from the parents. A few studies have measured cotinine, a metabolite of nicotine, in blood, urine, or saliva of the child and have been able to more accurately determine the association between OM and smoke exposure (21,68). More information about the pathogenesis, duration, and intensity of exposure is needed to clarify this association. Two studies have shown an association between middle-ear status and parental smoking. In children exposed to parental smoking, tympanostomy tubes stayed in place for 59 weeks compared to 86 weeks in children who were not exposed to smoking (69). Also, myringosclerosis was more prevalent in children with two smoking parents compared to those with no smoking parents (64% vs. 20%), and maternal smoking was associated with a highly increased risk of recurrent OM after insertion of tympanostomy tubes (70).

Breast-/Bottle Feeding

Breast-feeding for 6 months exclusively is recommended by most national and international authorities, including the American Academy of Pediatrics and the American Academy of Family Physicians, the World Health Organization (WHO), and the United Nations Children's Fund. In 2002, Kramer and Kakuma (71) published a comprehensive review of the world literature to determine health benefits of exclusive breast-feeding for 6 months compared to 3 to 4 months. They reported a decrease in the risk for gastrointestinal infection even in developed areas. It had not been shown previously that exclusive breast-feeding for 6 months or longer compared to 4 to less than 6 months in the United States provided greater protections against respiratory infections. Therefore, a secondary analysis of data from the National Health and Nutrition Examination Survey III, a population-based cross-sectional home survey conducted from 1988 to 1994, was undertaken (72). After adjusting for demographic variables, child care and smoke exposure, the data revealed statistically significant increased risk for both pneumonia (OR: 4.27; 95% CI: 1.27 to 14.35) and three or more episodes of OM (OR: 1.95; 95% CI: 1.06 to 3.59) in those children breast-fed 4 to less than 6 months. These findings further support the current recommendations that infants receive breast milk exclusively during the first 6 months of life.

Socioeconomic Status

Socioeconomic status and access to health care are factors that may affect the incidence of OM. It has been generally thought that OM is more common among the lower socioeconomic strata due to poor sanitary conditions and crowding. Paradise et al. (28) followed 2,253 infants for 2 years in the United States and found an inverse relationship between the cumulative proportion of days with MEE and socioeconomic status. However, many studies have not revealed any correlation between socioeconomic status of the child's family and the incidence of MEE.

Pacifier Use

Niemelä et al. (73) reported that pacifier use increased the annual incidence of AOM and calculated that pacifier use was responsible for 25% of AOM episodes in children younger than 3 years. They reported the results of an intervention trial in which parents in various well-baby clinics were taught that pacifier use was harmful and should be limited, while parents in other clinics were not provided with this information. This led to a 29% decrease in AOM in the group provided with pacifier information. Pacifier use has been theorized to contribute to the development of OM, possibly due to the sucking action of the child propelling nasopharyngeal secretions into the middle ear or by the pacifier acting as a fomite. However, Brook and Gober (74) cultured the surface of pacifiers from children with AOM but found no pathogens typical of AOM. The role of pacifier use in AOM remains unclear.

Obesity

Recent studies have indicated that there may be an association between OM and body mass index (BMI). Tympanostomy tube insertion and overweight were studied in a predominantly white cohort of children (97%) followed from birth to 2 years of age (75). Weight for length and BMI

for age were calculated using well-child visit data. A history of tympanostomy tube insertion significantly predicted risk of BMI index at both greater than 95th percentile and greater than 85th percentile at 2 years of age after controlling for risk factors and confounders. However, early weight status was not related to later OM, recurrent OM, or tympanostomy tube insertion. In another cohort of American Indian children, a history of recurrent AOM increased the likelihood of weight-for-length index greater than 95th percentile (76). The mechanisms are not clear, but it was suggested that inflammatory changes in the middle ear can result in objective gustatory changes.

PATHOPHYSIOLOGY AND PATHOGENESIS

The pathophysiology of OM is multifactorial with various overlapping factors (Fig. 99.3).

Eustachian Tube Function

The eustachian tube in the infant is shorter, wider, and more horizontal than in the adult, which leads to the high rate of OM in infants and children. By 7 years of age, when the tube has a more adult configuration, the prevalence of OM is low (77). The three physiologic functions of the eustachian tube are (a) *pressure regulation* (ventilation), (b) *protection*, and (c) *clearance* (drainage). Of these three functions, pressure regulation is the most important (36) (Fig. 99.4). Middle-ear pressure is equilibrated to atmospheric pressure through active intermittent openings of the eustachian tube caused by contraction of the tensor veli palatini muscle during swallowing, jaw movements, or yawning. If active function is impaired, negative pressure will develop in the middle ear. Pressure regulation can be impaired by failure of the opening mechanism *(functional obstruction)* or anatomical *(mechanical)* obstruction. In ears with normal eustachian tube function, the eustachian tube is collapsed when at rest. This protects the middle ear from nasopharyngeal sound pressure and reflux of secretions from the nasopharynx. The clearance of secretions produced within the middle ear into the nasopharynx is provided via the mucociliary system and through the "pumping action" of the eustachian tube during closing. The passive closing of the tube is initiated at the middle-ear end of the eustachian tube and progresses toward the nasopharyngeal end, which results in removal of the secretion.

Using a pressure chamber, Bylander et al. (78) evaluated eustachian tube function in children and adults who were considered otologically normal with intact TMs. While only 5% of the adults were not able to equilibrate negative middle-ear pressure, as many as 35.8% of the children

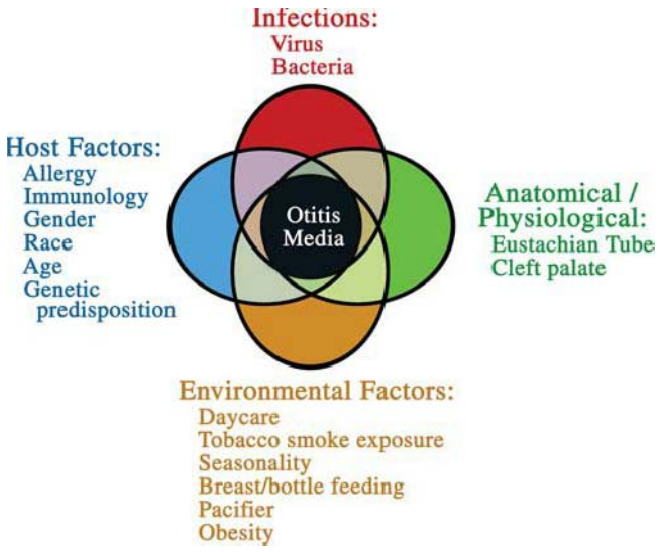


Figure 99.3 Various factors interact in the pathogenesis of OM. (Adapted from Casselbrant ML, Mandel EM. Acute otitis media and otitis media with effusion. In: Flint W, et al, eds. *Cummings otolaryngology—head and neck surgery*, 5th ed. Philadelphia, PA: Mosby Elsevier, 2010.)

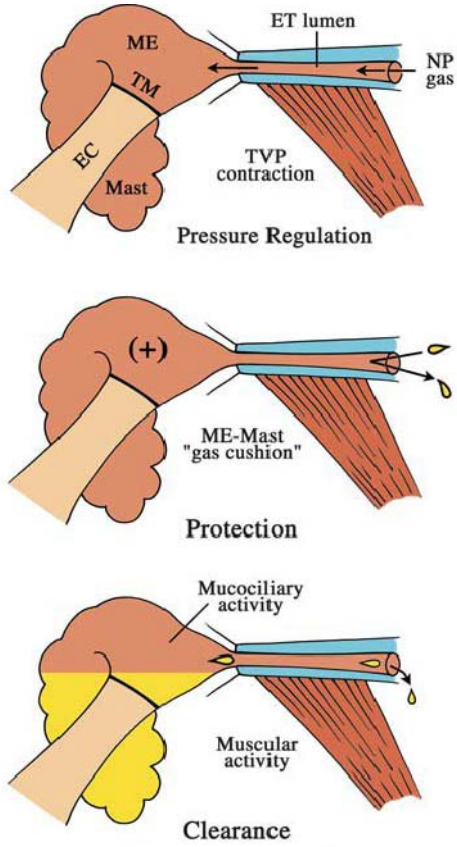


Figure 99.4 Functions of the eustachian tube (ET)–middle ear (ME)–mastoid (mast) gas cell system. Pressure regulation function is related to active dilation of the tube by contraction of the tensor veli palatini muscle (TVP) (*upper figure*). Protective function is dependent, in part, on an intact middle ear and mastoid gas cells to maintain a gas cushion (*middle figure*). Clearance function is enhanced by mucociliary activity and muscular activity during tubal closing (*lower figure*). EC, external canal; NP, nasopharynx; TM, tympanic membrane. In: Bluestone CD. *Eustachian tube: structure, function, role in otitis media.* Hamilton, ON: BC Decker, 2005:51.

could not equilibrate negative pressure. Children ages 3 to 6 years performed worse than children ages 7 to 12 years. These studies indicate that in even apparently otologically normal children, eustachian tube function is worse than in adults, but it does improve with age. The improvement in the eustachian tube function parallels the decrease in the incidence of OM. Stenström et al. (79) tested eustachian tube function in 50 otitis-prone children and 49 children with no history of AOM (controls) using a pressure chamber. The otitis-prone children had significantly poorer active tubal function than the normal controls, suggesting that recurrent AOM is the result of functional obstruction of the eustachian tube.

The forced response test (FRT) is designed to measure the passive and active function of the eustachian tube. In a recent pilot study, the FRT was used to test 3-year-old children 3 months after tympanostomy tube insertion with chronic OME (17 children, 24 ears) or recurrent AOM (15 children, 22 ears). The passive resistance and one measure of active function were significantly higher in the recurrent AOM group. The frequency of tubal dilation was not significantly different between the groups (80). However, based on the high variability in all the test parameters, the authors dismiss the possibility that an individual can be assigned to a particular disease expression based on the FRT test.

Infection

Bacteriology

Prior to the year 2000, studies in the United States reported that *S. pneumoniae* was the single most common bacterial pathogen in AOM, followed by *Haemophilus influenzae* and *Moraxella catarrhalis, Streptococcus pyogenes,* and other miscellaneous bacteria accounted for just a few cases. From ears with chronic OME, *H. influenzae* was the single most common pathogen, followed by *S. pneumoniae, M. catarrhalis,* and other bacteria accounting for a small percentage of cases each. Prevnar, a heptavalent conjugated pneumococcal vaccine (PCV7) for infants and young children, was licensed in the United States in 2000. Casey and Pichichero (81) examined the experience of children in a suburban Rochester, NY, practice in the years 2001 to 2003 (after the introduction of PCV7) compared to the years 1995 to 2000 and reported a 24% decrease in persistent AOM and AOM treatment failures. They also reported a decrease in recovery of *S. pneumoniae* from the ears of such children and an increase in *H. influenzae*. McEllistrem et al. (82) looked at middle-ear cultures obtained between 1999 and 2002 at five institutions. They reported that the percentage of AOM episodes due to non-PCV7 serogroups increased after 2000 from 12% in 1999 to 32% in 2002, and the nonvaccine serotypes were more frequent in those who received more than one dose of vaccine.

Nasopharyngeal carriage was also examined. Pelton et al. (83) enrolled 275 infants and children 2 to 24 months of age in a surveillance study in which nasopharyngeal swabs or nasal washes were obtained at all well-child visits and at visits for AOM. From 2000 to 2003, they noted a decrease in vaccine serotypes with an increase in nonvaccine serotypes. Tracking antimicrobial susceptibility, they found that the MIC50 and MIC90 for amoxicillin were stable until the last 6-month period when they both increased significantly. Jacobs et al. (84) examined the nasopharyngeal flora in children undergoing tympanostomy tube placement in March 2004 to March 2005 and also found a decrease in vaccine serotypes with a concomitant increase in nonvaccine serotypes, many of which were antibiotic-resistant strains.

Casey et al. (85) looked at the bacteriology of the nasopharynx and middle-ear fluid from children with no or infrequent episodes of AOM and from children with recurrent AOM during the years 2007 to 2009. Compared to their findings in 2001 to 2003, they found that, unlike shortly after the introduction of the conjugate pneumococcal vaccine, the frequency of non-PCV7 strains was nearly equal that of *H. influenzae*, with the nonvaccine serotypes, particularly 19A, replacing the vaccine serotypes. The frequencies of *S. pneumoniae* and *H. influenzae* were nearly equal, and the bacteria recovered from otitis-prone children were not different from that recovered from children with their first or second AOM episode.

Recently, a new vaccine with 13 serotypes of *S. pneumoniae* (PCV13) has replaced the 7-valent vaccine. In addition to the PCV7 strains, it includes serotypes 1, 3, 5, 6A, 7F, and 19A, which should add significant protection. As previously, there is a need for continued surveillance of the bacteriology of AOM with the use of this new vaccine.

Biofilms

Bacterial biofilms are sessile communities of interacting bacteria attached to a surface and encased in a protective matrix of exopolysaccharides rather than living in a motile "planktonic" or free-floating state. The matrix allows for protection from phagocytosis and other host defense mechanisms due to lack of accessibility by Igs and complement. The reduced metabolic rate of bacteria in the biofilm renders them resistant to antimicrobial treatment. The bacterial community relies on a complex intracellular communication system that provides for organized growth characteristics known as "quorum sensing." Biofilms have been known for a long time to exist on hard surfaces such as metal pipes, or teeth. Post et al. (86), using polymerase chain reaction methodology (PCR), found evidence of bacteria in 48% of culture-negative MEEs from children undergoing tympanostomy tube insertion for chronic OME. Hall-Stoodley et al. (87) obtained confocal laser scanning microscopy images from the middle-ear mucosa of 26 children scheduled for tympanostomy

tube insertion for recurrent/persistent OM and 8 controls (3 children and 5 adults) who underwent cochlear implants. Generic stains and species-specific probes for *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* were used to evaluate biofilm morphology. Mucosal biofilms were visualized in 92% of the mucosa from children with chronic and recurrent OM, but were not observed in any of the eight controls. The authors suggested that the findings supported the hypothesis that chronic middle-ear disease is biofilm-related. Biofilms have also been identified in the nasopharynx of children with OM, and it was suggested that the biofilm may act as a reservoir for bacterial pathogens resistant to antibiotics. The mechanical debridement of the nasopharyngeal biofilms may explain the observed clinical benefit associated with adenoidectomy in subsets of pediatric patients (88).

Nistico et al. (89), using a culture-independent molecular diagnostic methodology and confocal scanning, demonstrated that *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, and *S. aureus* were present in adenoids from children with "chronic otitis media" (rAOM and/or cOME) as well as in children with obstructive sleep apnea (OSA) in biofilm clusters on the mucosal surface and within adenoid crypts as well as intracellularly. The distribution of pathogens in the two groups was similar except that *H. influenzae* was significantly more common in children with chronic OM than in OSA (66.7% vs. 10%, $P = 0.005$).

Viruses

Until the introduction of PCR, viruses were not considered a major factor in the etiology of OM, probably due to technical difficulties in isolating the viruses. However, using the PCR technique, it has been possible to identify respiratory syncytial virus (RSV), influenza, adenovirus, parainfluenza, and rhinoviruses in MEE (65,90). There is strong evidence that viruses have a crucial role in the development of AOM (90). In the majority of children, viral infection of the upper respiratory tract mucosa initiates the whole cascade of events that finally leads to the development of AOM, and AOM may be regarded as a complication of a preceding or concomitant viral infection. In a study of 60 children (24 families) with at least 2 children between the ages of 1 and 5 years who were followed from October 2003 through April 2004 by daily parental recording of illness signs, weekly pneumatic otoscopy and viral PCR of nasal secretions collected during "colds" or when MEE was noted or from enrolled sibs without these conditions, one or more viruses were identified from 73% of secretions collected during a "cold" but from only 18% collected at a time without a "cold" (66). Of 93 episodes of OM (includes AOM and OME), 70% occurred during a "cold," and nasal secretions from 77% of children at the time of these episodes were positive for virus. For OM episodes, both with a "cold" and without, rhinovirus was the virus found most frequently; influenza and RSV were not found in episodes not associated with a "cold." When a virus was isolated from the nasopharynx with a cold or not, an associated episode of OM was classified as AOM in 8% of rhinovirus detections but in 33% and 38% of detections of RSV and influenza A virus, respectively (91). In a cohort of children 6 months to 3 years of age whose parents were instructed to present to the study when the child had a URI or AOM, Chonmaitree et al. (92) found AOM in 37% of URI episodes and OME in 24%. They found rhinovirus and adenovirus most commonly detected during URI, but the rate of OM associated with rhinovirus was lower than for other viruses.

Allergy and Immunology

Even though allergy is considered in the pathogenesis of OM, the causal mechanism is not understood, and well-controlled studies to prove the efficacy of antiallergic medication in the treatment of OM are lacking. Several mechanisms by which allergy may cause OM have been suggested: (a) the middle ear as a "shock organ" (target), (b) allergy-induced inflammatory swelling of the eustachian tube mucosa, (c) inflammatory obstruction of the nose, and (d) aspiration of bacteria-laden allergic nasopharyngeal secretions into the middle ear. The last three mechanisms involve an association between allergy and abnormal eustachian tube function. Prospective studies have reported a relationship between upper respiratory tract allergy and eustachian tube obstruction in a series of provocative, intranasal, allergen-inhalation challenge studies (93).

Recent studies focus on the analysis of the inflammatory markers in MEE to determine the role of allergy. Both Th (T-helper) 1 and Th2 inflammatory patterns have been found in OME. Th1 cytokines antagonize allergic inflammation and play a key part in the defense against viruses and intracellular pathogens, while Th2 cytokines promote IgE production, eosinophil growth, and mucus production (94). The chemoattractant cytokine RANTES (regulated upon activation, normal T cell expressed and secreted) and eosinophilic cationic protein (ECP), signs of a Th2 process, were assessed in MEE samples from 25 children with allergy and 20 nonallergic children, aged 5 to 11 years at the time of tympanostomy tube insertion (95). RANTES as well as ECP were significantly higher in the MEE samples from children with allergy than children without allergy ($P < 0.01$; $P < 0.05$, respectively). There was also a positive correlation between RANTES and ECP in MEE ($P < 0.01$) in children with allergy, which suggests that allergy is a contributing factor in the pathogenesis of OM.

Children with major immune deficiencies may have recurrent OM as part of their overall clinical picture, but most otitis-prone children may have only a subtle immunologic abnormality that predisposes them to recurrent infections (96). The three major OM pathogens—*S.*

pneumoniae, H. influenzae, and *M. catarrhalis*—frequently colonize the nasopharynx. There are many different strains of these organisms, and among the different strains, there are heterologous surface (strain-specific) antigens and conserved antigens. Conserved antigens induce broadly protective antibodies while strain-specific antigens induce limited protection. Otitis-prone children may display strain-specific immunity but fail to develop a broadly protective antibody response, which makes them susceptible to recurrent and persistent OM (97).

Recurrence of bilateral OME after tympanostomy tube insertion was more likely in children with poor eustachian tube function and low IgA or low IgG2 and decreased levels of mannose-binding lectin than in children with poor tubal function and high IgA and IgG2 measured at time of tube insertion (98). This suggests that an interaction between various immune factors may increase the risk for the development of OM.

Gastroesophageal Reflux

In 2002 Tasker et al. (99) reported finding pepsin/pepsinogen, using enzyme-linked immunosorbent assays, in 90.8% of 65 MEE samples obtained at the time of myringotomy in children. The pepsin/pepsinogen levels ranged from 0.8 to 213.9 μg/mL, which is 1,000 times higher than serum levels. He et al. (100), using a sensitive and specific pepsin assay, detected pepsin activity in 14.4% of 152 subjects undergoing tympanostomy tube insertion. The levels of pepsin ranged from 13 to 687 ng/mL. O'Reilly et al. (101) found pepsin in the middle-ear cleft of 20% of children (14% of ears) undergoing tympanostomy tube insertion for OM, compared to 1.4% of control children (1.5% of ears) undergoing cochlear implant who did not have a history of OM. Children with purulent effusions were more likely to have pepsin than those with mucoid or serous effusion (47% vs. 20% vs. 27%, respectively).

A prospective, uncontrolled before-and-after intervention study was performed in children with OM and GERD (102). Thirty-seven of the forty-seven entered children were evaluated 8 to 12 weeks following antireflux therapy (lansoprazole in the morning with ranitidine or nizatidine at bedtime) and were found to have improvement in hearing, quality of life scores, reflux questionnaires, fiberoptic laryngoscopy, otoscopy, and tympanometry.

PREVENTION OF DISEASE

Management of Environmental Factors

Promotion of breast-feeding in the first 6 months of life, avoidance of supine bottle feeding and pacifier use, and elimination of passive tobacco smoke may be helpful in reducing the risk of development of OM. Alteration of child care arrangements such that the child is exposed to fewer children may also be of benefit.

Vaccines

The three most common bacteria isolated from the middle ear are *S. pneumoniae, H. influenzae,* and *M. catarrhalis*. Presently, the *S. pneumoniae* vaccines (Pneumovax, Prevnar, and Prevnar 13) are the only bacterial vaccines available in the United States for OM. Although respiratory viruses, such as RSV, influenza, adenovirus, parainfluenza, and rhinovirus, have been isolated in MEE using PCR, influenza vaccine is the only available recommended viral vaccine today that may impact OM.

Bacterial Vaccines

Streptococcus pneumoniae

Pneumovax is a 23-valent polysaccharide vaccine [PPSV23], which is not efficacious in children 2 years or younger due to poor antibody production. *Prevnar is a* conjugated vaccine in which pneumococcal polysaccharides are conjugated to a nontoxic mutant of diphtheria toxin. The 7-valent vaccine (PCV7, serotypes 4, 6B, 9V, 14, 18C, 19F, 23F) was licensed for use in the United States in 2000 and recommended for use in children less than 6 years of age by the American Academy of Pediatrics (103). Prevnar 13 (PCV13) replaces PCV7. It was licensed for use in 2010 and includes six additional serotypes (1, 3, 5, 6A, 7F, and 19A) that can cause invasive pneumococcal disease, including the increasingly drug-resistant serotype 19A. The PCV 13 vaccine is recommended for all children 2 to 59 months of age and for children 60 to 71 months of age with an underlying condition that makes them more susceptible to pneumococcal disease. Children up to age 59 months who are fully (four doses) vaccinated with PCV7 should receive one dose of PCV13. (For further guidance by the American Academy of Pediatrics on use of PCV13 and PPSV23, see the Policy Statement, www.pediatrics.org/cgi/doi/10.1542/peds.2010-1280.)

There was great hope that the introduction and subsequent use of PCV7 for infants and young children would lead to a substantial decrease in AOM. Data from vaccine trials conducted in California (104) and Finland (105) revealed only a 7% and a 6% relative reduction, respectively, in AOM episodes. However, in the California study, children with recurrent OM benefited from the vaccine with a reduction of OM episodes varying from 9.3% to 22.8%, increasing as the frequency of episodes of AOM increased. In addition, immunized children were 20.1% less likely to require tube placement than controls. The PCV7 vaccine demonstrated a much higher efficacy (greater than 80%) in reducing invasive pneumococcal disease than reducing the burden of OM. Additional follow-up of the study subjects continued to demonstrate a modest amount of protection against episodes of AOM and tympanostomy tube insertion (106). Reduction in need for tympanostomy tubes after introduction of PCV7 was also shown in Tennessee and New York (107) and in Finland (108).

With use of the vaccine, pneumococcal colonization in the nasopharynx has changed as the vaccine has caused a reduction in the carriage rate of vaccine serotypes and replacement with nonvaccine serotypes (84,109). It should be noted that a reduction in nasopharyngeal carriage of vaccine serotypes and an increase in nonvaccine serotypes have also been seen in children younger than 7 months of age (83).

In the United States and Finland, the initial immunization with PCV7 is at age 2 months based on the results from the clinical trials. However, the question of whether or not the results obtained in the Finnish and US trials could be extrapolated to older children who already had a history of recurrent episodes of AOM was addressed by Dutch and Belgian trials (110,111). Seventy-eight and three hundred and eighty-three children with documented histories of recurrent AOM were enrolled in the Belgian and Dutch studies, respectively. In both trials, children between 1 and 7 years were immunized at entry with PCV7 followed by a booster immunization with a 23-valent pneumococcal polysaccharide vaccine 7 months later and followed up for a total of 18 months in the Dutch and 26 months in the Belgian trial. The results from these two studies did not lend any support to the use of pneumococcal conjugate vaccine to prevent AOM in previously unvaccinated toddlers and children with a history of recurrent AOM. In the infant studies, the PCV7 immunization may prevent or delay nasopharyngeal colonization of the most frequent pneumococcal serotypes and consequently delay pneumococcal episodes of AOM until a later age. In older children, who already are carriers of pneumococci, there is rapid replacement of pneumococcal vaccine serotypes with nonvaccine serotypes.

An 11-valent polysaccharide pneumococcal serotype vaccine conjugated to *H. influenzae*–derived protein D was evaluated in a clinical trial conducted in the Czech Republic enrolling a total of 4,968 children who were followed to the end of the second year of life with middle-ear cultures when episodes of AOM were diagnosed (112). The vaccine reduced the overall incidence of AOM episodes by 33.6%. Vaccine efficacy was 57.6% for episodes of AOM caused by pneumococcal serotypes included in the vaccine and 66% for vaccine-related cross-reactive pneumococcal serotypes. There was no significant change in number of AOM episodes due to nonvaccine serotypes. Of great interest is that there was 35.3% efficacy against AOM episodes caused by nontypeable *H. influenzae*. These results indicate that using the *H. influenzae*–derived protein D as a protein for conjugation of pneumococcal polysaccharides not only allowed for protection against pneumococcal otitis but also against OM due to nontypeable *H. influenzae*. The use of the *H. influenzae*–derived protein D and the two additional pneumococcal serotypes probably explains the 33.6% reduction in all types of AOM episodes by the vaccine, which is significantly higher than in the previously mentioned trials of PCV7 (104,105).

Haemophilus influenzae

As nontypeable *H. influenzae* is the second most common bacteria isolated from middle-ear fluid in AOM, much effort has been channeled into developing an effective vaccine. Many different approaches using animal models have been used to develop vaccine antigens for nontypeable *H. influenzae*–induced OM, including the following proteins: outer membrane protein (OMP) P5, 26, P2, P6, Htr protein, protein D, phosphorylcholine (ChoP), detoxified lipooligosaccharides (dLOS), and type IV pili. However, for the first time, it was possible to demonstrate an effective *H. influenzae* antigen for OM in a clinical trial using an 11-valent vaccine with the pneumococcal capsular polysaccharides conjugated to protein D, an outer membrane protein of *H. influenzae,* as previously mentioned (112). Although the efficacy for episodes of AOM caused by *H. influenzae* was only 35.3%, the results indicate that it would be feasible to develop an effective vaccine for this pathogen.

Moraxella catarrhalis

Moraxella catarrhalis is the third most common bacteria isolated from the middle ear. While the frequency of *M. catarrhalis* infections has previously been rather modest, recent studies have indicated that the frequency of nasopharyngeal colonization with *M. catarrhalis* in children with OM increased with the widespread use of the pneumococcal conjugate vaccine (113). Therefore, in order to have the greatest impact on reducing OM episodes, the development of a vaccine that contains *M. catarrhalis*, as well as *S. pneumoniae* and *H. influenzae* antigens, is necessary. Very little progress has been made in defining the protective immune response in *M. catarrhalis*. However, protective immune responses to *M. catarrhalis* in adults with chronic obstructive pulmonary disease have been identified (114). Candidate *M. catarrhalis* vaccine antigens that have been shown to induce potentially protective responses include outer membrane protein OlpA, CopB, filamentous hemagglutinin (FHA-like protein), and lipooligosaccharides (LOS).

Viral Vaccines

Based on evidence regarding the role of viruses in the pathogenesis in AOM, the development of viral vaccines should be strongly promoted (90). It should be recognized that bacterial vaccines only prevent the bacterial complications of a viral infection, while viral vaccines act at an earlier stage in the pathogenesis of AOM. Thus, viral vaccines have the potential to prevent viral URIs, thereby potentially preventing the development of AOM as a complication of bacteria in the nasopharynx.

Influenza Vaccine

The only commercially available viral vaccine today used for prevention of OM is the influenza vaccine, which is recommended for all children 6 months of age and older by the American Academy of Pediatrics Committee on

Infectious Diseases (115). Currently, there are two types of influenza vaccine available for children. Trivalent inactivated influenza vaccine (TIV) contains killed viruses and is given intramuscularly to children 6 months and older and adults. Live attenuated influenza vaccine (LAIV) is given intranasally and is currently licensed by the Food and Drug Administration for healthy individuals 2 through 49 years of age. A multicenter study enrolled and randomly assigned 8,475 children 6 to 59 months of age in a double-blind fashion to intranasal LAIV or TIV intramuscularly to assess the efficacy and safety of the vaccines (116). The LAIV was overall superior to the inactivated vaccine in preventing influenza episodes. There were 54.9% fewer cases of culture-confirmed influenza episodes in the group that received the LAIV ($P < 0.001$). The superior efficacy of LAIV was observed for both antigenically well-matched and drifted viruses. Rates of wheezing and hospitalization were higher in the youngest children who received the live attenuated vaccine compared to the inactivated vaccine.

For children younger than 6 months who are too young to receive any of the approved vaccines, it is recommended that close contacts be immunized to help protect those young children (115). The efficacy of maternal vaccination during pregnancy for preventing influenza in their young infants has been studied but findings are inconsistent. Although the U.S. Advisory Committee on Immunization Practices and the American College of Obstetricians and Gynecologists have recommended influenza immunization for all pregnant women in any trimester since 2004, only 10% to 40% of pregnant women are immunized. A study to look at the efficacy of maternal influenza vaccination is in progress (117).

A prospective study in children 13 years or younger was conducted during two respiratory seasons in Finland (118). The average annual rate of influenza was highest (179 cases/1,000 children) among children younger than 3 years of age. AOM developed as a complication of influenza in 39.7% of children younger than 3 years of age. For every 100 influenza-infected children less than 3 years of age, there were 195 days of parental loss of work (mean 3.2 days). The investigators concluded that vaccination of children less than 3 years of age might be beneficial to reduce the direct and indirect costs in children.

Two clinical trials have addressed the efficacy of inactivated influenza vaccine in preventing OM. Hoberman et al. (119) conducted a randomized double-blind, placebo-controlled 2-year clinical trial in 786 children ages 6 to 24 months in Pittsburgh, PA. The investigator did not identify any significant reduction in the burden of AOM from administration of inactivated trivalent influenza vaccine. However, in the first year of the study, the efficacy of the vaccine against culture-confirmed influenza was 66%, while in the second year of the study, the efficacy was −7%. The low efficacy rate in the second year may be explained by the attack rate of influenza virus in the second year not reaching epidemic proportions compared to the first year (3.3% vs. 15.9%, respectively) in the placebo group. The second study was single-blinded and evaluated the efficacy of inactivated influenza vaccine in preventing OM. The study was carried out in 119 children ages 6 to 60 months in day care in Turkey. The efficacy of the vaccine against AOM, OME, and OM was 51%, 18%, and 18%, respectively (120).

Block et al. (121) identified eight randomized trials of efficacy of LAIV for AOM in children 6 to 83 months of age. In six studies, they found that LAIV reduced influenza-associated AOM by 85% compared to placebo. In two studies comparing TIV to LAIV, the reduction was 54%. The reductions trended higher in children 24 months and older compared to the younger children. In children who developed influenza despite vaccination, LAIV recipients also had less AOM, with a reduction of 38.2% compare to those who received placebo.

Respiratory Syncytial Virus Vaccine

The seriousness of RSV in infants and children and the need for an RSV vaccine are widely recognized. In addition to lower airway infections, the RSV virus is one of the major viruses contributing to the development of AOM (64). A clinical trial in the 1960s of a formalin-inactivated RSV vaccine led to exacerbated disease upon natural infection with virus and two deaths. Thereafter, live attenuated vaccines were investigated, but a vaccine that produces safe, long-lasting immunity to RSV is still not a reality (122). At present, costly antibody prophylaxis with RespiGam and Synagis is used to prevent severe lung disease in high-risk infants.

An alternative approach to preventing RSV infection is maternal immunization. Munoz et al. (123) conducted a study to assess safety and immunogenicity of an RSV purified fusion protein 2 (PFP-2) subunit vaccine in 35 pregnant women in their third trimester. The transplacental transfer of vaccine-induced maternal antibodies was efficient, and there was no increase in frequency or severity of respiratory tract infections in the immunized infants. The infants were born healthy, and no adverse events related to maternal immunization were documented. In an unrelated study, Stensballe et al. (124) found that infants less than 6 months of age with high levels of RSV neutralizing antibody from their mothers had fewer hospitalizations for RSV. At present, maternal immunization is not universally recommended.

TREATMENT

The treatment of OM involves medical and surgical therapies.

Acute Otitis Media

Observation

In an effort to reduce antibiotic use and stem increasing bacterial resistance, observation without use of antibiotics is listed as an option for selected children with AOM in the guidelines document published by the American Academy

of Pediatrics and American Academy of Family Physicians in 2004 (125). Children for whom this is an option are to be selected based on diagnostic certainty, age of the child, illness severity, and access to medical care. Severe disease is defined as moderate to severe otalgia, fever greater than 39°C (102°F) orally or 39.5°C rectally, or a toxic appearing child. Children less than 6 months of age should be treated with antibiotics regardless; healthy children 6 to 23 months with nonsevere disease *and* an uncertain diagnosis could be observed, but if AOM is certain or severe, the child should be treated with antibiotics; and children 24 months or older could be watched if disease is nonsevere *or* the diagnosis is uncertain but treated if AOM is severe.

Already a popular method of management in several countries outside the United States, observation or "watchful waiting" is predicated on the results of several earlier studies showing the high spontaneous cure rate of AOM (126–131). Wald (132), however, cited problems with the earlier studies: The definition of AOM used in the various studies may have allowed for the inclusion of subjects with asymptomatic OME; children less than 2 years of age were not included in some studies and were underrepresented in others; the sickest children were often not selected for these studies; and the antibiotic selected may have been inappropriate and the doses used were often insufficient, all of which would make the efficacy of antimicrobial treatment appear lower. A metaanalysis of studies of AOM with an observation group found that children with bilateral AOM, especially those less than 2 years of age, were more likely to have prolonged symptoms when not given antimicrobial treatment (133). Recommendations for absolute and relative contraindications for observation without antimicrobial therapy are seen in Table 99.1.

Nonetheless, the practice of not treating AOM immediately with antibiotics, often giving a "backup" prescription in case of persistence of symptoms, is undergoing further scrutiny in this country and elsewhere. McCormick et al. (134) reported their randomized trial of immediate antibiotics plus symptom medication versus symptom medication only in 223 subjects with "nonsevere" AOM, of whom 57% were less than 2 years old. At day 12, 69% of TMs and 25% of tympanograms were considered to be normal in the antibiotic group, compared to 51% of TMs and 10% of the tympanograms in the nontreated group; 66% of the watchful-waiting group completed the study without antibiotics. Nasopharyngeal cultures at day 12 of the study revealed that *S. pneumoniae* was eradicated in most of the antibiotic-treated subjects, but the strains that were cultured were more likely to be antibiotic-resistant. Parental satisfaction with the assigned "treatment" was the same in both groups. Spiro et al. (135) randomly assigned children 6 months to 12 years of age diagnosed with AOM (definition left to discretion of physician) to either immediate antibiotic treatment or a "wait-and-see" prescription, to be filled if the child was not improving or was worse at 48 hours. Performed in an emergency room population, the mean age of subjects was 3.2 years; approximately 84% had unilateral AOM. The investigators found that 62% of the group given instructions to delay filling the prescription did not fill the prescription compared to 13% given the instructions to start the medication immediately ($P < 0.001$). The presence of fever and/or otalgia was associated with filling the prescription.

Vernacchio et al. (136) surveyed physicians in a national practice–based pediatric research network regarding their preferred management of AOM. In spite of the studies showing that the use of observation or delayed prescribing may allow for spontaneous recovery in many children and the option of observation was offered in the AOM guidelines, they found that while 83% considered observation a "reasonable option," it was used only in a median of 15% of cases.

The option of observation/no antibiotic treatment in young children was recently challenged by two clinical trials of antibiotic versus placebo. Hoberman et al. (137) undertook a randomized placebo-controlled trial to assess the extent to which antimicrobial treatment affects the course of symptoms and signs in children age 6 to 23 months of age with a certain diagnosis of AOM. Children were randomly assigned to amoxicillin–clavulanate (90 mg/kg/day of the amoxicillin component in two divided doses for 10 days) or placebo. There was no significant dif ference between the amoxicillin–clavulanate and placebo groups in regard to initial resolution of symptoms but sustained resolution (two successive days of recording a low symptom score) at days 2, 4, and 7 occurred earlier in the amoxicillin–clavulanate group than the placebo group (20, 41, 67% vs. 14, 36, 53%, respectively, $P = 0.04$). The rate of clinical failure (persistence of symptoms and/or signs) was lower among children treated with amoxicillin–clavulanate than placebo before the visit on day 4 or 5 (4% vs. 23% respectively, $P < 0.001$) and before visit day 10 to 12 (16% vs. 51%, respectively, $P < 0.001$). Tähtinen et al. (138) from Finland published a similar randomized placebo-controlled clinical trial also using amoxicillin–clavulanate (but at 40 mg/kg/day for the amoxicillin component for 7 days) in children ages 6 to 35 months to assess the efficacy of antimicrobial treatment of AOM when strict diagnostic

TABLE 99.1 CONTRAINDICATIONS FOR AOM OBSERVATION

Absolute contraindications

- Age <6 mo
- Immune deficiency or disorder
- Severe illness or treatment failure
- Inability to ensure follow-up and rescue antibiotic

Relative contraindications

- Relapse within 30 d
- Otorrhea
- Bilateral AOM if age <2 y
- Syndrome, craniofacial malformation

criteria are used as well as adequate active treatment. There were fewer treatment failures (a composite outcome of six components) in children receiving amoxicillin–clavulanate compared to placebo (18.6% vs. 44.9%, respectively, $P < 0.001$), and this was apparent already at day 3 (13.7% vs. 25.3%, $P < 0.001$). Overall, amoxicillin–clavulanate reduced the need for rescue medication by 81%. Diarrhea was significantly more common in the amoxicillin–clavulanate children than those treated with placebo (47.8% vs. 26.6%, $P < 0.001$). While these studies show an advantage of antimicrobial treatment in these young children, not all subjects given only placebo did poorly. Further studies will be needed to define the group requiring antibiotic treatment and the group that may do well without antibiotic; presently, these groups cannot be distinguished.

Pain Medication

The guidelines (125) strongly recommended treatment to reduce pain in children with episodes of AOM, which was based on randomized clinical trials with limitations and a relative balance of benefits and risk.

Antibiotics

While antibiotics remain the mainstay of treatment of AOM, there are considerable efforts to reduce the inappropriate use of antibiotic through better diagnostic skills in distinguishing AOM from OME, for which antimicrobial treatment is not now indicated, and in being able to identify the subgroup of children with AOM who will do well without antibiotic treatment. Many antibiotics are available, but according to the AAP-AFP guidelines (125), amoxicillin is still the first-line antibiotic for nonsevere episodes of AOM and, recommended at 90 mg/kg/day in two divided doses, is aimed at covering for *S. pneumoniae*, including resistant strains. For severe episodes of AOM, amoxicillin–clavulanate (amoxicillin 90 mg/kg/day and clavulanic acid 6.4 mg/kg/day in two divided doses) is recommended and will provide coverage for beta-lactam–producing *H. influenzae* and *M. catarrhalis*. According to these guidelines, cephalosporins should only be considered as accepted first-line treatment for patients with penicillin allergy. Macrolides should be prescribed for patients with penicillin and cephalosporin allergies. The child is considered a treatment failure if symptoms and signs persist/recur 48 to 72 hours after initial treatment assignment. The diagnosis should then be reassessed to confirm the diagnosis of AOM and antibiotics started if not given previously or changed to a more broad-spectrum agent if antibiotics were previously prescribed (amoxicillin–clavulanate if amoxicillin failed and ceftriaxone for 3 days if amoxicillin–clavulanate failed). Pichichero and Reed (139) reviewed the literature on amoxicillin absorption and found high variability in children, such that poor intestinal absorption may be responsible for some of the treatment failures with this drug. Tympanocentesis should always be considered if the child does not respond to the antibiotic treatment in order to identify the bacteria in the middle-ear effusion and select an appropriate antibiotic.

Duration of Treatment

Ten days of antibiotic treatment has been the standard, but in an effort to reduce cost and the incidence of antibiotic resistance, the efficacy of shorter courses has been investigated. Studies have found the 10-day course has resulted in fewer early treatment failures in younger children (36), in children recently treated for AOM (140), and in those presenting with spontaneous perforation of the tympanic membrane (141) compared to a 5-day course. The recent US guidelines (125) recommend the standard 10-day course of therapy for younger children and for children with severe disease, while for those 6 years of age and older with mild to moderate disease, a 5- to 7-day course may be used. Several short courses of antibiotics have been approved by the FDA for use in AOM. Cefpodoxime proxetil and cefdinir have been approved for a 5-day course; azithromycin may be given for 1-, 3-, and 5-day courses; and one dose of IM ceftriaxone may be given, although results for penicillin-resistant *S. pneumoniae* are better with a 3-day course (142).

Longer courses of antibiotics have also been proposed. In a randomized, double-blind trial of 10 days of amoxicillin versus 20 days of amoxicillin or 10 days of amoxicillin with an additional 10 days of amoxicillin–clavulanate, no advantage in treatment failure or duration of MEE was found with the longer courses (143).

Decongestants/Antihistamines

A metaanalysis of studies of decongestants and/or antihistamine for AOM found little clinical benefit of these medications for AOM persistence, symptoms, or longer-term sequelae. Although some benefit of the combination was found in the number of subjects with persistent AOM at the 2-week end point, the five- to eightfold risk of side effects and the fact that finding benefit was inversely correlated with study quality led the authors to not recommend the routine use of decongestant/antihistamine for AOM (144). In 1994, Chonmaitree et al. (145) reported increased levels of histamine in middle-ear fluid from children with AOM and speculated that antihistamine may be clinically beneficial in reducing inflammation. However, antihistamine administered with an antibiotic for AOM did not result in improved clinical outcome and prolonged the duration of effusion (146). At this point, neither decongestants or antihistamines, nor their combinations, are recommended for the treatment of AOM.

Steroids

Studies in rats suggested that steroid given with antibiotic reduced inflammatory changes in the middle-ear mucosa to a greater extent than treatment with antibiotic alone (147).

McCormick et al. (148) found no reduction in histamine or leukotriene B4 in children treated with oral antibiotic and steroid compared to children receiving antibiotic alone but did find a lower rate of treatment failure during the first 2 weeks and a shorter duration of MEE in those treated with steroid. However, when a larger sample of subjects was studied, the same group found that corticosteroid (2 mg/kg given for 5 days) administered with antibiotic did not provide any improvement in clinical outcome (146).

Recurrent Acute Otitis Media

Antibiotic Prophylaxis

There have been many studies of the efficacy of antibiotics to prevent AOM in children with frequently recurrent episodes. Many antibiotics have been studied, particularly amoxicillin and sulfisoxazole, used at half their recommended daily dose given once per day for months. Studies have generally concluded that antimicrobials are effective in preventing disease (149). However, this method of managing children with recurrent AOM is not recommended because of the potential for increasing resistant organisms. Rather than daily medicine given for months at a time, treating intermittently at the time of upper respiratory tract symptoms has been tried, but efficacy is less than with continuous medication (150).

Other Preventatives

Other medications/substances have been tried in an effort to prevent recurrent AOM, including xylitol (151,152), propolis and zinc (153), and osteopathic manipulation (154), but further studies are needed to define their role, if any, in the prevention of AOM.

Surgical Treatment

Myringotomy/Tympanocentesis

For episodes of AOM, a myringotomy/tympanocentesis is helpful for relief of pain and allows samples to be obtained for culture to identify the pathogen and to guide in the selection of antibiotics but provides no advantage in duration of effusion or recurrence of episodes of AOM (128).

Myringotomy with Tympanostomy Tube Insertion

Myringotomy and tympanostomy tube insertion (M&T) is currently the most common surgical procedure in children that requires general anesthesia. The rationale for tympanostomy tube insertion is promotion of ventilation of the middle ear and drainage through both the eustachian tube and the tympanostomy tube. Also, the aeration of the middle ear may promote normalization of the middle-ear mucosa. The removal of MEE restores conductive hearing. However, reflux of nasopharyngeal secretions may occur in an ear with a tympanostomy tube, causing otorrhea due to loss of the middle-ear air cushion effect.

When preventive and medical treatments for recurrent AOM (usually defined as three or more episodes in 6 months or four or more episodes in 12 months) have failed, tympanostomy tube insertion is recommended. A randomized clinical trial to evaluate the efficacy of M&T versus sulfisoxazole prophylaxis versus placebo enrolled 65 children 4 years or younger with recurrent AOM and followed them for 6 months or longer (155). Treatment failure was defined as two episodes of AOM or otorrhea in less than 3 months. In the M&T group, 5 of 22 children failed compared to 12 of 20 children in the placebo group ($P = 0.02$) and 8 of 21 children in the prophylaxis group. In a similar study to determine the efficacy of amoxicillin prophylaxis versus M&T versus placebo, 264 children ages 7 to 35 months with recurrent AOM were randomized to one of the three arms and followed for 2 years (156). The average proportion of time with OM (AOM and/or otorrhea) was 10% in the amoxicillin, 15% in the placebo, and 6.6% in the tube groups (placebo vs. tube; $P < 0.001$). Rates of new episodes of any type per child were 0.6 in the amoxicillin, 1.08 in the placebo, and 1.02 in the tube groups (amoxicillin vs. placebo; $P < 0.001$). The low rate of new episodes must be viewed in light of the fact that the study subjects proved not to be at as high risk of AOM as had been anticipated. However, compared to placebo, children with tympanostomy tubes spent less time with OM. It should be kept in mind that episodes of otorrhea with tympanostomy tubes are usually less severe, without fever and otalgia, and in most cases resolve with ototopical drops and do not require oral antibiotics.

Adenoidectomy with and without Tonsillectomy

The rationale for removal of the adenoids in children with OM is that the enlargement of the adenoids may cause obstruction of the nasopharynx and blockage of the eustachian tube, preventing ventilation of the middle ear/mastoid system (157). Also the adenoid tissue in children with OM has been found to have increased bacterial colonization, which may predispose to recurrent infections (158). Coticchia et al. (88) have demonstrated that the adenoids are covered with biofilm and may act as a reservoir for bacteria causing middle-ear disease. This may explain the improvement in the condition after mechanical debridement of the adenoids has been performed. The effect of adenoidectomy for OM is independent of the size of the adenoids (159,160).

Two parallel randomized clinical trials compared the efficacy of adenoidectomy (A) and adenotonsillectomy (AT) in 461 children ages 3 to 15 years with persistent and/or recurrent OM who had not previously undergone tympanostomy tube placement (161). Children without recurrent throat infections were randomized to A, AT, or no surgery (no A or AT) and children with recurrent throat

infections to AT or no surgery. The majority of children (91%) had a history of recurrent AOM. The efficacy of surgery in both trials was modest and limited mainly to the first follow-up year. The largest difference was in the three-way trial between AT and no surgery with a mean annual AOM rate of 1.4 versus 2.1 ($P < 0.001$) and mean estimated percentage of time with OM of 18.6% versus 29.9% ($P = 0.002$). Based on the short-term efficacy of A and AT as well as the morbidity and cost of these procedures, it was suggested that neither procedure should be considered as the initial surgical procedure.

In a randomized clinical trial assessing the efficacy of adenoidectomy versus placebo versus long-term antimicrobial prophylaxis in preventing episodes of recurrent AOM, 180 children ages 10 to 24 months were enrolled and followed for 24 months. No significant differences were observed between the groups in the number of episodes of AOM, visits to doctors, antibiotic prescriptions, and days with symptoms of respiratory infection. The authors concluded that adenoidectomy cannot be recommended as the primary treatment in this age group of children (162).

Hammaren-Malmi et al. (163) conducted a clinical trial in children 12 to 48 months of age with recurrent AOM (≥3 episodes in 6 months or ≥5 episodes in 12 months) to evaluate the efficacy of adenoidectomy in children receiving tympanostomy tubes. The children were randomized to tympanostomy tube insertion with (M&T-A) and without (M&T) adenoidectomy and followed for 12 months. During follow-up, the mean number of AOM episodes was 1.7 in the M&T-A children compared to 1.4 in the M&T children. The authors concluded that adenoidectomy at time of tympanostomy tube insertion does not significantly reduce the incidence of AOM in otitis-prone children younger than 4 years of age.

Adenoidectomy may provide modest improvement in children with recurrent AOM but is not recommended as a first-line procedure unless indicated for airway obstruction. Tonsillectomy, in conjunction with adenoidectomy, provides no significant advantage compared to adenoidectomy alone and the risks outweigh the benefits.

Otitis Media with Effusion

Observation

Because of the high spontaneous resolution rate of OME episodes (164), "watchful waiting" should be considered for children not at risk for speech and language or learning disabilities as recommended by the OME guidelines (Table 99.2) (165). Hearing testing should be done if MEE persists for 3 months or longer or at any time that language delay, learning difficulties, or significant hearing loss is suspected. If the average hearing level is less than 20 dB, watchful waiting is suggested, but if it is greater than 40 dB in the better ear, surgery is recommended. For children with hearing levels in the better ear between 21 and 39 dB, management is based on the duration of effusion and severity of symptoms. For children not at risk, examination at 3- to 6-month intervals until the fluid has resolved is recommended. If persistent hearing loss and language or learning delays are identified or there are suspected structural abnormalities of the ear drum, surgical treatment may be considered (166).

TABLE 99.2 RISK FACTORS FOR DEVELOPMENTAL DIFFICULTIES[a]

- Permanent hearing loss independent of OME
- Suspected or diagnosed speech and language delay or disorder
- Autism spectrum disorder and other pervasive developmental disorders
- Syndromes (e.g., Down) or craniofacial disorders that include cognitive and linguistic delays
- Blindness or uncorrectable visual impairment
- Cleft palate, with or without syndrome
- Developmental delay

[a]Rosenfeld RM, Culpepper L, Doyle KJ, et al. Clinical practice guideline: otitis media effusion. *Otolaryngol Head Neck Surg* 2004;130(115):S95–S118.

Medical Treatment

Decongestant/Antihistamine

Decongestant, with or without antihistamine, was a popular treatment for OME, but clinical trials found no efficacy of these medications (167–170). In studies of OME at the Children's Hospital of Pittsburgh, no efficacy of an oral decongestant–antihistamine combination either alone (171) or when given with an antimicrobial agent (172) was found.

Antibiotics

Antibiotics came into prominence as treatment for OME toward the end of the 1970s/beginning of the 1980s when studies showed the ineffectiveness of decongestant/antihistamine combination. In addition, although thought to be sterile, studies showed that MEE from asymptomatic children contained bacteria (173,174). Mandel et al. (172) reported the results of their double-blind, randomized trial in which 518 children with OME of varying durations were divided into three treatment groups: (a) amoxicillin (40 mg/kg/day) for 14 days plus a decongestant/antihistamine combination for 28 days, (b) amoxicillin for 14 days (plus placebo for decongestant/antihistamine) for 28 days, or (c) placebo for both amoxicillin and decongestant/antihistamine. At 4 weeks, the rate of resolution of MEE was twice as high in those treated with amoxicillin, with or without decongestant/antihistamine, as those who received placebo (percentages effusion-free: 31.6, 28.8, and

14.1 in the amoxicillin plus decongestant–antihistamine, amoxicillin alone, and placebo groups, respectively); the addition of the decongestant/antihistamine made no difference. Recurrence of effusion occurred in most subjects within 3 months after completing treatment. Other antibiotics, including amoxicillin–clavulanate, ceftibuten, and penicillin, have been tested in clinical trials to determine whether all antibiotics provided the same efficacy, but none has been clearly shown to have any long-term advantage over the others (175–177). Mandel et al. (178) compared the efficacies of cefaclor and erythromycin–sulfisoxazole to that of amoxicillin. Besides not being better than placebo, cefaclor and erythromycin–sulfisoxazole showed no increased efficacy at 2 and 4 weeks after starting treatment compared to amoxicillin. Antibiotic used in prophylactic doses (generally half the total daily dose used for AOM given once daily for months) has also been examined in the treatment of OME, but its efficacy is linked more to preventing AOM than treating OME (179). Despite short-term efficacy (149,180), antibiotics are not recommended for routine treatment of OME due to lack of long-term efficacy, the high spontaneous cure rate, and concern about overuse of antibiotics.

Steroids

Theoretically, glucocorticoids should be efficacious in the treatment of OME: the antiinflammatory properties due to inhibition of phospholipase A_2, which then inhibits formation of arachidonic acid and the subsequent synthesis of inflammatory mediators, upregulation of transepithelial sodium transport promoting fluid removal from the middle ear, and decreasing mucin production by suppressing MUC5AC (181). In clinical trials, systemic steroids have demonstrated an advantage in resolving MEE compared to placebo, but due to the high recurrence rate after treatment, steroids are not recommended for long-term management (182).

Because of the side effects with use of systemic steroids, especially for prolonged courses of treatment, other routes of administration have been investigated. Tracy et al. (183) used prophylactic antibiotics with and without (both an untreated group and a placebo group) intranasal beclomethasone to treat 59 children with chronic OME and recurrent AOM. While all groups improved initially, there was no difference among the groups as to OME resolution by the 12-week visit. Cengel and Akyol (184) found, in a nonblinded, randomized (every other subject assigned to active treatment with nasal mometasone spray for 6 weeks, others assigned to no treatment) study of patients with documented MEE of at least 3 months' duration, 42.2% of treated subjects resolved at 6 weeks compared to 14.5% of untreated subjects ($P < 0.001$); no long-term follow-up was reported. A more recent trial in 217 children found intranasal mometasone furoate ineffective for the treatment of OME (185).

Leukotriene Inhibitors

A small study of montelukast for OME was stopped early because of lack of efficacy (186).

Autoinflation

Popularized by Politzer over 100 years ago, devices to insufflate air through the eustachian tube have been tried for the treatment of OME. However, studies using a number of devices have failed to show consistent efficacy (187–190), and so autoinflation is not recommended for routine use at this time. In their metaanalysis, Perera et al. (188) concluded that because of its low cost and absence of adverse effects, autoinflation might be considered for use while awaiting spontaneous resolution of the effusion.

Surgical Treatment

Myringotomy

Myringotomy alone has been shown to be ineffective for long-term management and is not recommended for chronic OME (159,191). Laser-assisted myringotomy (OtoLAM) has been described as an alternative to the standard myringotomy in children with chronic OME, and the procedure can be done under local anesthesia and is considered safe. However, the mean time to closure of the perforation is only 2 to 3 weeks (192,193).

Myringotomy with Tympanostomy Tube Insertion

In children with persistent MEE, the decision of whether to insert tympanostomy tubes is based on the child's hearing status and risk for developmental problems. Several randomized clinical trials have demonstrated evidence-based indications for the use of tympanostomy tube insertion for chronic OME.

The efficacy of M&T for the management of OME has been the subject of many studies. Mandel et al. (194) reported the results of a 3-year clinical trial of 109 children, 7 months to 12 years of age, with OME of 2 months' duration or longer who were unresponsive to medical management and who were randomly assigned to receive myringotomy alone (M), M&T, or no surgery. During the first year, over 50% of subjects in the M and the no surgery groups met preset treatment failure criteria and underwent M&T. A second study (191) designed to correct some of the design flaws of the first study and to extend the time until treatment failure involved 111 children with OME for at least 2 months and whose pure-tone averages bilaterally were ≤35 dB. This study also found high rates of treatment failure in children in the M group (70%) and the no surgery group (56%). The percentages of time with MEE during the first year in the M, M&T, and no surgery groups were 61%, 17%, and 64%, respectively ($P < 0.001$). From these studies, it was concluded that M offered no advantage over no surgery in regard to percentage of time with effusion, number of AOM episodes, and number of repeat

surgical procedures and M&T provided more disease-free time and better hearing than M or no surgery.

Gates et al. (159) studied the effects of various surgical treatments in children 4 to 8 years of age with chronic OME; 127 children were randomly assigned to M and 150 were assigned to M&T. Compared to M only, M&T provided less time with effusion, more time with better hearing, and necessitated fewer surgical retreatments.

The previously mentioned studies (191,194) were performed at a time when it was considered "unethical" to allow a child to have MEE for more than 2 to 3 months because of the associated hearing loss and the possible detrimental effects on speech and language development. A more recent study by Paradise et al. (195) randomly assigned 429 children less than 3 years of age with persistent or recurrent OME to either prompt M&T or to M&T up to 9 months later. Eighty-five percent of children in the promptly treated group and forty-one percent of children in the late treatment group had undergone M&T by 6 years of age. On developmental testing at 6 years, there were no significant differences between the groups on 30 measures. Interestingly in both the randomized clinical trial and in children randomly selected from those followed in the study but did not meet criteria for randomization, sociodemographic variables seemed to be the most important factors influencing developmental outcomes.

Adenoidectomy

A study by Maw (196) enrolling children 2 to 11 years of age with chronic OME showed that adenoidectomy (A) alone and M&T alone provided better results than no surgery, but the combination of the two surgical procedures provided better results than either alone. The addition of tonsillectomy to adenoidectomy provided no additional benefit for middle-ear fluid resolution. In the previously discussed study by Gates et al. (159), the children randomly assigned to the M-A and the M&T-A groups both had a lower percentage of time with effusion than those who received M&T alone. Thus, based on these results, Gates et al. recommended M-A as the "first-line" procedure.

Paradise et al. (160) studied 213 children 1 to 15 years old with recurrent AOM or OME who had previously had M&T. Children were randomly assigned to adenoidectomy or no adenoidectomy; M&T was also performed at the same time for specific indications. Of the 99 subjects who were randomized, there was a significant reduction in time with OM during the first 2 years in the children who underwent adenoidectomy compared to those who did not. For the remaining children followed but whose parents chose not to allow random assignment, the results favored adenoidectomy compared to no adenoidectomy.

A clinical trial enrolling 98 children ages 24 to 47 months with bilateral OME for 3 months or longer, or unilateral for 6 months or longer, or after extrusion of prior tympanostomy tubes randomized the subjects to M&T versus M-A with and without insertion of tubes (197). In these young children, adenoidectomy with M&T provided no advantage over M&T alone in regard to mean percentage of time with MEE during the first 18 months (18.1% vs. 11.9%, respectively, $P = 0.21$) or the entire 36 months of follow-up (20.6% vs. 18.6%, respectively, $P = 0.87$). However, the mean percentage of time with MEE in the M-A group (35.7% by 18 months, 31.1% by 36 months) was significantly higher than in both the M&T and M&T-A groups ($P < 0.001$ and $P = 0.003$, respectively, at 18 months, $P < 0.001$ and $P = 0.02$ at 36 months). During the 36 month follow-up, M-A resulted in 24% of the children needing an additional procedure (M&T) compared to 29% in the two groups with initial M&T.

Several *retrospective* studies have looked at the efficacy of adenoidectomy in addition to M&T. Boston et al. (198) evaluated risk factors for additional tube insertion in 2,121 patients undergoing bilateral M&T. In 19.9% of the children, two or more tube insertions were performed. After the initial tube insertion, as many as 45.1% of the patients needed an additional surgical procedure (M&T, A, and/or tonsillectomy). Patients younger than 18 months at the initial procedure were significantly more likely to have a second procedure (26.3% vs. 15.9%, $P < 0.001$). Adenoidectomy was performed at the time of the initial M&T in 527 patients (24.5%). This reduced the probability of needing a second set of tubes (0.08 vs. 0.24, $P < 0.001$). Also the probability of needing a third set of tubes was reduced when adenoidectomy was performed at or before the second set of tubes (0.15 vs. 0.40, $P < 0.001$). The presence of craniofacial abnormalities and a family history of A, T, or M&T increased the risk of subsequent tube insertions ($P < 0.001$). Sex and race were not risk factors for subsequent tube insertion.

Another retrospective study evaluated the effect of adjuvant A or A-T at time of M&T on the rate of reinsertion of tubes and rehospitalization for OM-related conditions in 37,316 Canadian children (≥19 years) who received tubes as their first surgical procedure (199). As compared to tube insertion alone, A was associated with a reduction in the likelihood of reinsertion of tubes (RR 0.5, 95% CI: 0.5 to 0.6; $P < 0.001$) as was A-T (RR 0.5, 95% CI: 0.5 to 0.6; $P < -0.001$). Performing A or A-T at the time of the M&T substantially reduced the likelihood of additional hospitalization and operations related to OM among children 2 years or older.

A third large retrospective study assessing the benefits of adjuvant pharyngeal surgery (A, A-T, and T) at the time of M&T examined the records of 51,373 children less than 10 years of age (200). Twenty-nine percent of the children had pharyngeal surgery at the time of the first M&T. The

authors concluded that having A or A-T at the time of first or subsequent M&T was associated with reduced risk of further tube insertion.

Guidelines

In 2004 a revised Clinical Practical Guidelines for OME was published jointly by the American Academies of Family Physicians, Otolaryngology-Head and Neck Surgery, and Pediatrics (166). The guidelines were evidence-based and the quality of the evidence was assessed. The recommendations reflected the quality of the evidence and the balance between benefit and harm that is anticipated when recommendations are followed. The guidelines apply to children 2 months through 12 years with and without developmental disabilities or underlying conditions that predispose to OME and its sequelae. The decision regarding surgery for OME depends largely on hearing status, associated symptoms, the child's developmental risk (Table 99.2), and the anticipated chance of timely spontaneous resolution of the effusion. Surgical candidates are children with (a) OME lasting for 4 months or longer with persistent hearing loss or other signs or symptoms, (b) recurrent or persistent OME in at-risk children regardless of hearing status, and (c) OME and structural damage to the TM or middle ear.

Tympanostomy tube insertion is the initial preferred procedure. Adenoidectomy should not be performed unless a distinct indication exists (nasal obstruction, chronic adenoiditis). Repeat surgery consists of adenoidectomy plus myringotomy with and without tympanostomy tube insertion. Tonsillectomy alone or myringotomy alone should not be used to treat OME.

Quality of Life Assessment

The first validated quality of life (QOL) outcome study for OM was the OM-6 instrument developed by Rosenfeld et al. (201) representing six domains including physical stress, hearing loss, speech impairment, emotional distress, activity limitation, and caregivers' concerns. A large, moderate, or small improvement after M&T was documented in 56%, 15%, and 8% of children, respectively, using this instrument (202). Trivial changes were noticed in 17% of children, and 4% of children had a poor outcome after tube insertion. The results indicate that M&T produces large short-term improvement in QOL for most children.

A quality of life outcome study assessed the parents' appreciation of their child's general condition using the OM-6 scale before, after, and retrospectively before M&T in a group of Dutch children 12 to 36 months of age (203). The results from the retrospective assessment of the child's general condition prior to M&T indicated that the parents underestimated the effects of OM before surgery. In particular, following M&T, parents were able to appreciate the extent of presurgical hearing loss.

TYMPANOSTOMY TUBES

Selection of Tympanostomy Tubes and Indications

Many different tympanostomy tubes have been developed, but most tympanostomy tubes are variations of the grommet or the T-tube. The duration of time before extrusion is shorter for grommet tubes than for T-tubes. Weigel et al. (204) performed a randomized prospective trial of four different types of tympanostomy tubes in 75 children. During the first 2 years, 93% of Shepard tubes, 80% of Armstrong tubes, 66% of Reuter-Bobbin tubes, and 31% of Goode T-tubes had extruded. In studies from Pittsburgh, the tube life of the Armstrong-type tube was approximately 1 year; 50% had extruded by 12 months and 75% by 18 months (191). The time to extrusion is a function of the size, shape of the medial flange, absence of a lateral flange, and the material of the tube. Also the coating of the tube may affect the time to extrusion as it may prevent infections (205,206).

In a young child with a history of recurrent or persistent OM, a tympanostomy tube that remains in place for at least a year is preferable. If the child has recurrent OM after the tubes have become nonfunctional or extruded, a similar type of tube should be recommended. Grommets with shorter duration are recommended in older children who may not continue to have problems after the present season. T-tubes or long-term tubes are recommended for older children with persistent problems due to poor eustachian tube function. Also they are recommended for children who have an atrophic TM after multiple sets of tympanostomy tubes as a regular grommet tube may be very quickly extruded.

Peri- and Postoperative Ototopical Drops

In an effort to reduce early postoperative otorrhea and tube blockage, ototopical antimicrobial drops have been recommended to be placed at the time of surgery, especially if MEE was present (207,208). Only FDA-approved ototopical agents such as ofloxacin (Floxin) and ciprofloxacin with dexamethasone (Ciprodex) should be used.

Postsurgical Follow-Up

All patients should have a follow-up visit a few weeks after surgery for an otoscopic examination to assess the status of the tympanostomy tube. In addition, all patients should have an audiologic examination postoperatively to document that the hearing is normal. Patients are also usually evaluated 6 to 12 months after the insertion of the tubes

and every 6 months thereafter or when problems occur to assess the status of the tube and TM.

Complications and Sequelae of Tympanostomy Tubes

Otorrhea

Otorrhea through a tube or perforation is a common problem after M&T and has been recorded in as many as 50% of children with tympanostomy tubes (209). Transient otorrhea occurred in the postoperative period in 16% (range 8.8 to 42.0) and later in 26% (range 4.3 to 68.2) of patients; recurrent otorrhea occurred in 7.4% (range 0.7 to 19.6) and chronic otorrhea in 3.4% (range 1.4 to 9.9) of patients (210). If untreated, it can develop into chronic suppurative OM. Pathogens typical of AOM (*S. pneumoniae, H. influenzae, M. catarrhalis,* and *S. pyogenes*) were found in 42% and *P. aeruginosa* and *S. aureus* in 44% of all episodes of acute otorrhea in 246 children with tympanostomy tubes followed prospectively (208). The typical AOM pathogens were more common in children under 6 years of age than in older children (50% vs. 4.4%; $P < 0.001$). *P. aeruginosa* was more common in children 6 years or older than in the younger children (43.5% vs. 20.5%; $P = 0.052$). Roland et al. (211) recovered 1,309 isolates from 956 acutely draining ears and identified *S. pneumoniae* in 17%, *H. influenzae* in 18%, *S. aureus* in 13%, *P. aeruginosa* in 12%, and fungus in 5%. Several clinical trials have demonstrated that ototopical agents such as ofloxacin otic solution and ciprofloxacin–dexamethasone otic suspension are effective when acute otorrhea occurs through a tympanostomy tube or perforation, even when no systemic antibiotic is given (212). In a child who has severe systemic symptoms, a systemic antibiotic should be added. The ciprofloxacin–dexamethasone combination has been shown to be superior to ofloxacin in resolving granulation tissue (213). The use of other ototopical agents in a nonintact TM has not been approved by the U.S. Food and Drug Administration (FDA) as they can be ototoxic, especially those that contain aminoglycoside. If the drainage does not resolve in 7 to 10 days, suctioning of the ear canal should be performed, and a culture from the opening of the tube should be obtained to determine the causative pathogen. If yeast is the predominant organism, treatment with a topical antifungal drop such as clotrimazole should be initiated. Repeated aural toilet is a very important part of the treatment. However, it may be difficult for a child and the parent to comply with frequent suctioning. If aural toilet and topical treatment fail and the organisms are not sensitive to oral antibiotics, culture-directed intravenous antibiotics, removal of the tube(s), or rarely simple mastoidectomy should be considered. CT scan of the temporal bones should be obtained prior to possible mastoidectomy to look for complications such as coalescent mastoiditis. In older children with recurrent episodes of otorrhea, removal of the tubes is the treatment of choice, as in these children the eustachian tube may have matured and secretions from the nasopharynx may be refluxing into the middle ear. Also, the tube may occasionally act as a foreign body, causing a foreign body reaction with granulation tissue and infections. Recently, biofilms have been implicated (214).

Tympanosclerosis, Atrophy, and Retraction Pockets

A metaanalysis reviewing 134 articles estimated the incidence of TM sequelae after tube extrusion and reported that tympanosclerosis occurred in 32% (range 7.2 to 64.3), focal atrophy in 25% (range 1.6 to 75.0), and retraction pockets in 3.1% (range 0 to 22.7) of ears (210). The type of tube (short-term vs. long-term) had no significant impact on these rates.

The sequelae of M&T in children with chronic OME followed for 8 years was reported by Daly et al. (215). One hundred thirty-eight children (275 ears) followed for 3 years and eighty-four of these children (167 ears) followed for 8 years were evaluated in regard to TM myringosclerosis, atrophy, retraction pockets or perforations, hearing loss, and static admittance. In general, the annual incidence of sequelae was greater at the 4- to 5-year follow-up than at the 6- to 8-year follow-up. While atrophy developed in 67% of the ears, myringosclerosis in 40%, and perforation in 3% between the 3- and 8-year follow-up evaluations, the annual risk of new sequelae declined considerably throughout the 3- to 8-year follow-up for most sequelae studied. However, atrophy and pars tensa/flaccida retraction were present in 55% of ears at the 8-year follow-up, which may put children at risk for continuing middle-ear problems during adolescence and adulthood. These results support the need for long-term follow-up in selected patients.

Johnston et al. (216), reporting the incidence of TM abnormalities in children in the previously cited trial (195) of prompt versus delayed tube insertion, found that children who underwent intubation had more segmental atrophy and tympanosclerosis at age 5 years than children who did not receive tubes. There was no significant relationship between hearing levels at 6 years of age and the presence or type of TM abnormalities.

The overall prevalence of TM pathology was assessed in 168 subjects 25 years after M&T in the right ear and myringotomy (M) in the left ear for chronic OME (217). Myringosclerosis and late atrophy were more prevalent in M&T ears. Prevalence of TM retractions decreased over time, while myringosclerosis remained unchanged in M&T ears and increased in M ears. The extension of myringosclerosis increased in M&T ears, while atrophy and pars tensa retraction decreased over time regardless of treatment modality. Hearing, tympanometric pattern, and eustachian tube function were unrelated to prior treatment modality.

Persistent Perforation

The incidence of persistent perforation after extrusion of tympanostomy tubes has been estimated at 2.2% (range 0% to 12.3%) for short-term tubes and 16.6% (range 0% to 47.0%) for long-term tubes (210). The perforations caused by tympanostomy tubes are usually small and consequently hearing loss is very mild. The perforations are easily managed with a simple fat graft, gelfoam, or paper patch/Steri-strip myringoplasty. Sckolnick et al. (218) found that the success rate with gelfoam myringoplasty was higher than with fat graft or paper patch. Prior to closing the perforation, it is important to make sure that eustachian tube function is good; otherwise, there is a risk of nonclosure or reaccumulation of fluid in the middle ear. As a rule the TM in the opposite ear should be intact and free of infection for a year.

Cholesteatoma

For all types of tubes, the combined incidence of cholesteatoma is 0.7%, but for short-term tubes, the incidence is 0.8% (range 0% to 6.5%) and for long-term tubes 1.4% (range 0% to 3.0%) (210). There are several mechanisms responsible for the development of cholesteatomas. Tympanostomy tubes may be inserted to prevent the development of cholesteatoma in a retraction pocket. However, cholesteatoma may result from ingrowth or transplantation of keratinized epithelium into the middle-ear cleft around a tympanostomy tube. Also an intratympanic cholesteatoma may develop after surgical manipulation of the TM. Patients with tympanostomy tubes should be routinely followed during the time the tubes are in place and after extrusion to assess the TM and middle ear for cholesteatoma development.

Early Extrusion

Premature extrusion of tubes occurs in approximately 3.9% of ears (210). This is most likely due to infection in the middle ear that pushes the tube into the external ear canal. The tube may not have been properly inserted especially if the TM is thickened due to an infection at the time of tube insertion. An atrophic TM may also allow early tube extrusion.

Blockage of Tube

The lumen of the tympanostomy tube may become obstructed from dried blood or mucus, granulation tissue, or a polyp caused by infections in the middle ear. The incidence of plugging of the tube is 6.9% (range 0% to 37.3%) of ears (210). The tube can sometimes be unplugged using a pick, suction, or a Rosen needle or ototopical drops for 10 to 14 days. If the blockage cannot be resolved but the middle ear is effusion-free with normal middle-ear pressure, the tube can be left in place and watched until extrusion. On the other hand, if fluid has accumulated in the middle ear or recurrent infections continue, replacement of the tube should be considered.

Displacement of Tympanostomy Tube into the Middle Ear

The incidence of displacement of a tympanostomy tube into the middle ear is 0.5% (range 0% to 1.3%) (210). It occurs most commonly at the time of surgery, but it can also be seen later due to infection or trauma, which is very rare. If the tube is displaced into the middle ear during surgery, attempts should be made to retrieve the tube at the time of surgery. However, if a tube is visualized behind an intact TM, risks versus benefits have to be assessed as a child would require general anesthesia and an incision of the TM to retrieve the tube. A tympanostomy tube displaced behind an intact TM rarely causes problems.

Retained Tympanostomy Tubes

A tympanostomy tube is usually not removed surgically as most tubes extrude spontaneously. However, in some children, the tube remains in place in the TM and has to be removed surgically. Indications for removing a tympanostomy tube include:

- One tube is retained while the other tube has extruded and the middle ear has been free of disease for 1 year or longer in a child 5 to 6 years or older.
- Bilateral retained tubes in an older child with good eustachian tube function
- Chronic or recurrent episodes of otorrhea that are not able to be managed medically, especially in an older child who previously has not had recurrent episodes of otorrhea, as this could be a sign of reflux of secretions from the nasopharynx due to maturation of the eustachian tube
- The tympanostomy tube is imbedded in granulation tissue and the tube is blocked.

In children, most retained tubes are removed under general anesthesia. After the tube has been removed, a paper patch or gelfoam myringoplasty is performed. Soft long-term T-tubes may be removed in the office with older, cooperative children. These children must be followed to see if the perforation closes spontaneously or requires myringoplasty.

Water Precautions

Several studies have been published, including two meta-analyses (219,220) demonstrating no increase in episodes of otorrhea in patients with tympanostomy tubes not using water precautions compared to those using water precautions. In a clinical trial to assess the need for water precautions for children with tympanostomy tubes, 201 children, ages 6 months to 6 years, were randomized to swimming and bathing with and without ear plugs and followed monthly for 1 year and whenever an episode of otorrhea occurred (221). At least one episode of otorrhea was documented in 47% of children who used ear plugs

compared to 56% in children with no ear plugs ($P = 0.21$). The mean rate of otorrhea per month for children who used ear plugs compared to children not using ear plugs was 0.07 versus 0.10 ($P = 0.05$). Although children who do not use ear plugs have a higher incidence of episodes of otorrhea, the clinical impact of using ear plugs is small, and their use should be individualized rather than recommended on a routine basis.

A clinical survey was conducted in the Pacific Northwest to determine the recommendations given to parents/patients regarding water precautions for swimming with tympanostomy tubes (222). A total of 263 physicians returned the survey (23.5% response rate). Based on this study, most primary care physicians (83%) and approximately half of the otolaryngologists (47%) still recommend water precautions for swimming with tympanostomy tubes.

COMPLICATIONS OF OTITIS MEDIA

Judicious use of antimicrobial therapy, including observation without antimicrobials for AOM, has been promoted by guidelines in many different countries due to the development of increased bacterial resistance to the most common antibiotics. However, delaying antimicrobial therapy may increase the risk of development of complications. Schilder et al. (223) compared the national prescription rate of antibiotics for AOM and the national incidence rate of acute mastoiditis across countries. The study showed a slightly higher incidence rate of acute mastoiditis in children, that is, about 4 per 100,000 person years, in the Netherlands where only 31% of patients with AOM receive antibiotics as compared to 2 per 100,000 person years in the United States where almost all cases of AOM are treated with antibiotics. More recent studies have shown that use of antibiotics to treat AOM in children might not influence the subsequent development of acute mastoiditis (224). Also, there is no difference in the proportion of pediatric mastoiditis caused by *S. pneumoniae* in the preconjugated pneumococcal vaccine versus postvaccine eras (225).

Complications and sequelae of OM can be divided into intratemporal and intracranial (Table 99.3). The intratemporal and intracranial complications are rare in developed countries but are common in third-world countries. However, even though these may be rare in developed countries, they still remain a challenge when they arise and are associated with significant morbidity. Therefore, it is imperative that any physician or health care provider who cares for young children at risk for OM is vigilant with a high index of suspicion and has knowledge of the early signs and symptoms of potential complications, the diagnostic assessment including CT scan and MRI, and the indications for medical and surgical management (see Chapter 149).

Hearing Loss, Speech–Language, and Child Development

Most children with MEE have conductive hearing loss that can be fluctuating or persistent. It is usually a mild to moderate conductive loss averaging between 20 and 30 dB in the low to midfrequency range (226). Rarely, a permanent sensorineural hearing loss may result from AOM or OME, possibly due to spread of the infection through the round or oval windows, or a suppurative complication. However, behavioral hearing thresholds in the high frequencies (12 to 20 kHz) are significantly higher in children with histories of OM even when the middle ear is effusion-free (227–229). Many studies have investigated the association between OM and speech–language and child development. Some studies have found an association while others have failed to do so. Paradise et al. (230) reported that there was no difference between children with OM with early versus late tympanostomy tube insertion with regard to hearing, speech–language, and behavioral testing up to 9 to 11 years of age. Johnson et al. (231) also found no relation of MEE in the first 3 years of life to language outcomes at 7 years of age. However, as indicated in the OME Guidelines (166), it is recommended that each child with OME undergo hearing testing every 3 to 6 months and be assessed for tympanostomy tube placement if they are at risk for any developmental difficulties due to OM, such as significant speech delay.

A recent study assessing tympanostomy tube outcomes in children at risk and not at risk for developmental delays was performed using a Likert-type outcome questionnaire administered to the caregiver by telephone (86%) or mail (14%). Two hundred and twenty-nine children aged 0.5 to 13 years were eligible of whom 55% had at least one condition placing them at risk for developmental delays. The mean pure-tone average at baseline for the better-hearing ear was 32 dB HL. After tube insertion, 89% of caregivers stated that their child's life was "much better." Speech and language as well as learning and school performance was "much better" for 55% of the children, and this was more often in at-risk children. However, hearing improvement was reported by 84% with no relationship to at-risk status. Overall, caregivers reported favorable outcomes regardless of their child's at-risk status, but children at risk had better reported outcomes for speech, language, learning, and school performance (232).

Balance Problems

During an episode of MEE, balance and vestibular function seem to deteriorate, and when the effusion resolves or tympanostomy tubes are inserted, these functions improve (233). Also, children with OM may be more visually dependent as a result of the deterioration of vestibular function causing excessive reliance on other nonvestibular sensory cues to maintain balance (234).

Children may have delayed motor coordination skills such as walking or may be clumsy, which may make them more accident-prone. Stenström and Ingvarsson (235) reported that Swedish otitis-prone children were seen more often in the orthopedic and general surgery departments compared to children who were not otitis-prone.

HIGHLIGHTS

- The presence or absence of signs and symptoms and findings on the otoscopic examination provide the basis for diagnosis of the difference types of OM.
- Proper treatment depends on differentiation between AOM and OME.
- The highest incidence of OM occurs between the ages of 6 and 11 months and decreases with age.
- Risk factors include both host and environmental factors.
- Prevention of disease through use of vaccines and risk factor reduction is desirable.
- For children 2 years of age or older with nonsevere AOM, published guidelines have given the option of observing rather than treating with antibiotics immediately.
- Antihistamines and steroids are ineffective for the treatment of OM.
- Tympanostomy tube insertion is effective in reducing recurrent episodes of AOM and persistent middle-ear effusion.
- Adenoidectomy is not recommended for the initial surgical treatment of OM unless nasal obstruction is present but is recommended for children in whom a repeat surgical procedure is needed.
- Careful follow-up is needed to identify complications and sequelae of otitis media as well as of its treatment.

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Pediatric Audiology and Implantable Hearing Devices

100

David H. Chi *Diane L. Sabo*

Universal newborn hearing screening (UNHS), the lower age of identification of hearing loss, and the need to move rapidly through the evaluation and management process have resulted in a change in pediatric audiology. The population of children who are referred for audiologic evaluations now has a higher percentage of young infants. This has resulted in a greater reliance on physiologic measures for hearing assessment and changed the counseling that needs to be done when hearing loss is identified. Prior to newborn hearing screening, most parents were referred or sought audiologic evaluations for their child who had delays in speech development. Now, with newborn hearing screening, the child presents soon after birth, and families have not had time to think about the possibility of hearing loss or the implications of their child having a hearing loss. The clinician has to consider the impact on the family that a child with a hearing loss can have. In addition, all members of the health care team need to work cohesively to unify terminology, results, and recommendations and to lessen any confusion the families may have when they hear differences. It is important, therefore, for the otolaryngologist and audiologist to have a close working relationship with respect to the diagnosis and ongoing treatment of children with hearing loss.

Congenital hearing loss occurs commonly and is more frequent than other conditions for which newborns are routinely screened (1). Data from newborn hearing screening programs show that the incidence of hearing loss is twice as high as all other diseases screened at birth, occurring in about 2 to 4 per 1,000 births compared to about 1.2 per 1,000 births for the combined totals for all other diseases (2–5). In the United States, about 8,000 to 12,000 babies are born each year with permanent hearing loss (compiled by the National Institute on Deafness and Other Communication Disorders [NIDCD]). When combined with progressive, unilateral, and conductive hearing loss, as many as 15 per 1,000 will have some degree of hearing dysfunction (6).

Hearing loss in infants, when left undetected, can affect speech and language acquisition leading to poor language and literacy skills. In addition, other areas can be impacted, including academic achievement and social and emotional development (7–11). If hearing loss is detected early, however, poor outcomes can be diminished, and even eliminated, through early intervention. Studies have shown that communication skills comparable to age-matched hearing peers can be achieved when hearing loss is identified early, and children receive early intervention services (12–15).

NEWBORN HEARING SCREENING

Identification of hearing loss in infants and children has gone through tremendous changes over the past 10 years. The single most influential reason for this change is UNHS. With implementation of UNHS, hearing loss is being identified at earlier ages compared to prior to newborn hearing screening. A recent study demonstrated that for infants screened for hearing loss compared to those unscreened there was a 24.8-month difference in median age at diagnosis of hearing loss, a 23.6-month difference for fitting of amplification, and a 19.9-month difference for enrollment in intervention (16).

Early hearing loss detection and intervention has been a goal for almost 40 years. Previously, risk factor screening was the only means available to try to identify infants with hearing loss. A 1972 statement by the Joint Committee on Infant Hearing (JCIH) (17) delineated the first high-risk factors for hearing loss and recommended following infants with these high-risk factors: history of hereditary childhood hearing impairment; congenital infection acquired *in utero*, such as rubella or other nonbacterial fetal infection like cytomegalovirus (CMV), syphilis, and herpes; craniofacial anomalies including those with morphologic abnormalities of the pinna and ear canal; birth weight less than 1,500 g; and a bilirubin level greater than 20. In 1982, bacterial meningitis and severe asphyxia were included with

additional risk indicators added between 1982 and 1994. Although this list was expanded and the name changed to risk indicators, risk indicator screening identified only 50% of infants with significant hearing loss.

Because hearing loss affects a large number of children and risk indicator screening is ineffective, and age of identification and habilitation of hearing loss is important, the National Institutes of Health's (NIH) Consensus Development Conference on Early Identification of Hearing Loss (18) concluded that all infants should be screened for hearing impairment, preferably prior to hospital discharge. The following year, JCIH endorsed the goal of universal detection of hearing loss in infants and recommended that physiologic tests be used. The JCIH (19) position statement became a comprehensive guide for early hearing loss detection and intervention for hearing loss and was subsequently revised in 2007. Some of the changes in the 2007 position statement were the expansion in the definition of hearing loss to include auditory neuropathy/dyssynchrony for infants admitted to the neonatal intensive care unit (NICU). Prior to this, the definition included only permanent bilateral, unilateral sensory, or permanent conductive hearing loss. The 2007 position statement also included separate protocols for NICU and regular-care nurseries to address neural hearing loss that occurs more commonly in the NICU. Infants in the NICU for more than 5 days are to have auditory brainstem response (ABR) included as part of their screening so that neural hearing loss will not be missed. For NICU infants who do not pass the ABR, the recommendation is that they are referred directly to an audiologist for rescreening and/or comprehensive evaluation including ABR testing. In addition, if any infant is readmitted during the first month of life for conditions associated with potential hearing loss (e.g., hyperbilirubinemia that requires exchange transfusion or culture-positive sepsis), a repeat hearing screening is recommended before discharge.

The 2007 Position Statement by JCIH (9) also recommended that all newborns be screened for hearing loss by 1 month of age. If the child fails the screening process, an audiologic diagnostic evaluation should occur before 3 months of age, and when a hearing loss is confirmed, the child should be enrolled in early intervention before 6 months of age. These guidelines, commonly referred to as the 1-3-6 model, have been widely adopted by such organizations as NIH/NIDCD, Health Resources and Services Administration/Maternal and Child Health Bureau, American Speech-Language Hearing Association (ASHA), American Academy of Audiology (AAA), and American Academy of Pediatrics (AAP). The JCIH 2007 (9) also contains a section on the role of otolaryngologist in the care and evaluation of newly diagnosed hearing losses in infants.

Because hearing loss can occur after the child leaves the hospital, the JCIH also recommends that periodic audiologic examination of infants be conducted to detect delayed-onset hearing loss. Children with indicators of progressive or delayed-onset hearing loss should be referred for an audiologic assessment at least once by 24 to 30 months of age. Children with risk indicators that are highly associated with delayed-onset hearing loss, such as having received extracorporeal membrane oxygenation (ECMO) or having CMV infection, should have more frequent audiologic assessments.

JCIH risk indicators that are associated with progressive or delayed onset of hearing loss in childhood are listed in Table 100.1.

TABLE 100.1 JCIH RISK INDICATORS ASSOCIATED WITH PROGRESSIVE OR DELAYED ONSET OF HEARING LOSS IN CHILDHOOD

1. Caregiver concern regarding hearing, speech, language, or developmental delay.*
2. Family history of permanent childhood hearing loss.*
3. Neonatal intensive care of more than 5 d or any of the following regardless of length of stay: ECMO*, assisted ventilation, exposure to ototoxic medications (gentamicin and tobramycin) or loop diuretics (furosemide), and hyperbilirubinemia that requires exchange transfusion.
4. *In utero* infections, such as CMV*, herpes, rubella, syphilis, and toxoplasmosis.
5. Craniofacial anomalies, including those that involve the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies.
6. Physical findings, such as white forelock, that are associated with a syndrome known to include a sensorineural or permanent conductive hearing loss.
7. Syndromes associated with hearing loss or progressive or late-onset hearing loss*, such as neurofibromatosis, osteopetrosis, and Usher syndrome; other frequently identified syndromes include Waardenburg, Alport, Pendred, and Jervell and Lange-Nielson.
8. Neurodegenerative disorders*, such as Hunter syndrome, or sensory motor neuropathies, such as Friedreich ataxia and Charcot-Marie-Tooth syndrome.
9. Culture-positive postnatal infections associated with sensorineural hearing loss*, including confirmed bacterial and viral (especially herpes viruses and varicella) meningitis.
10. Head trauma, especially basal skull/temporal bone fracture that requires hospitalization.*
11. *Chemotherapy

Note: Risk indicators that are marked with a "*" are of greater concern for delayed-onset hearing loss.

SCREENING BEYOND THE NEWBORN PERIOD

Given that hearing loss can occur at any time or be of a progressive nature, screening for hearing loss beyond the newborn period is important. In fact, screening for hearing loss in children and middle-ear disorders has been around for many years in schools, clinics, and health departments. Although there is this long history, variability in procedures remains. Routine hearing screening often starts with the preschool-age child who can perform developmentally appropriate pure-tone procedures. These screenings are conducted in daycares, preschools, and in some primary care physician offices. There is currently an initiative to capture the 0- to 3-year-old population who attend early head start programs using otoacoustic emissions (OAE) as the screening tool (20).

Hearing screening in the school-age population has had a variety of policies and procedures as not all states have legislative mandates, and policies can be written by individual school districts or health departments. The AAA (21) and the ASHA (22) recommend pure-tone screening at the child's initial entry into school, annually in kindergarten through third grade, seventh grade, and eleventh grade. Screening should be conducted at 20-dB HL for frequencies of 1,000, 2,000, and 4,000 Hz. Failure to respond at any frequency in either ear necessitates rescreening. Failure on rescreening requires a referral for audiologic evaluation within 1 month of rescreening and no later than 3 months after the initial screening.

Routine screening of middle-ear disease is not recommended as a stand-alone screening but may be done as part of a comprehensive hearing screening protocol in children who are at risk for otitis media (23). Because of the transient nature of middle-ear disease and resolution of the middle-ear disease without treatment, routine tympanometric screening can lead to too many children being referred to their physicians without middle-ear effusion at the time of the visit.

DEVELOPMENT OF AUDITORY BEHAVIOR

Although infants are born with the ability to hear, some developmental changes occur with respect to their perception of sound, and neural processing ability continues to develop well into childhood and adolescence. The auditory system is intact early and becomes functional during the third trimester at around 25 weeks gestation (24). The central pathway, however, continues to develop well into adolescence with increase in myelinization and neural pathway development. Brainstem myelinization is complete by 1 year of age but the central structures complete myelinization at 10 years or older. These changes can be reflected in evoked potentials that undergo changes in amplitude and latency of the responses, although not in threshold.

Early on in life, infant's responses to sounds are often of a reflexive nature until they develop the motor control for a more organized response. With increasing age, the intensity level of the auditory stimulus that is needed to elicit a response from the infant decreases. Beginning about 5 to 6 months of age, when formal audiologic techniques can be utilized, adult-like values can be obtained to auditory stimuli. These changes in response levels are not indicative of sensitivity differences but in the minimal stimulus level needed to elicit a response.

Infants begin to localize sounds first in horizontal and then vertical planes. Between 3 and 6 months of age, infants search for the sound, respond to the sound of their name, and respond differentially depending on the tone of voice the parent is using. By about 5 to 6 months, formal and reliable behavioral-audiologic testing can begin. Between 6 and 10 months, infants can seek out the source of sound and respond to common sounds in their environment. They respond to both loud and soft sounds and pay attention when the parent talks to them. Between 10 and 15 months of age, babbling increases and begins to more closely resemble speech. Between 15 to 18 months, a baby is able to directly localize to most sounds, understand simple phrases, identify familiar objects such as body parts, and follow simple directions. A child at 18 months should have an expressive vocabulary of 20 or more words and short phrases.

TEST BATTERY

For pediatric assessment, the cross-check principle, originally developed by Jerger and Hayes (25), is utilized. Use of the cross-check principle helps to minimize mistakes in diagnosis and develop an audiometric profile that best represents the child's auditory abilities. This principle relies on a combination of behavioral and physiologic tests to provide a comprehensive picture of hearing sensitivity and auditory status. Behavioral tests, although usually considered more subjective because of their reliance on patient participation, are combined with the results of objective physiologic tests that do not require active participation by the child/infant. At very young ages or in the case of significant developmental delay, the electrophysiologic test (e.g., ABR) findings often predominate in the initial decision making about the management of the child with a hearing loss. As the child develops and can participate in behavioral testing, the behavioral findings will serve as validation of electrophysiologic findings, as well as document sequential development of auditory skills. For older children with developmental skills adequate for behavioral testing, audiologic findings with or without ABR supporting data are used to determine management of the hearing loss.

The goal of behavioral audiologic assessment is to establish the degree and nature of any hearing loss for each ear so that management of hearing loss, including

hearing aid fitting, can be done. The evaluation includes a comprehensive history, observation of the child's awareness of or use of sound, as well as multiple tests to assess various aspects of the auditory system, including cursory otoscopic examination, tympanometry, assessment of acoustic reflexes (ARs), and behavioral audiometric testing (air conduction and bone conduction) to both speech- and frequency-specific stimuli.

SPECIAL TESTS

Auditory Brainstem Response Testing

For the very young child, physiologic assessment procedures using auditory evoked potentials, such as ABR, are particularly important. The ABR can be used for both identification and assessment of hearing and can provide accurate estimates of threshold sensitivity (26). Under good recording conditions, and using frequency-specific stimuli, the ABR can provide reliable estimates of sensitivity across the frequency range of hearing (27) in children of all ages. Although this is the test of choice in children under 6 months of age, the ABR is used for older children who cannot be tested behaviorally. Typical recommendations for the ABR include failure to obtain behavioral audiologic thresholds after two attempts, or a high suspicion that a hearing loss exists and that continued testing would only delay diagnosis.

The ABR follows neuromaturation of the central auditory nervous system and shows wave latency changes until about 18 months of age. Wave I is mature early on in life and show little if any latency change with age, whereas the later waves continue to decrease in latency with increase in age to about 18 months of age, with the most rapid changes occurring in the first 3 months after birth. The interwave latency difference between wave I and V therefore goes from about 5.0 at birth to about 4.0 milliseconds when mature. Thresholds do not change over time if hearing is stable. The ABR is best conducted while the infant is sleeping to eliminate background myogenic noise, which can overshadow the neural response. Young infants can often be tested during a natural sleep, following a feeding. Older infants may need to have sedation. ABR done under sedation is now more routinely done in procedure centers where there is a physician and nursing support for sedation monitoring throughout the test session.

The ABR may be used to estimate an audiogram, but some drawbacks exist. The major limitation is the choice of stimuli available that can be used to elicit a response. Synchronous neural firing of multiple neurons is essential to record a response. The best stimulus to elicit a response is a rapid or abrupt onset stimulus such as a click that stimulates a broad area of the basilar membrane and therefore generates synchronous neural discharge in a large number of neurons. The ABR to click stimuli will provide an overall assessment of the integrity of the auditory pathway and provide a basis on which to start investigating thresholds at specific frequencies.

The click stimulus, however, is not frequency specific but contains energy in a broad frequency range and responses obtained to click stimuli cannot detect frequency-specific impairment. The responses to click stimuli have been found to correlate best with audiometric findings in the higher frequency range from about 1,000 to 4,000 Hz frequency range (28–32). Use of this stimulus solely can either underestimate or miss a hearing loss at a particular frequency or frequencies depending on the degree and configuration of the hearing loss (33,34). While the use of age-appropriate latency-intensity functions together with the threshold search will help to identify impairments, exact quantification of the impairment at each frequency cannot be done using the click stimulus. Rather more frequency specific or tonal stimuli need to be used.

The stimulus that is commonly used to obtain frequency-specific information is a brief duration tone burst referred to as a tone pip. With the use of this stimulus, fairly good synchronous neural firing can occur. The trade off in becoming frequency specific or tonal by increasing the rise time of the stimulus is the reduction in the synchronous neural discharge. The aim is to achieve a balance of tonality with enough synchronous neural firing to elicit a response. It is necessary to maintain a fast enough rise time to elicit a response yet reduce the acoustic splatter to frequencies above and below the nominal frequency of the stimulus. While producing a stimulus that does not have contributions from other frequencies is important, it will not ensure a place-specific region of excitation on the basilar membrane. Physiologically there is an upward spread of excitation on the basilar membrane as the intensity level of the stimulus is increased beyond 70-dB sound pressure level (SPL) (35). Spread of energy to frequencies with better hearing will result in an underestimation of threshold level. For children with severe to profound hearing losses, the intensity level of the stimulus will be sufficiently high that there is to be expected some spread of energy on the basilar membrane.

ABRs should be obtained to both air and bone conducted stimuli and thus can provide information about type of hearing loss. Bone conduction should be elicited to at least a click stimulus to assess presence or absence of air-bone gaps. While there are intensity output limitations in bone conduction testing, such testing often confirms the type of auditory impairment. Threshold differences of greater than 15 dB with better bone conduction thresholds than air conduction thresholds are indicative of conductive involvement and warrant further otologic evaluation.

The ABR measures the integrity of a portion of the auditory system through approximately the level of the midbrain and does not measure "hearing" in the true sense of the word. Although it is well established that agreement exists between behavioral thresholds and ABR thresholds for children with typical sensory hearing loss, there

are instances where they will not agree and further investigation is necessary. Examples include cases of normal ABR with no ability to recognize or use sound to "hear." Conversely, the absence of an identifiable waveform on an ABR test does not necessarily equate to thresholds in the severe to profound range or to "no hearing." The limits of the ABR equipment should be recognized. Output is more limited than most audiometers used to test behaviorally. Consequently, an absent response on ABR should not be interpreted as the absence of residual hearing. Additionally, the ABR will be affected by the neurologic status of the child. If the auditory system is damaged and neurons cannot fire synchronously, or if there are disruptions of the auditory pathway due to an insult, then the integrity of the ABR may be compromised resulting in no identifiable ABR waveform or a partial waveform with later waves absent, despite the fact that the end organ of hearing, the cochlea, may be functioning normally. With the availability of technology to monitor OAE from the cochlea, discrepancies between behavioral audiologic findings and the ABR, where behavioral audiologic findings show better responsivity to sound than can be predicted by the ABR, are being substantiated by the presence of OAEs. These hearing losses are either auditory neuropathy or neural hearing loss. Auditory neuropathy represents good outer hair cell function but a disruption in the peripheral nerve, whereas neural hearing loss is a breakdown in nerve transmission that occurs more centrally.

Auditory Neuropathy Spectrum Disorder is a term that found more and more frequently in the literature and is being used indiscriminately in cases where OAEs are present and the ABR is absent or abnormal. Rapin and Gravel (36,37) delineate clearly the distinction between neural, sensory, sensorineural, central hearing losses, and auditory neuropathy. They point out that neuropathy means that there is peripheral nerve pathology, yet much of the literature contains cases where this was not shown. For example, neonates with hyperbilirubinemia and resulting hearing losses show abnormal ABRs and normal OAEs, yet the primary site of pathology is the central auditory pathway, that is, vestibular and cochlear nuclei and basal ganglia and not the VIII nerve, yet it is often said that hyperbilirubinemia is a risk factor for auditory neuropathy. Combining all children with abnormal ABRs and present OAEs into one category will present challenges for managing the hearing losses effectively. Furthermore, until there is clearer differentiation, we will be unable to help families understand their child's hearing loss and expected outcomes. This is clearly an area where the audiologist and otolaryngologist need to work closely together to ensure proper diagnosis of hearing loss.

An emerging physiologic evoked potential test, the auditory steady-state response (ASSR), holds promise for predicting frequency-specific thresholds in individuals who cannot provide reliable or valid behavioral thresholds, for example, in young infants and children (38–41). The advantage of this measure is that it is truly an objective measure because the response presence or absence is based on statistical analysis and not on visual detection methods as with the ABR.

The generation of the 80-Hz ASSR, like the ABR, is believed to be primarily in the brainstem (42). ASSR uses relatively tonal stimuli (carriers) that are amplitude- and/or frequency-modulated to evoke a response and can provide accurate frequency-specific estimates of air conduction hearing levels. For pediatric applications, the modulation occurs at a frequency appropriate for infants and children (about 80 to 100 Hz). Single or multiple stimuli presented simultaneously have been used to elicit the ASSR (43). Furthermore, the 80 Hz ASSR can be obtained in infants and young children who are asleep (44). The test has the ability to monitor both ears simultaneously, making it attractive for possible reduction in test time compared to the ABR, although more research is needed in this area before conclusions can be drawn as to whether there is truly a time savings. Threshold prediction using the ASSR conducted on adults and children with hearing loss has been shown to provide fairly accurate estimates of the behavioral audiogram (41,45–51).

Hearing thresholds have been estimated within about 10 to 15 dB in adults with normal hearing and hearing loss using the multifrequency ASSR (39,52). Fewer data, however, exist regarding the use of the ASSR for measurement of hearing in infants and children. Perez-Abalo et al. (53) found that although they were able to determine hearing loss in the severe and profound range, only fair agreement was seen between ASSR thresholds and hearing levels in children with mild hearing loss or normal hearing.

Few data exist regarding the use of ASSR employing bone conduction stimulation. Small and Stapells (54) used multiple bone conduction stimuli that were both frequency and amplitude modulated in a group of preterm infants (32 to 43 weeks) and a group of full term infants (0 to 8 months). The results obtained in infants were different from those obtained in adults; in infants, the threshold estimates were better in the lower frequencies and poorer in the higher frequencies when compared to adult data. Swanepoel et al. (55) evaluated bone conduction stimulation in a group of older children and concluded that the stimulus artifact prevents determination of type of hearing loss in most cases of sensorineural hearing loss but interferes less when conductive hearing losses are present. However, results vary with frequency in both cases.

The influence of age on the ASSR suggests that maturation has some bearing on threshold determination in very young infants. Rance and Rickards (56) found that the prediction of hearing thresholds was similar between young (1 to 8 months of age) infants and older subjects with hearing loss. However, results obtained from infants with normal hearing have suggested that maturational factors, which are sufficient to affect the differentiation

between normal hearing and mild-to-moderate hearing loss, may influence the findings of ASSR assessments carried out in the first few weeks of life (38,47,57–60). Recently, Rance and Tomlin (61) evaluated neonates and young infants with normal hearing and found their ASSR threshold levels were different from those observed in older subjects. They concluded that when the ASSR is used clinically, it is necessary to take into account developmental changes occurring in the first weeks of life. Furthermore, their findings indicated that ASSR thresholds in normal-hearing babies at 6 weeks of age were not yet mature. Clearly, this is a tool that has much promise for assessment of infants and young children, but further research and refinement are needed in all aspects of the ASSR to determine if it will produce accurate audiogram predictions in all infants.

Otoacoustic Emission Testing

The test that helped to propel newborn hearing screening into the standard of care for all newborns are OAEs. OAEs are sounds that originate from physiologic activity inside the cochlea and that can be recorded in the ear canal. The literature is rich with evidence that this activity is associated with normal to near normal hearing processes (62,63).

The sensory, or outer hair cells, within the organ of Corti are thought to be responsible for the generation of OAEs, specifically the electromotility of the outer hair cells (64). Thus, the OAEs give us the ability to view the functioning of the cochlea, although not without contribution of the middle ear. That is, the sounds created in the cochlea are passed through the middle ear via the ossicular chain and eardrum. These sounds are then recorded by placing a microphone in the ear canal. Consequently, healthy middle ears that can transmit sound to and from the cochlea effectively are essential to being able to record the OAEs.

OAEs are classified according to whether there is a stimulus used to record them. Spontaneous Otoacoustic Emissions are recorded when no stimulus is present and Evoked Otoacoustic Emissions (EOAEs) are recorded following a stimulus. The two clinically useful EOAEs are Transient Evoked Otoacoustic Emissions (TEOAEs), which are recorded following a brief acoustic stimulus (click), and Distortion Product Otoacoustic Emissions (DPOAEs), which are recorded following two simultaneously presented pure tones.

The click, as it does in the ABR, produces a broadband stimulus and therefore a response from a wide range of frequencies. While the click stimulus used to elicit the response is not frequency specific, TEOAEs, unlike the ABR to click stimuli can be analyzed in frequency bands to provide information that is frequency specific. The stimulus level of 80 to 84 dB SPL is used to elicit TEOAEs because this level is optimal for obtaining a response. The response amplitude is recorded over a 20-millisecond time window following the stimulus. The higher frequencies are recorded in time first because they originate closer to the base of the cochlea and have shorter latencies. The lower frequencies come from more apical portions of the cochlea and consequently have longer latencies and are recorded next. Presence or absence of a response is determined by evaluating the response amplitude relative to the noise floor and the response reproducibility of the waveform (two waveforms are generated for each test), assuming that the stimulus is maintained at a proper intensity level. In general, the TEOAEs response amplitude is higher in children than in adults, many times making it easier to obtain a response from a young child.

DPOAEs are recorded following the simultaneous presentation of two pure tones that are related in frequency. The interaction of the tones produces a third tone emitted from the cochlea, not present in the original stimuli. Distortion products are by-products of a normal nonlinear system, in this case the outer hair cells. DPOAEs allow for more frequency-specific stimulation of the cochlea as compared to the click stimuli used to elicit TEOAEs. The intensity level of the two stimuli is either equal or the lower frequency stimulus has a higher intensity by approximately 10 to 15 dB. DPOAEs are plotted on a DP gram with DPOAEs response amplitude as a function of frequency. Absolute amplitude of the response or amplitude relative to the noise level determines presence or absence of a response. Like TEOAEs, the amplitude of DPOAEs is larger in children than in adults.

Recording OAEs allows measurement of cochlear function objectively and noninvasively. OAEs are generated exclusively by outer hair cells. Most hearing losses do not involve inner hair cell damage without outer hair cell damage; that is, outer hair cells are generally more vulnerable to disease and damage than inner hair cells. Therefore, the presence of an emission provides us with reasonable assurance that hearing thresholds are 30 to 40 dB or better in the frequency range where the emission is present. OAEs may be absent due to middle-ear dysfunction, resulting in inability of the emission to be transmitted, or to sensory hearing loss affecting production of the emission. Prediction of hearing levels is not possible by measuring OAE. The absence of OAE can be associated with hearing loss of mild to moderate degree and greater, and their presence does not ensure normal hearing. When measuring OAEs in young children, their amplitude may be reduced in the low-frequency regions (1,000 Hz and below) because of interference from the low-frequency physiologic and ambient noise in this region. Consequently, absent OAEs in low-frequency regions alone are insufficient for determining presence or absence of hearing loss. OAEs should constitute one test in a battery of tests for accurate interpretation. OAEs are sensitive to hearing losses and can be absent with as little as a 20 to 30 dB HL hearing loss. The absence of OAEs must be viewed within the context of the status of

the middle ear, since both the stimulus and the response pass through the middle ear. Therefore, the absence of an OAE is diagnostically significant for sensorineural hearing loss only when middle-ear function is relatively normal.

Immittance Testing

Other tests that are important to the test battery used for the audiologic assessment of infants and young children are acoustic immittance tests of tympanometry, equivalent ear canal volume, and AR threshold monitoring. These tests are especially important when one considers the high incidence of otitis media with effusion (OME) in young children. Acoustic immittance testing serves to differentiate and/or substantiate other test findings. Tympanometry, an indicator of tympanic membrane mobility and middle-ear pressure, is used to infer middle-ear function. Tympanometry assesses the movement of the tympanic membrane in response to mechanically varied air pressure and indirectly measures tympanic membrane mobility by measuring the amount of reflected sound, or inversely by the amount of sound passing through the tympanic membrane to the middle ear. Standard tympanometry uses a low-frequency probe tone of 220 or 226 Hz for measurement. However, the interpretation of the tympanogram and AR findings may be compromised when this probe tone is used with infants less than 4 months of age. Specifically, findings in the ears of infants with middle-ear fluid show normal-appearing tympanograms (65). The most likely explanation for this false reading is related to the fact that mass and stiffness contributions are different between adults and children—children have a more mass dominated system as compared to an adult stiffness dominated system at low frequencies. Therefore, the use of a higher probe frequency (e.g., 1,000 Hz) is recommended in order to obtain tympanograms that are a more valid indication of middle-ear function for infants aged 6 months or less (66–72).

Tympanometry using a high-frequency probe tone cannot be interpreted in the same manner as those tympanograms that were obtained with a 226 Hz probe tone. The volume readings are higher and only volume readings from 226 Hz should be used or erroneous diagnosis can be made. Furthermore, there are no established large-scale normative values available at this time as the shape of the tympanogram can vary widely from those obtained with a standard 226 Hz probe tone.

With a flat tympanogram, equivalent volume measurements may provide information of probe tip occlusion, intactness of the tympanic membrane, and tympanostomy tube patency. A very small volume may indicate probe tip occlusion or external auditory canal stenosis or blockage. A large volume may indicate a tympanic membrane perforation or open tympanostomy tube. The equivalent ear canal volume varies with age as infants may be approximately 0.3 mL (73), children aged 3 to 5 years are 0.7 mL and adults are 1.1 mL.

AR testing monitors stapedius muscle response to loud sound, which indicates middle ear and auditory brainstem activation. The AR can be a very useful part of the audiologic evaluation in infants. A present reflex is added support for normal middle-ear function, as well as information about the integrity of a portion of the auditory brainstem pathway. These tests are both objective measures but abnormal acoustic immittance findings and/or the presence of fluid does not determine hearing levels. Furthermore, the tests used for assessment of hearing do not determine the presence of fluid. Therefore, acoustic immittance measures in combination with hearing assessment measures help to provide a complete picture of the status of the Ear Hear and can help the examiner to make proper recommendations.

Wideband energy reflectance, wideband impedance or generally defined as wideband acoustic immittance, is a relatively new method of assessing middle ears of infants and children. Wideband reflectance research is emerging with some supporting literature that it offers improved diagnosis of middle-ear conditions compared to single-frequency tympanometry (74–76).

Pure-Tone Testing

The reliance on physiologic measures shifts to behavioral measures typically around the developmental age of 6 months. As with physiologic testing, the goal of the behavioral test battery is to obtain ear- and frequency-specific thresholds to both air and bone conducted stimulation. Similar to adults testing, behavioral testing of infants is conducted in a sound-treated room, but for children the booth needs to be larger in size than those used for adults. Behavioral response levels can be obtained using Behavior Observation Audiometry (BOA), visual reinforcement audiometry (VRA), play audiometry, and conventional audiometry for the older child.

Behavioral Observation Audiometry

For infants from birth up to 5 or 6 months of age, behavioral assessment is limited to this technique of observing response changes (e.g., cessation of sucking, eye movement, and startle) to auditory stimuli. Since infant responses will occur at levels above threshold and are quite variable, BOA cannot be used to assess threshold. For the very young infant, reliance on physiologic measures for threshold estimation is necessary. BOA is important, however, for understanding infant's responses to sounds and can be beneficial for families and clinicians to understand the infant's auditory development.

Visual Reinforcement Audiometry

For children developmentally 5 to 6 months of age, it is possible to use a conditioned auditory response, called

VRA, to measure hearing threshold levels. This is an operant conditioning paradigm that reinforces a motor activity, usually a head turn, with an appealing visual display, usually a lighted, animated toy or simple video display (Fig. 100.1). The auditory signal or stimulus cues the infant that a response, that is, head turn, will result in reinforcement. Studies have shown that frequency-specific thresholds can be obtained from infants at developmental levels of 5 to 6 months, producing accurate measures of hearing sensitivity (77–83).

VRA can be conducted using insert earphones (the transducer of choice), for ear-specific responses, and a bone conduction vibrator. If the child will not tolerate the use of earphones, results can be obtained using stimuli presented via sound field (presentation via speakers) into the test booth or sound isolating room.

Conditioned Play Audiometry

As children get to be about 2 years of age, they can usually perform testing using a play task, called play audiometry. The child is conditioned to respond to pure tones by playing a simple game using toys such as stacking rings, peg boards or simple puzzles or a combination of play activities to maintain interest. Standard testing techniques are used and thresholds obtained using play audiometry in a cooperative child is assumed to be adult-like.

Conventional Behavioral Audiometry

Conventional behavioral audiometry can be conducted using a hand raise response and can be done starting at developmental age of 5 years. When testing children, however, testing methods may need to change in order to maintain interest and participation of the child patient. Flexibility is key to maximizing obtaining needed information to diagnose a child with a hearing loss.

As with adult testing, speech testing (word recognition testing) is a component of the evaluation but is typically not done until the child has sufficient language proficiency to participate for the testing. This is typically around developmental age of 3 to 4 years. Like behavioral testing, adaptations are made to ensure that the child is capable of participating in the task and their attention can be maintained. Thus speech testing often begins with a picture pointing test such as the Northwestern University Children's Perception of Speech, Word Intelligibility by Picture Identification (WIPI), or Pediatric Sentence Identification test.

In addition to conductive, sensorineural, mixed hearing loss, and neural hearing losses, children with processing disorders need to be identified. Auditory processing involves not only the perception of sounds but interpretation and understanding of sound, even in less than optimal conditions. Children can present, therefore, with normal hearing sensitivity yet may not be able to follow directions well or understand complex sounds, especially in difficult listening situations, such as a noisy classroom. Clinical features of auditory processing disorders (APDs) include: (a) easy distractibility, (b) delayed responses, (c) difficulty following directions, and (d) unexplained behavioral problems. Children need to have normal cognitive function and the ability to cooperate for a battery of tests in order to be evaluated for APDs. There are no standard protocols for such testing, and each clinician develops their own protocol. Furthermore, there is no gold standard against which to evaluate the diagnostic tools that are used and there is lack of data on the rehabilitation protocols. Regardless of these issues, there is agreement that the problem does exist and this is an area that falls within the scope of practice of the audiologist (84). Management of APD involves (a) improving the listening environment in the classroom with preferential seating or an frequency modulated (FM) system, (b) utilizing compensatory strategies such as repetition or cueing, and (c) therapy to improve auditory skills such as memory or perceptual training.



Figure 100.1 VRA. An 10-month-old infant is conditioned to turn his head to a video display when an auditory stimulus is detected.

Degree of Hearing Loss

For children, the classification of degree of hearing loss is often more stringent, as hearing loss in this population can significantly affect the development of speech and language and can have negative educational impacts, if left undetected. At average conversational levels, the unvoiced consonants: *s*, *p*, *k*, *th*, *f*, and *sh* fall at or below normal adult hearing levels, so better hearing is needed for more-consistent detection of these sounds. This is the reason for setting the critical range of hearing at 0 to 15 dB for a young child. The ASHA classifies hearing loss as tabulated in Table 100.2.

REVIEWING TEST RESULTS

The pediatric audiologic evaluation, in comparison to the adult evaluation where hearing loss can be defined in one clinic visit, often requires repeated visits scheduled in close proximity before the exact configuration and degree and sometimes nature of the hearing loss is defined. The audiologic assessment of children, but in particular, for the very young infant with a hearing loss is a time-intensive and an on-going process. While a comprehensive audiometric profile is always the goal and necessary before the hearing aid fitting process can be completed, reliable estimates at critical frequencies can be used to initiate the amplification and habilitation process, with refinements and adjustments of the hearing aid fitting occurring as more and more precise information is obtained. Delays in habilitation are not acceptable even when only partial information is available, and valuable time should not be wasted waiting for complete information.

TABLE 100.2 HEARING LOSS CLASSIFICATION

Degree	Hearing Level (dB)	Impact on Child
Normal	0–15	Child will hear all speech sounds
Slight	16–25	Child will hear vowel sounds clearly, but might miss some consonant sounds
Mild	26–40	Child will hear only some of the speech sounds
Moderate	41–55	Child will hear almost no speech sounds at a normal speaking level
Moderate to severe	57–70	Child will hear no speech sounds at a normal speaking level
Severe	71–90	Child will hear no speech and almost no other sounds
Severe to profound	>90	Child will hear only few other sounds

MANAGEMENT OF HEARING LOSS

Management of hearing loss in children starts first with counseling the family about the hearing loss, supporting their emotional needs as they deal with the diagnosis, helping them to understand the modes of communication available, finding opportunities for financial support for hearing aids, then moving onto fitting of amplification, and enrollment into an educational program, such as early intervention, geared to helping develop communication for those with hearing loss. The majority of families of children with hearing loss opt to provide amplification for their child (Compiled by the NIDCD).

In those instances where there are family members with hearing loss, careful exploration of the family's wishes needs to occur to ensure that they are respected in their beliefs, while also trying to achieve accuracy in their understanding of the hearing loss and what options are now available for their child. While the hearing aid fitting process is beginning, referral to and enrollment into an early intervention program is a must so that the families have the educational help and support that they need on an ongoing basis.

THE ROLE OF THE OTOLARYNGOLOGIST IN THE ASSESSMENT AND REHABILITATION

The otolaryngologist has the primary responsibility to assess for the etiology of the hearing loss. History may reveal risk factors for hearing loss such as perinatal events, ototoxin exposures, head trauma, or family history of early onset hearing loss. Physical exam may identify stigmata of syndromes. Further evaluation may involve genetic testing, radiographic imaging, ophthalmologic referral, and other indicated laboratory tests.

The otolaryngologist also provides medical clearance for hearing aids. The United States Food and Drug Administration requires that clearance occurs within 6 months of the fitting of hearing aids in children less than 18 years. The otolaryngologist works in close conjunction with the audiologist and monitors for progressive change in hearing and discusses when other options, such as cochlear implants, are indicated. Routine exams also are required to monitor for factors (e.g., excessive cerumen, earmold size) that may interfere with hearing aid fitting.

Hearing Aid Fitting

The goal of amplification is to make speech audible, which is often the primary mode of communication chosen by parents as most hearing losses in children occur in families who hear. Children learn spoken communication skills from hearing the sounds around them and the ability to hear consonant sounds carries with it

information critical to understanding the spoken message. The most common form of amplification is a personal hearing aid for these children, and as they grow, other assistive technology may be added and include such things as FM systems or implantable devices such as cochlear implants.

Advances in technology have helped with better outcomes for children with hearing loss. In general, the hearing aids have become smaller and stay on small ears better, have more options, and have better strategies to enhance speech in the background of noise. Research on adults has shown that the newer technology appears beneficial. Little research has been done on children to prove that these same technologies are of benefit to them. Several reasons why this has not been done is that it is hard to measure benefit for children who are prelingual and it is hard to control for all factors that can affect outcome. New technology has been designed for people who have hearing loss in the high frequencies, a range where traditional hearing aids have not been able to amplify well. This technology is designed to give access to the higher frequency sounds by either compressing the frequency range to be within a person's range of hearing, that is, low- and mid-frequency range or moving the higher frequency sounds to regions of better hearing. These technologies are referred to as frequency compression and frequency transposition, respectively. Older children have shown that they can receive benefit, but little is known about speech and language development in the prelingual child with a high-frequency hearing loss using these technologies. More research using these and other technologies are needed in the pediatric population.

Hearing aid fitting starts with having sufficient frequency-specific information to fit the hearing aid. The use of click data from the ABR is insufficient to fit a hearing aid, and thresholds from at least 500, 1,000, 2,000, and 4,000 Hz are needed. The hearing aid fitting is refined as more complete auditory information is obtained as the child grows. The child's ear, which is smaller in nature and has different resonances, alters the output of the hearing aid differently than when it is fit in an adult size ear. Standard measurement of output of a hearing aid is closer to what an adult may hear but only measurement of the amplified sound in the ear can verify the actual sound reaching the ear drum. The bony portion of the external auditory canal alters size through 7 years of age, and the pinna grows until approximately 9 years of age. The primary postnatal change in the middle ear is a positional change of the tympanic membrane and ossification of the bones in the middle ear. These changes that continue to occur in childhood affect the output of the hearing aid as measured in the ear canal of the child. Consequently, there is a need to account for the child's ear canal acoustics.

In general, the smaller the ear relative to the adult ear results in a higher intensity of sound in the young child's ear, and this can vary by upwards to 15 dB, resulting in uncomfortable or even damaging levels in the young child's ear. Since there is great variability among ears in ear canal acoustics, it is imperative that measurements be made in the ear using real-ear measurement systems. For young children, this can be a challenge, as the patient needs to remain still and not vocalize during these measurements. An alternative approach is to use the real-ear to coupler difference (RECD) measure to determine the acoustic response in an occluded ear canal without repetitive real ear measures. The RECD is calculated by first determining the SPL using the child's earmold seated in the child's ear (or a standard ear tip) that is coupled to an insert earphone transducer. A second SPL measure is made and that is of the 2 mL coupler. The RECD is the difference between these two measures or the difference between the SPL across the frequency range of the signal from the insert earphones transducer measured in the ear and the SPL of the same signal measured in the 2 mL coupler. This measure is then added to the hearing aid output measured in the 2 mL coupler to estimate the amount of amplification being delivered to that child's ear. Average values are available but not recommended as there is wide range of variability in the RECD measure among children of the same age. The hearing aid gain is adjusted following a prescriptive formula such as the Desired Sensation Level Multistage Input/Output Algorithm (DSL m[i/o]) v 5.0a as it was developed specifically for use with children. Verifying that targets have been reached is a critical step in the hearing aid fitting process and again, with children, since real-ear measures most likely will not be able to get completed successfully, the RECD is used to accurately predict real-ear measurements. The RECD is also used to help during the hearing aid fitting process to convert the dB HL thresholds to dB SPL, the measurement used for hearing aid output. The RECD needs to be remeasured with growth of the ear and is usually done with every earmold change. During the very early months in life, earmold changes occur about every 2 to 3 months and slows to about every 6 months after about 18 months of age. New RECD values dictate altering the hearing aid output to ensure proper amplification received by the child. The hearing aid process, like the diagnostic evaluation and counseling, is ongoing throughout the child's life as their needs change.

Today's digital hearing-aid technology provides a wide selection of amplification options and flexibility for optimizing gain, frequency response, and resulting speech audibility. For children, this flexibility is critical to ensuring optimal amplification. The behind-the-ear style hearing aid is the most widely used for the young children due to its greater flexibility in fitting of all degrees of hearing loss, durability, and less expensive option of replacing only the earmold as the ear grows compared to having to recase an in-the-ear (ITE) style hearing aid. ITEs may be appropriate when the child is older. The disadvantage is that they cannot be used with some hearing assistive technology that is used in classrooms, for example, FM systems. The

benefits of binaural amplification are well documented, for example, for sound localization and better ability to discriminate what is said in noise. Thus, binaural hearing aids are fit whenever residual hearing is apparent or until continued testing proves this to be detrimental or of no measurable benefit.

Because hearing aids amplify all sounds, noise is amplified along with speech. In the classroom, children with hearing loss often struggle to hear the teachers due to the high levels of background noise found in classrooms. The ability to hear and understand verbal information is important for learning. FM systems are a commonly used hearing assistive technology that allows the child (or anyone using this technology) to hear verbal information (speech) clearly. A microphone is worn close to the teacher's mouth and the speech signal is sent to the child's hearing aid, thus creating a situation that is like having the speaker close to the child's ear. The FM system uses radio transmission to send the signal from the microphones to a small receiver worn by the listener. This receiver is now often built into or attaches onto the hearing aids. While FMs are more commonly used in classrooms, they can be used in the home environment as well. FMs can also use speakers that can be portable or mounted in the classroom, thus potentially benefiting all children in the classroom. In addition to FM, other assistive technology such as induction loop and infrared systems are used and can be found in public settings such as theaters. Nowadays, Bluetooth is being used to connect to electronic devices such as cell phones and MP3 players.

Implantable Hearing Devices

Discussion of cochlear implants and implantable hearing devices is in Chapter 163. This section highlights the aspects unique to the pediatric population.

Implant Evaluation

Cochlear implantation is considered when conventional hearing aids are insufficient to provide the adequate auditory input for appropriate speech and language development. In pediatric populations, multidisciplinary evaluation helps determine candidacy. Otolaryngologists, audiologists, speech and language pathologists, psychologists, and social workers collaborate to assess infants and children prior to cochlear implantation. The preoperative speech and language evaluation determines whether developmental language or articulation disorders are present, defines the child's current communication abilities, and develops expectations and plans for speech therapy after implantation. The psychological evaluation assesses the intelligence and may identify cognitive disabilities that could affect a child's performance with a cochlear implant. As younger age children are receiving implants, families are counseled that some conditions such as autism and attention deficit disorders may not be evident until the child reaches 2 years of age. These evaluations are essential to establish appropriate expectations for parents prior to a cochlear implant. Current FDA guideline based on age for cochlear implants are in Table 100.3.

TABLE 100.3 PEDIATRIC COCHLEAR IMPLANT CANDIDACY

Ages 12 to 24 mo
Bilateral profound hearing loss
Lack of auditory skills development
Minimal benefit from hearing aid
No medical contraindication
Ages 24 mo to 18 y
Bilateral severe-to-profound hearing loss
Lack of auditory skills development
Minimal hearing aid benefit
No medical contraindications

In infants, speech perception tasks are not readily attainable and decisions about implant depend on electrophysiologic measures and detection thresholds. Most children will have an ABR as a component of the assessment. Unaided and aided threshold measurements corroborate ABR results and determine implant candidacy. Speech perception testing in children depends on their language abilities. The Meaningful Auditory Integration scale is a questionnaire for parents to assess the infant's response to sounds at home. Young children may participate in some closed-set measures such as objects or pictures (e.g., Early speech perception or WIPI). Open-set testing refers to tests when answer choices are not provided and may be performed in older children. Testing in children often involves the use of a 50 word list, the Lexical Neighborhood Test. For those children with vocabulary of a 5-year-old, the Phonetically Balanced Kindergarten test is used. For children with previous language acquisition, the Hearing in noise Test—Children may be utilized.

Early Implantation

Because of newborn hearing screen, children with hearing loss are being identified at an earlier age. The shift to an earlier age of implant is possible and questions about implants under the 12 months of age are raised. Evidence for the benefits of early implants was already demonstrated in those who were less than 24 months when they received an implant. These children had better perception and oral language scores than those who were implanted after 24 months of age (85,86). Even in children implanted at 12 to 18 months had overall better communication behaviors compared to those implant 19 to 36 months (87).

Evidence also supports that children implanted less than 12 months have even further benefits when compared to those who were implanted between 12 and 24 months (88–91). These studies demonstrate that language trajectories of infants implanted prior to 12 months old exceed that of children implanted after 12 months of age.

The surgical and anesthetic safety of infant implantation has been reported (92–94). Anatomically, infants are candidates as the cochlea is adult size at the time of birth. The surgical considerations in implanting infants and young children are that the physician has to be aware of blood loss. The mastoid also may be less pneumatized and more vascular because of the marrow and hemostasis has to be controlled meticulously, especially when bilateral simultaneous implantation is performed. Secondly, the skin flap over the device has to be maintained. Unlike in adults, in whom the skin flap has to be thinned on occasion to allow for the external magnet to adhere to the internal device, the surgeon has to be careful in maintaining the thickness of the flap over the device and minimize possibility of wound breakdown. Lastly, the skull thickness is less in younger children. This makes the likelihood of dural exposure greater in the infant when the bony seat or tie-down holes are drilled. Potential trauma to the dura or the surrounding vasculature has resulted in reported cerebrospinal fluid leaks, epidural and subdural hematomas, cerebral infarction, and lateral sinus thrombosis (95–98). Surgeons recently advocated not creating the bony seat to avoid these potential intracranial complications without device migration or flap issues (99,100).

The issues of bilateral cochlear implants are relevant in children as they are in adults. Bilateral implants provide the recipient improved hearing in noisy environments. This advantage is primarily from the head shadow effect with additional benefits from squelch and binaural summation (101). Sound localization is also improved with bilateral implants. This benefit is especially important in children in academic settings to track various speakers in classrooms. Moreover, these abilities provide children environmental safety to identify sources of sound such as when they cross streets.

Other benefits of bilateral implants in children is that since both ears have implants, the child will be assured to have one functional ear in case one of the implants, whether it is the internal receiver-stimulator or the external processor, malfunctions.

Performance with the implant is influenced by various factors including: age of implantation, duration of deafness, residual hearing, speech and language experience prior to surgery. Other factors that are relevant include higher ratings of parent–child interactions and higher socioeconomic status (102).

Otitis Media

Because the incidence of otitis media is higher in young children, the potential for OME or recurrent otitis media has to be addressed prior to and after implant surgery. Options for management of otitis prior to implant include prophylactic antibiotics, tympanostomy tubes, or mastoidectomy. The management of tympanostomy tubes at the time of implant surgery has been variable. A response to a survey of implant surgeons demonstrated that a majority proceeded with cochlear implantation with the tympanostomy tube in place. Others have advocated tube removal with myringoplasty at the time of cochlear implantation (103). Overall, a child who is a cochlear implant candidate with OME should have tympanostomy tubes placed. Cochlear implant then can be performed at a separate surgery. A child with a cochlear implant who has symptoms of otitis should be evaluated promptly and treated with antibiotics when otitis media is diagnosed. If the child develops recurrent otitis media then tympanostomy tubes may be considered.

Vaccination for Meningitis

Cochlear implants are associated with a small but present increased risk for meningitis. The incidence of streptococcal meningitis in cochlear implant patients is 0.14%. This number is a 30-fold increase compared to age-matched controls. Moreover, bacterial meningitis is higher in those who had an implant with a positioner or in those with radiographic evidence of an inner ear malformation (104). It is thus recommended that children with cochlear implants follow the recommendations for pneumococcal vaccinations. In February 2010, a 13 valent conjugate vaccine (Prevnar 13) was licensed by the FDA (105). It currently succeeds the previous 7 valent conjugate vaccine (Prevnar 7). Prevnar 13 contains polysaccharides of the capsular antigens of 13 serotypes of *Streptococcus pneumoniae*, conjugated to a nontoxic diphtheria carrier protein. The other vaccine currently in use is the 23 valent pneumococcal capsular polysaccharide vaccine (Pneumovax, PPV23). This vaccine contains pure capsular antigens from 23 serotypes. The conjugated 13 valent vaccine is necessary in infants and very young children because the immune system is immature to develop a response to pure antigens. More specifically, bacterial polysaccharides are T-independent antigens that stimulate mature B-lymphocytes but not T-lymphocytes. The very young respond poorly to T-independent antigens. Conjugation of bacterial polysaccharides to proteins changes the response to T-dependent and leads to substantial primary response among infants (106).

Key recent changes because of the PCV13 are:

Children less than 24 months, who have not received any previous dose of PCV7, should receive PCV13 as it is universally recommended.

Children 2nd through to their 6th birthdays should receive two doses of PCV13, if they have not received any doses of PCV7 or PCV13 previously. If they have already

completed the four-dose PCV7 series, they should receive one dose of PCV13 through age 71 months.

Children 6 through 18 years of age with cochlear implants may receive a single dose of PCV13, regardless of whether they received a PCV7 or Pneumovax.

Children older than 2 should also receive one dose of Pneumovax after completing all recommended doses of PCV13.

Bone Anchored Hearing Appliances

The primary indications for the bone-anchored device are for conductive hearing loss and for single-sided sensorineural hearing loss. In pediatric applications compared to adults, bone-anchored hearing appliances are more commonly indicated in those who have craniofacial malformations (e.g., bilateral aural atresia) that prevent a traditional hearing aid. Other indications include chronic ear conditions such as persistently draining ears, or patients with reactions to materials with molds or dermatologic external canal skin conditions.

The indication for a bone anchored hearing device for unilateral deafness has been increasing (Fig. 100.2). The rationale is that the device on the deaf side may allow the child to have improvement when hearing in noise. Overall, patients appear more satisfied with the device than with contralateral routing of signal hearing aids (107,108).

A traditional bone-conduction hearing aid may be used but has its disadvantages. The sound has to pass through soft tissue, and some sound energy is lost. When sound reaches the skull, they are transmitted with lower attenuation. This limitation is addressed with devices that directly couple the transducer to the skull such as with osseointegrated implants anchored into the temporal bone. The device depends on a percutaneous abutment in the postauricular area. A sound processor attaches to the abutment. A microphone within the sound processor receives sound, and vibrations are transmitted to the cochlea directly, bypassing the external and middle ear.



Figure 100.2 A 7-year-old girl with unilateral right profound hearing loss has a well concealed bone anchored hearing appliance.

The surgery usually is single stage in adults. A period of 3 to 4 months is necessary for osseointegration before the external processor is attached. In pediatric patients, the surgery is two staged because of the thinner skull, softer bone, and greater concerns about osseointegration (109). The fixture is placed subcutaneously with the initial step. After 3 to 6 months, the second stage surgery consists of thinning the skin flap and attaching the transcutaneous abutment to the fixture. For surgery in children with microtia and aural atresia, the position of the device is more posterior than the standard location. This permits for future ear reconstruction without potential compromise of the blood supply to the soft tissue.

Current FDA guidelines is for children 5 years and older, but the device has been placed in children less than 2 years of age. A nonsurgical strap may be used to secure the speech processor against the skin until the surgeon and patient is ready to proceed with surgery (110).

Complications associated with bone anchored prosthesis are not uncommon. The most frequent is problems with the surrounding soft tissue. In a large series of 149 patients, soft tissue reactions occurred in 3.4% of patients with three requiring removal of the device from the skin reaction (111). Others have reported the soft tissues complications around 7% (112) with pediatric series having higher complication ranging from 5.8% to 15.6% (113–115), but a recent publication of pediatric implants with longer term follow-up described the complication rate as high as 46.1% with 41.9% returning to the operating room for soft tissue revision (116). This risk was increased in those with a craniofacial syndrome.

Other main limitations of bone anchored appliances are the cosmesis and the need for daily management of the abutment that may be more accentuated in children. Recent advances in technology have resulted in newer options. The hearing appliance may be secured with an implanted magnet and thus adhere transcutaneously avoiding the need of a percutaneous abutment (117). Another novel mechanism is bone conduction through an orally worn device (118).

CONCLUSIONS

The newborn hearing screen has been important for the early diagnosis and habilitation of pediatric hearing loss. The shift to an earlier age of presentation has resulted in increase in initial physiologic assessment of hearing. The audiologist and otolaryngologist work in close collaboration for the diagnosis and management of pediatric hearing loss to assess auditory sensitivity and identify treatment options. These interventions have resulted in improving the speech and language outcomes of children with the hearing impairment.

HIGHLIGHTS

- 2 to 4 of every 1,000 infants born have hearing loss.
- Newborn hearing screen is possible with physiologic ABR and OAE.
- The goal of newborn testing is to screen by 1 month of age, diagnose hearing loss by 3 months of age, and initiate intervention by 6 months of age.
- Screening based on risk factors only detects 50% of infants with substantial congenital hearing loss.
- VRA permits behavioral threshold testing of infants at age 5 to 6 months.
- ABR testing provides essential information necessary for hearing aid fitting.
- The use of amplification by children is an ongoing process and necessitates frequent monitoring by the audiologist and otolaryngologist.
- Bilateral cochlear implants have their benefits with hearing in noisy environments and sound localization.
- Bone anchored hearing appliances provide an alternative to children who are not able to wear conventional hearing aids because of anatomical limitations or are poor surgical repair candidates.

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Nongenetic Hearing Loss 101

Margaret A. Kenna

INTRODUCTION

Hearing loss is the most common congenital sensory impairment. Bilateral severe to profound hearing loss is present in 1 to 2/1,000 live births, and if unilateral and mild to moderate hearing losses are included, the number rises to 4/1,000. According to a recent National Health and Nutrition Examination Survey (NHANES) study, by the age of 12 to 19 years, the rate is 19.5% for any degree of hearing loss (1). The purpose of pediatric hearing evaluation is to identify the degree and type of hearing loss and its etiology and outline a comprehensive strategy that supports language, communication, and social development. Significant strides have been made in the early identification of hearing loss, as well as in diagnostic studies and long-term management. This chapter reviews newborn hearing screening and many of the nongenetic causes of hearing loss in infants and children.

History of Newborn Hearing Screening

The evolution and institution of newborn hearing screening occurred for several reasons: (a) availability of technology that provides rapid and accurate identification of hearing loss in newborns; (b) recognition that hearing can be tested easily and accurately in newborns; (c) recognition that early intervention in an infant with hearing loss supports significantly improved language outcomes compared to those identified later; and (d) the development of technologically improved assistive listening devices, including hearing aids, FM systems, and cochlear implants, which provide markedly improved hearing and awareness of useful sound in almost any infant or child with hearing loss.

Hearing screening has been performed in school-aged children in the public schools since 1927 and was able to identify hearing loss that could be educationally handicapping (2). Subsequently, in recognition that early identification of hearing impairment might lead to improved language, attempts were made to screen younger children aged 2 to 5 years. In 1979, Victor Goodhill, in his book *Ear Diseases, Deafness and Dizziness*, notes that "Parents are often *incorrectly* told that a child of this age cannot have accurate hearing testing" (3). However, appropriate services to support language development would not be provided until there was concrete evidence of the hearing loss.

In 1970, the Joint Committee on Infant Hearing (JCIH) recommended infant hearing screening as a research need and also recommended the widespread use of a high-risk register, which included one or more of the following: (a) history of hereditary childhood hearing impairment; (b) rubella or other nonbacterial intrauterine fetal infection (e.g., cytomegalovirus [CMV], herpes); (c) defects of the ear, nose, or throat; (d) malformed, low-set, or absent pinnae; cleft lip; or palate; (e) any residual abnormality of the otorhinolaryngologic system; (f) birth weight less than 1,500 g; and (g) bilirubin greater than 20 mg/100 mL serum. They further recommended that infants falling into any of these categories should be referred for an in-depth audiologic evaluation during the first 2 months of life, with regular follow-up evaluations even if the initial testing was normal. However, since only about 10% of newborns fall into the "high-risk" category and 50% of infants with communicatively significant hearing loss do not have any obvious high-risk features, it is apparent that the use of the high-risk register alone as a basis for hearing screening would miss up to half of the affected infants (4).

One of the significant early problems with newborn hearing screening was the lack of a reliable, rapid and easy to perform, and economical audiometric test. In 1896, Dr. Thomas Barr, in his Manual of Diseases of the Ear, noted that "we may employ the sound of a bell, a sharp whistle, or a very loud tone of voice, taking care that the

child does not see the source of the sound" (5). This essentially reflected the state of the art until the 1940s, when, in recognition of the difficulty in eliciting reliable behavioral responses in young infants, nonbehavioral audiometric techniques were developed. These included, in the 1940s and 1950s, electrodermal response audiometry, which used a conditioning paradigm that paired an auditory stimulus with a mild electric shock, with measurement of the galvanic skin response as an outcome. Additional tests based on conditionable autonomic responses included heart rate response audiometry (1950s to 1960s) and respiration audiometry (1960s to 1970s).

Subsequently, the Crib-O-Gram was developed by Blair Simmons at Stanford University (1974). It involved a motion-sensitive transducer that was placed on or under the infant's crib. A strip chart recorded any infant motor activity stronger than an eye blink or facial grimace before, during, and after presentation of auditory stimuli. The test was automated, noninvasive, and fairly easily performed. Using the Crib-O-Gram, the Stanford research group tested over 12,000 infants from 1974 to 1984. They found an incidence of hearing loss of 1:1,000 in the well-baby nursery and 1:52 in the neonatal intensive care unit (NICU), similar to current numbers for bilateral severe to profound hearing loss obtained using newer physiologic techniques. However, a number of variables affected the results, including a need to test when ambient noise was low and when the newborn's behavioral state was "right." Other issues included uncertainty about the optimal auditory stimulus, high false-positive and false-negative rates for babies with less than severe to profound losses, lack of ear-specific information, and poor test–retest reliability (6). The Auditory Response Cradle, developed in England in 1980 and similar to the Crib-O-Gram, was designed to evaluate several specific infant motor responses following programmed auditory stimuli. However, it was never widely used in the United States (7,8).

By 1986, six states had active statewide infant hearing screening programs, and in 1990, Blake and Hall reported that although 14 states had legislative mandates for newborn hearing screening, most of the other states still had no statewide policy. In addition, many states with legislative mandates did not have full implementation due to lack of funding, diversity of geography and population, lack of consensus about the most effective screening methods, and lack of follow-up programs (9). In 1990, the United States Public Health Service established the Healthy People 2000 project (10). Recommendations included a goal to "reduce the average age at which children with significant hearing impairment are identified to no more than 12 months." In 1993, the National Institute on Deafness and Other Communication Disorders sponsored a consensus conference on the *Identification of Hearing Impairment in Infants and Young Children* (11). The panel recognized that 50% of newborns with significant hearing loss did not have any high-risk factors and only about 10% of all newborns fell into any of the high-risk categories. Because use of the high-risk register alone would continue to miss many infants with congenital hearing loss, the panel recommended that universal newborn hearing screening be implemented during the first 3 months of life. A two-stage protocol of evoked otoacoustic emission (EOAE) screening followed by auditory brainstem response (ABR) screening for infants who failed the EOAE screen was recommended. In their 1994 position statement, the JCIH recommended that all newborns with hearing loss be identified by 3 months and that intervention be started by 6 months. The statement did not recommend ABR over otoacoustic emission (OAE) but recognized the advantages and limitations of each technique (12).

Three early universal hearing screening programs gave further weight to the need for universal newborn hearing screening. The first, in Florida in 1983 at Winter Park Memorial Hospital, screened 15,000 infants between 1983 and 1993 using automated ABR. Improved prenatal parent education and increased physician awareness that screening was possible were cited as two major positive outcomes. The second, in Colorado, occurred over three decades and by 1997 involved 22 hospitals. An incidence of 4:1,000 of bilateral or unilateral hearing loss was found, with no high-risk factors noted in 57% of the hearing loss group. The third study evaluated the Rhode Island Hearing Assessment Program. Based on extensive research on the detection of newborn hearing loss performed in Rhode Island in late 1980s and early 1990s, Rhode Island Public Law 23-23-13 became effective on July 1, 1993, mandating universal hearing screening of infants born in all 8 RI hospitals. Detection of transient evoked otoacoustic emissions (TEOAE) was chosen as the screening method, and all infants who failed a first TEOAE screen were rescreened using TEOAE. From January 1, 1993, to December 31, 1996, 52,659 babies were screened. Of the 10% referred for a second stage screen, 111 were found to have a permanent hearing loss, 45% NICU graduates and 55% well-baby nursery graduates. The NICU hearing loss rate was 9.75% and the well-baby nursery rate was 1.27%, for a combined rate of 2.12% (8).

In 1998, Christine Yoshinaga-Itano and her group in Colorado published the results of a study looking at language acquisition in children with hearing loss that was identified early (before 6 months) versus late (after 6 months). For all hearing impaired groups, there was significantly better language development in the early identification group (13). Finally, in 1999, the American Academy of Pediatrics published "Newborn and Infant Hearing Loss: Detection and Intervention" (14). This report recommended universal newborn hearing screening by 3 months of age with intervention by 6 months of age. The recommendations for screening were based on the fact that the five criteria for universal newborn hearing screening had been met: (a) easy to use test(s) with a high degree of sensitivity and specificity; (b) there was no other way to

detect the condition clinically (and in a timely fashion); (c) effective interventions were available; (d) early identification and intervention were associated with an improved outcome; and (e) the screening procedure was within an acceptable cost-effective range.

The current national goals for hearing screening were developed by the federal Early Hearing Detection and Intervention program. The first three goals, often called the 1-3-6 plan, are (a) all newborns will be screened for hearing loss by the age of 1 month, preferably prior to discharge from the hospital; (b) all newborns who screen positive will have a diagnostic audiologic evaluation before the age of 3 months; and (c) all infants with an identified hearing loss will receive appropriate early intervention services by the age of 6 months (15). The 2007 JCIH guidelines have been adopted by their member organizations, including the Alexander Graham Bell Association for the Deaf and Hard of Hearing, the American Academy of Audiology, the American Academy of Otolaryngology-Head and Neck Surgery, the American Academy of Pediatrics, the American Speech–Language–Hearing Association, the Council on Education of the Deaf, and the Directors of Speech and Hearing Programs in State Health and Welfare Agencies (16). In addition, hearing screening by age 1 month has been incorporated as one of the Healthy People 2020 Objectives (17,18). Currently all states and the District of Columbia screen over 95% of their newborns (19). However, neither the newborn hearing screening laws nor the implementation are uniform. Payment for hearing aids and early intervention services vary greatly, and follow-up continues to be a significant challenge in most states. Some of the reasons for loss to follow-up include underfunded newborn screening programs, challenging geography (rural areas with difficult access to follow-up facilities), cultural diversity, home births, between hospital transfers, and out of state births.

What Are the Downsides of Newborn Hearing Screening?

Newborn hearing screening is not without areas of concern. The physiologic tests used, ABR and OAE, are not 100% sensitive and specific; both false positives and false negatives do occur. The tests may need to be repeated several times, first in a screening mode and then in a diagnostic mode to give a definitive diagnosis. An infant may pass a screen only to be found after discharge to have a hearing loss, this may represent a false-negative test, the infant may have hearing loss that is too mild or in a frequency range that it is not detected by the screen, the hearing loss develops after discharge, or the screen used OAEs and the infant has auditory dyssynchrony. Errors in pass/fail parameters (i.e., how the machine is set) may "pass" patients when they should actually "fail" or "refer." It is also statistically possible that an infant can "pass" if the screen is repeated often enough, as most screens are designed with a balance in their sensitivity and specificity; for this reason, most newborn screening programs only allow one repeat screen, and if the infant still fails, then a diagnostic auditory evaluation is recommended. A "pass" may actually delay a hearing loss diagnosis. If the baby "passed" in error, or if a hearing loss occurred after birth but the baby passed the initial screen, the parents (and the primary care physician) will have a false sense of security, even if they feel the baby does not hear normally. A third possibility, recognized since screening programs became widespread, is that in protocols that use OAEs to screen rather than ABR, patients with auditory dyssynchrony spectrum disorder will often be missed.

Tests Used for Newborn Hearing Screening

Since auditory dyssynchrony spectrum disorders comprise up to 10% of hearing loss in infants, the use of both ABR and OAE as part of a hearing screening program in many ways would be ideal. In many cases, ABR or OAEs alone are able to detect even mild conductive or sensorineural hearing impairments. However, the use of both modalities is needed to make a definitive diagnosis of auditory dyssynchrony, especially in a neonate. In an infant with auditory dyssynchrony, robust OAEs may be present, yet on ABR tracings only a cochlear microphonic, followed by indistinct or absent ABR waveforms, will be seen. In screening programs using only OAEs, the diagnosis of auditory dyssynchrony may therefore be missed. It is important, therefore, that no matter which test is used for screening, follow-up diagnostic testing should utilize both modalities (20) (see Chapter xxx for further discussion of ABR and OAE testing).

The Role of the Otolaryngologist

The otolaryngologist is often one of the first physicians that the family and infant or child will meet in the course of the diagnosis of hearing loss. They may meet them at the time of their initial diagnostic ABR, for medical clearance for a hearing aid, or for further investigation into the etiology of the hearing loss. To be effective, the otolaryngologist must have some basic understanding of the support services needed and how to access them, and they should also be able to provide the family with some basic information about the possible causes of hearing loss. The otolaryngologist should be prepared to have at least a working knowledge of OAEs and ABR. and behavioral audiometry, as well as interventions including hearing aids, FM systems, and cochlear implants.

CAUSES OF HEARING LOSS IN INFANTS AND CHILDREN

Defining the cause of the hearing loss can provide prognostic as well as educational information to the family. Careful evaluation can now pinpoint a definite or probable cause of the hearing loss 50% to 60% of the time. The etiologies

of hearing loss have often been divided into congenital and acquired. However, many of the causes that are congenital were "acquired" *in utero* and may only present at a later time (e.g., delayed onset of sensorineural hearing loss [SNHL] from CMV); this is in contrast to those truly acquired after birth (e.g., secondary to extracorporeal membrane oxygenation [ECMO], meningitis, or trauma). Although it is important to know if the hearing loss is pre- or postlingual in onset for management purposes, a more useful way to look at hearing loss etiology is to divide the etiologies into infectious, anatomic, genetic, traumatic, ototoxic (and other issues related to NICU stays), and other. The degree and laterality of the hearing loss in many of the causes of hearing loss are similar, with potential overlap between some of these causes, making the identification of a definite etiology more challenging. Some examples of this include children with enlarged vestibular aqueducts (EVAs) and mutations in the SLC26A4 gene (a genetic cause with an anatomic presentation); NICU stays involving possible combinations of ototoxicity, ECMO, prolonged ventilation, and hyperbilirubinemia; and more than one statistically common cause presenting in the same child, for example, congenital CMV and mutations in the *GJB2* (Connexin 26) gene. Similarly, "genetic" may be a more accurate way to describe "hereditary" hearing loss, as many families think hearing loss can be genetic only if it presents in a dominant pattern, while most genetic congenital and early onset hearing loss is recessive (so the parents do not usually manifest the hearing loss). Other common inheritance patterns that may result in hearing loss include X-linked recessive (the mothers/sisters who are carriers do not usually have the hearing loss), X-linked dominant (mother would be symptomatic), mitochondrial (which is highly variable so the mother may be asymptomatic), or multifactorial (gene and environment interaction). Similarly, some genetic causes of hearing loss may be due to *denovo* mutations (arising in germ cells or in the embryo itself) so that neither parent would be expected to have that same mutation. See Chapter xxxx for an in-depth discussion of genetic causes of hearing loss.

Infectious Causes

Infectious causes of hearing loss can occur both before and after birth. Historically, the TORCHES (**T**oxoplasmosis, **O**ther, **R**ubella, **C**ytomegalovirus, **H**erpes virus, **S**yphilis) organisms are described as common causes of congenital hearing loss due to prenatal exposure. However, as the epidemiology of these organisms has changed, only one, CMV, is currently a substantial cause of congenital hearing loss in many countries.

Toxoplasmosis

Toxoplasmosis is caused by the protozoan parasite *Toxoplasma gondii* and, if acquired prenatally, can cause SNHL. Toxoplasmosis is acquired by exposure to undercooked meat, cat feces, soil, or water containing the parasite. The overall prevalence and incidence of congenital toxoplasmosis varies by region and country. In much of the United States, toxoplasmosis is not considered a reportable disease, making it difficult to get accurate incidence figures. Reporting is seriously hampered by the fact that primary infection in most adults (and therefore pregnant mothers) is asymptomatic. In 2000, the Centers for Disease Control and Prevention (CDC) reported that there were an estimated 400 to 4,000 cases of congenital toxoplasmosis in the United States, based on the seroconversion rate of pregnant mothers (21). Massachusetts began screening newborns for toxoplasmosis in 1986, and in 1994 a study from the New England Regional Newborn Screening Program found the incidence of toxoplasmosis in newborns to be 1/10,000 (22). From 1986 to 1998, a total of 99 cases was detected through this program in Massachusetts, but at least 6 cases eventually diagnosed cases were missed by the screening. The incidence of congenital toxoplasmosis varies outside the United States, estimated at 6 per 1,000 births in France, 2 per 1,000 births in Poland, 7 to 10 per 1,000 births in Colombia, and 3 per 1,000 births in Slovenia (23).The NHANES from 1999 to 2000 reported that of the 2,221 women aged 18 to 49 years tested for IgG antibodies to *Toxoplasma* 14.9% were positive, meaning that the remainder of the women were susceptible to primary infection. Mothers who become primarily infected with *T. gondii* have approximately a 30% to 50% chance of transmitting the infection to their fetus. Although the most severe disease is experienced by fetuses becoming infected during the first trimester, transmission of infection, which is transplacental, is much more common later in pregnancy, especially during the third trimester, or during delivery. Eighty-five percent of infants with congenital toxoplasmosis are asymptomatic at birth, with those infected later in pregnancy most likely to be asymptomatic. Although vertical transmission of infection is most likely to occur with primary maternal infection, immunocompromised women with chronic infection may also pass on the disease. If new infection is detected in the mother early in pregnancy, treatment with oral spiramycin, which does not cross the placenta, can prevent transmission to the fetus. If infection occurs later in pregnancy, and/or if the fetus is also infected, treatment with pyrimethamine, sulfadiazine, and folinic acid (pyrimethamine is a folic acid antagonist) may prevent transmission to the infant by treating the mother and may also treat the fetus (24).

The classic symptoms of congenital toxoplasmosis are chorioretinitis, hydrocephalus, and intracranial calcifications. Other symptoms, which can also be seen in other congenital infections including CMV, herpes, and rubella, may include hepatosplenomegaly, jaundice, anemia, microcephaly, and lymphadenopathy. Although a recent systematic review by Brown et al. (25) did not find any cases of hearing loss in infants with congenital toxoplasmosis, others have reported an incidence from 0% to 20%. Earlier studies with a higher incidence of SNHL

often included untreated infants, while most infants in recent studies had been treated, suggesting that adequate treatment decreases the occurrence of SNHL. Treatment of congenitally infected infants with pyrimethamine and sulfadiazine is generally effective, although infants who present without neurologic disease have somewhat better outcomes than those who present with neurologic impairment. In addition, babies asymptomatic at birth may develop signs later in life, including chorioretinitis (25).

Rubella

Rubella is caused by a togavirus of the genus Rubivirus. Until the introduction of the rubella vaccine, rubella was the most common viral cause of congenital SNHL. The rate of congenital rubella syndrome (CRS) for infants born to women infected during their first 11 weeks of pregnancy is 90%; if infected during the first 20 weeks of pregnancy, it is 20%. The most common features of CRS are cataracts, heart defects, and hearing impairment. During the 1962 to 1965 global rubella pandemic, there were an estimated 12.5 million rubella cases in the United States, and 20,000 infants developed CRS. Following the licensure of live attenuated rubella vaccines in the United States in 1969, the number of reported cases of CRS declined 99%, from 77 cases in 1970 to one imported case in 2004. Although rubella is no longer endemic in the United States, it continues to be endemic in many other countries, where vaccination rates may also not be uniformly high in postpubertal females. Therefore, babies with congenital hearing loss born outside the United States in areas where rubella remains endemic, or born to mothers who may not have been vaccinated, may be more likely to have CRS as a cause of their hearing loss. According to the World Health Organization, the number of countries that have incorporated rubella vaccine into their immunization programs increased from 83 countries (13% of the birth cohort) in 1996 to 127 countries in 2008. In addition, the development of CRS is a theoretical risk in infants of mothers vaccinated during pregnancy, although this has not been reported in the literature. Any infant with CRS can shed the virus for up to 1 year after birth, so that all unvaccinated female caretakers should be aware that they may be at increased risk to become infected (26,27) (http://www.who.int/immunization/newsroom/Global_Immunization_Data.pdf).

Cytomegalovirus

Prenatal exposure to CMV, a beta-herpes virus, is the most common congenital viral infection and currently the most common viral cause of congenital SNHL. A 2008 study in Dallas, Texas, by Stehel et al. documented a 6% incidence of congenital CMV in babies with confirmed hearing loss. The prevalence of congenital CMV infection is approximately 0.4% to 2.3% of all newborns. If the mother has a primary CMV infection during pregnancy, there is a 40% chance that the infant will become infected, and if she has a reactivation infection, there is about a 2% chance. The chance of transmission of primary infection from mother to child is 25% in the first trimester, 50% in the second, and 75% in the third. However, infants exposed to the virus during the first trimester are the most likely to develop serious neurologic sequelae. Although 90% of infants with congenital CMV are asymptomatic at birth, 10% to 15% will develop hearing loss, while 65% to 70% of infants with symptomatic CMV infection will develop hearing loss. In the study by Stehel et al. (28), 75% of the infants with congenital CMV were only diagnosed because they had hearing loss. However, since CMV hearing loss may be present at birth or it may not develop until later in infancy/childhood, the diagnosis can easily be missed (29). Infants with symptomatic CMV may present at birth with microcephaly, intrauterine growth restriction, developmental delay, hepatosplenomegaly, chorioretinitis, jaundice, petechiae, thrombocytopenia, hyperbilirubinemia, anemia, and hearing loss. The diagnosis of congenital CMV is made in the first few weeks of life by shell vial culture using saliva or urine. Recently, investigators have evaluated CMV polymerase chain reaction (PCR) using dried blood spots, liquid and dried saliva, and dried umbilical cord (30). Although PCR from any of these sources has not been found to be as sensitive as shell vial culture in the newborn period, positive PCR using dried blood spots can confirm a diagnosis of congenital CMV outside the newborn period when shell vial or CMV IgG cannot differentiate between congenital and postnatally acquired infection (31). In addition, PCR technology may be a basis for large-scale screening. Currently, treatment for the hearing loss involves at least 6 weeks of ganciclovir, or, more recently, valganciclovir, a pro drug of ganciclovir (32,33). The optimal duration of therapy remains unclear, with some evidence supporting a longer course of therapy (up to 6 to 12 months). Although several studies support improved hearing with either of these drug regimens, the numbers of treated patients remain small, the follow-up is variable, and progression of the hearing loss may occur after the drugs are stopped. Side effects of ganciclovir and valganciclovir include bone marrow suppression (neutropenia, thrombocytopenia, anemia) and kidney and liver toxicity. Teratogenesis, mutagenesis, inhibition of spermatogenesis, and impaired fertility have been reported, primarily in animal studies, as a result of exposure to these agents. In addition, treatment of older children with progressive hearing loss due to congenital CMV has not been studied.

Once the baby is out of the newborn period, making a definite diagnosis of congenital CMV is difficult. It can be suspected, however, based on findings of developmental delay, microcephaly, and hearing loss. Visual impairment may be present in 10% to 20% of symptomatic babies and includes strabismus, optic atrophy, macular scarring, pigmentary retinitis, and visual loss. Boppana et al. (34) has reported late onset or reactivation chorioretinitis in 7/31 (23%) of children after 1 to 10 years of age. Imaging findings can help narrow the diagnosis in older children, or

confirm the diagnosis in newborns. Intracranial calcifications, migrational abnormalities (e.g., polymicrogyria), cerebral and cerebellar volume loss, ventriculomegaly, and white matter disease are commonly seen on a combination of ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT). Characteristic imaging findings in association with neurodevelopmental delay strongly suggests a diagnosis of congenital CMV.

The prevention of congenital CMV is a major public health issue. CMV infection in healthy adults and children is common, often silent, and chronic, with viral shedding in urine and saliva continuing for months or years. This makes avoidance of infected individuals by pregnant women, although desirable, almost impossible. The timing of pregnancy related to when the mother developed a primary CMV infection has been found to affect whether subsequent infants develop CMV. Fowler et al. (35) found that for mothers who were initially CMV nonimmune or immune, a shorter interval between the birth at which the mother's serologic status was established and the subsequent birth was associated with an increased risk of congenital CMV. It was also clear from this study that maternal CMV infection that occurs before getting pregnant still results in a substantial risk of congenital CMV.

However, because preconception maternal CMV immunity may confer a significant degree of protection against vertical transmission of the virus compared to primary infection during pregnancy, vaccination of young women before they get pregnant is an obvious route to protection (35). Although the development of an effective CMV vaccine has been difficult, Schleiss (36) has recently reported interim results of a phase II trial of a deoxyribonucleic acid (DNA) vaccine against CMV in a guinea pig model. Further population-based studies of transmission rates, severity of disease related to when the mother and fetus become infected, and vaccine development will be key to decreasing the overall prevalence and transmission of CMV in the population.

Herpes Simplex

Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) are double-stranded DNA viruses that commonly infect humans (37). Neonatal HSV infections occur in approximately 1/3,200 births in the United States, with the majority being HSV-2 (37). Kimberlin (38) reported that 85% of transmission is peripartum, 10% is postnatal, and 5% is *in utero*, with primary maternal infection resulting in a higher transmission rate than reactivation disease. Approximately 50% of neonatal HSV infections have central nervous system (CNS) involvement. The incidence of hearing loss in children with neonatal HSV is unclear. A recent systematic review of the incidence of SNHL in neonates exposed to HSV was published in 2008 (39). They found that SNHL occurs rarely in infants with exposure to HSV and that there was no evidence of delayed onset of SNHL in infants with asymptomatic perinatal HSV infection. The few papers that reported audiometric data found hearing loss in association with intrauterine HSV-2 infection 0% to 33% of the time, with all infants also having severe CNS disease. However, all studies were small and audiometric techniques varied. The standard treatment for symptomatic perinatal HSV infection is acyclovir, but the effect of treatment on hearing loss is unclear. Based on the limited information available, Westerberg et al. (39) did not find that routine serologic screening for HSV infection in otherwise asymptomatic neonates with SNHL was justified.

Syphilis

Transplacental mother-to-child transmission of syphilis has been recognized since the 15th century. Congenital syphilis (CS) and syphilis acquired after birth are caused by *Treponema pallidum*, a gram-negative spirochete bacterium. Worldwide, 2 million mothers test positive for syphilis during pregnancy, comprising 1.5% of all pregnancies, and can lead to stillbirths and neonatal death. In the United States, however, CS is uncommon, with the result that hearing loss due to CS may be missed. A systematic review of CS cases and articles contained in multiple databases, including Medline (1950 to March 2008), EMBASE (1980 to March 2008), CINAHL (1982 to March 2008), BIOSIS Previews (1969 to March 2008), and Cochrane databases, was published in 2009 (40). These authors found no reported cases of SNHL in infants with CS born to mothers with syphilis acquired during pregnancy in any of the articles they reviewed. Between 2003 and 2005, the number of CS cases reported annually in the United States declined from 10.6 cases per 100,000 live births in 2003 to 8.2 in 2005, but then increased back to 10.1 per 100,000 live births in 2008. This increase in CS followed a 38% increase in the primary and secondary syphilis rate among US females from 2004 to 2007. In 2008, infants born to black mothers accounted for 50% of CS cases, infants of Hispanic mothers for 31% of cases, and infants of white, Asian/Pacific Islander, and American Indian/Alaskan Native mothers for 15%, 2%, and 1%, respectively. Despite this recent increase, however, CS remains uncommon in the United States, and therefore CS and any associated hearing loss may not be as readily recognized as in countries where it is more common. Hutchinson described the classic triad of late CS as interstitial keratitis, notched incisors, and SNHL (41). In 1970, Fiumara and Lessell (42) added to this triad Clutton joint (symmetrical hydrarthrosis especially of the knees) and mulberry molars (malformed first molar resembling a mulberry). Although any infant who presents with nonimmune hydrops, osteochondritis, periosteitis, hepatosplenomegaly, jaundice, rhinitis, mucocutaneous skin rash, and/or pseudoparalysis of an extremity should be suspected of having CS, there are no studies looking at the array of symptoms in infants who are actually serologically positive, raising the question whether hearing loss could be the only symptom of CS. Prenatal diagnosis involves testing pregnant mothers, with nearly complete elimination

of any serious complications in the baby if the mother is treated before 24 weeks gestation. For babies with CS identified after birth, appropriate treatment with penicillin (dose and duration dependent on formulation) usually results in a cure. If there is uncertainty about whether the mother has been adequately treated, evaluation of both the mother and infant should be undertaken shortly after birth. Syphilis acquired after birth may present as progressive and/or sudden hearing loss or vertigo. Therefore, the diagnosis of acquired syphilis should be considered in any sexually active patient who presents with recent onset hearing loss and/or vertigo, as these symptoms often improve with penicillin and steroids.

Other Infectious Diseases Associated with Hearing Loss

HIV

Audiologic and vestibular symptoms can occur in children infected with human immunodeficiency virus type 1. These include conductive hearing loss (often due to otitis media), SNHL, tinnitus, vertigo, and ataxia. Hearing loss may occur due to direct infection of the inner ear with human immunodeficiency virus (HIV), or secondary to opportunistic infections (e.g., CMV, syphilis, tuberculosis, cryptococcal meningitis) or ototoxic drug therapy. In a 2008 study, 23 Mexican children with HIV on highly active antiretroviral therapy aged 5 months to 16 years underwent pure tone audiometry, speech discrimination testing, ABR testing, electronystagmography, and rotary chair testing. Most children had acquired their HIV perinatally. Although not every child was able to be tested using all techniques, six children had conductive hearing loss (related to a history of otitis media), one had SNHL, one had a mixed hearing loss, others had abnormalities on ABR reflecting dysfunction at varying levels, and several had vestibular hyporeflexia. Although not statistically significant, there was a suggestion that lower CD4 counts, longer time with HIV, and higher viral load were associated with an increased prevalence of audiologic or vestibular symptoms (43).

Measles (Rubeola)

Measles is a paramyxovirus spread via the respiratory route and, in the prevaccine era, was an identified cause of acquired hearing loss, although the incidence was not well defined. Although measles was reported to have been eradicated in the United States in 2000, hundreds of cases have been reported since then, occurring mainly in children born outside the United States, children too young to vaccinate, and in those children whose parents have intentionally not vaccinated them. Live attenuated measles virus is included in the standard measles vaccine. A paper using information from the Vaccine Adverse Event Reporting System in the United States from 1990 to 2003 estimated the reporting rate of SNHL possibly related to mumps/measles vaccine to be one case in 6 to 8 million doses (44). Measles virus has also been possibly implicated in the development of otosclerosis, although whether this is an association or causation remains unclear (45,46).

Lyme Disease

Lyme disease is caused by the bacterium *Borrelia burgdorferi* and is transmitted to humans by the bite of an infected black-legged tick. The incidence is highest in the United States in east coast states and Wisconsin and Minnesota but has been reported in all 50 states. Although people of any age and both genders are susceptible to tick bites, Lyme disease is most common among boys aged 5 to 19 and persons aged 30 or older. The CDC reported an 8% incidence of facial palsy among 119,965 patients with Lyme disease between 1992 and 2004. Hearing loss in association with Lyme disease, however, is infrequently reported (47). A 2010 retrospective review by Wilson et al. of patients 18 years of age and older presenting with asymmetric SNHL of uncertain etiology showed that of the 88 who were tested for Lyme disease, 3 were positive. Although the endemic nature of Lyme disease in many parts of the country can make confirming a relationship between Lyme disease and hearing loss challenging, Wilson et al. (48) felt that of the many tests ordered in this study, Lyme titers and tests for syphilis were potentially the most useful and cost-effective.

Mumps

Mumps is a paramyxovirus that results in an acute viral illness characterized by unilateral or bilateral parotitis, and complications include SNHL, aseptic meningitis, encephalitis, and, in postpubertal age groups, orchitis, oophoritis, and mastitis. Approximately 20% to 40% is asymptomatic, and many symptomatic patients only have respiratory symptoms. Mumps is endemic in most of the world, and by July 2010 was included in the vaccine programs of 117/193 (61%) of the World Health Organization member states. Live mumps vaccine was licensed for use in the United States in 1967, with a drop in incidence of mumps cases to 0.1 cases/100,000 persons (314 cases total) in the United States by 2005. However, there have been two large outbreaks of mumps since then, in 2006 and 2009. The incidence of SNHL after mumps is unclear, but a 2009 study from Japan suggested an incidence of 0.1%, with the hearing loss being unilateral and in the moderate to profound range (49). Hearing loss associated with mumps may occur before or after the parotitis and in otherwise asymptomatic cases. The vaccines against rubella, measles, and mumps contain live attenuated virus, and hearing loss in association with measles, mumps, and rubella vaccine has also been, although rarely, reported (50). A 2007 paper from the CDC estimated the reporting rate of SNHL related to vaccine use to be one case in 6 to 8 million doses. Because of the rarity of these reports, a causal relationship between mumps, rubella, and measles vaccination and SNHL requires further study (51,52).

Bacterial Meningitis

Hearing loss is a well-documented sequela of bacterial meningitis. A 2010 systematic review and metaanalysis of 132 papers from around the world published between 1980 and 2008 reported a 33.6% incidence of hearing loss due to bacterial meningitis from all causes (*Streptococcus pneumoniae, Haemophilus influenza type B (HIB), Neisseria meningitidis*, other) (53). Although HIB meningitis was the most common, hearing loss occurred most often after pneumococcal meningitis. Worsoe et al. (54) studied a Danish cohort of patients who had pneumococcal meningitis between January 1999 and December 2003. Of the 502 original patients, they located 343 (many had died or emigrated), and of those, 240 had audiometric testing. They found an overall incidence of hearing loss in these 240 patients of 54%; 47% under the age of 2 years had hearing loss, and 79% of individuals over the age of 2 had hearing loss. Seven percent had unilateral profound SNHL and seven percent had bilateral profound SNHL. In addition, many patients who were not suspected of having hearing loss at the time of discharge after the meningitis were later found to have SNHL, supporting the need for close follow-up. The use of systemic steroids in the management of meningitis remains controversial (54). In 2010, Van de Beek et al. (55) published a metaanalysis of individual patient data from 2,029 subjects (41% children less than 15 years) who participated in one of five prospective randomized double blind placebo controlled trials of dexamethasone use in acute bacterial meningitis. In HIV-negative adults, dexamethasone was associated with a reduction in death or severe neurologic sequelae, including severe bilateral hearing loss. However, this effect of dexamethasone was not present in HIV-negative children, or in HIV-positive children and adults. A Cochrane database review, also from 2010, looked at 24 randomized controlled trials of corticosteroids (4,041 subjects) for acute bacterial meningitis. For the group as a whole, they found a significantly reduced rate of hearing loss and neurologic sequelae, although overall mortality was not reduced. Of interest, the data supported the use of corticosteroids in high-income, but not low-income, countries, as no beneficial effect of steroids was found in low-income countries (55). Finally, a study by Peltola et al. (56) of children aged 2 months to 16 years with bacterial meningitis found that age and clinical presentation, but not whether the patients got steroids or glycerol, had a measurable association with hearing outcome. The benefits of dexamethasone or other steroids in the prevention of hearing loss or other neurologic sequelae due to bacterial meningitis continue to remain unclear (56,57).

Bacterial meningitis–related hearing loss has its onset early in the course of the disease, and the incidence has not been decreased by any specific antibiotic regimen. Although otitis media with direct spread through labyrinthine windows may precede onset of the disease in some cases, a more likely route is penetration of bacteria and bacterial toxins via the cochlear aqueduct or internal auditory canal contents, resulting in perineuritis or neuritis of the cochleovestibular nerve and/or suppurative labyrinthitis. Other pathophysiologic mechanisms operative in producing hearing loss may include serous or toxic labyrinthitis, thrombophlebitis or embolization of labyrinthine vessels, and hypoxia or anoxia of the eighth nerve and central auditory pathways.

If a child with meningitis has normal audiometric studies after the first few days of antibiotic therapy, it is unlikely that significant SNHL will develop later, and some children with initially abnormal hearing may improve, suggesting a resolving serous labyrinthitis. A few individuals with documented mild to moderate hearing losses after discharge have shown some improvement over time, while more severe losses, in some children, have fluctuated for as long as a year after hospital discharge. Well-documented late progression of postmeningitic SNHL after years of stability has been reported in a few cases.

HEARING LOSS SECONDARY TO TRAUMA

There are many different categories of trauma that can result in hearing loss in children, including head trauma, exposure to ototoxic medications, chemotherapy and radiation therapy, ECMO, iatrogenic injury due to surgery, and noise. Of all of these, environmental noise is the most common.

Noise-Related Hearing Loss

Decades ago, investigators found that the human ear, when exposed to loud sounds long enough, will permanently lose some hearing. The outer hair cells in the cochlea, when exposed to loud noise, initially experience transient damage that causes a temporary threshold shift in the hearing; if the person is exposed long enough, the damage becomes permanent. Standard pure tone audiometric tests do not capture these early changes, so by the time you can "see" the hearing loss in the audiogram, permanent damage has been done. Governmental agencies, including the Occupational Safety and Health Administration and the National Institute for Occupational Safety and Health, have guidelines for occupational and industrial noise exposure and require that individual workers exposed to sound levels greater than 85 dB wear ear protection. These guidelines are based on a calculation of noise "dose," using formulas that include total time of exposure at a specific noise level. These guidelines show how, above 85dB, the potential for permanent hearing loss increases rapidly with seemingly modest increases in decibel level. Because decibels are measured on a logarithmic scale for every 3 dB increase in sound pressure, the amount of allowable exposure to noise above 85 dB is cut in half (58,59).

Technology has made music, news, videos, and other media instantly available. Personal cassette players were

introduced in the 1970s, CD players in the 1980s, and MP3 players in the late 1990s. Because of this, hearing loss due to noise exposure is no longer limited to construction workers, hunters, and rock musicians; now anyone can get it. Several studies since the 1980s have documented the potential dangers to hearing secondary to portable music players. These studies found that, in addition to listening to music devices for several hours a day, many people listen in the presence of background noise, thus turning up their music players above a safe level. Since the average background noise level of an occupied cafeteria is 85 dB and the interior of a moving car 40 to 80 dB (depending on road surface, etc.), it is easy to see why people might turn up their music players (60–64).

A 2004 report found that the output levels of common earphones, including insert, supra-aural, vertical, and circumaural, varied across type and manufacturer, but generally the sound pressure level in decibels was highest for the smallest earphones, and that insert earphones increased the output level 7 to 9 dB. In a few CD player–headphone combinations, output exceeded 130 dB. Currently, all common MP3 players can produce sound pressure levels of more than 100 dBA using the earbuds supplied with the players. A recent 2007 article recommends that people using a standard personal music player and headphone combination should limit their listening to no more than 60% volume for 60 minutes (or less) for a CD player and no more than 90 minutes (or less) at 80% volume for a MP3 player during any 24-hour period. Additional recommendations are to use sound-isolating earphones in the presence of significant background noise (and if difficulty hearing your background noise does not pose a safety issue). The use of these earphones has been shown to provide as much as 25 dB of sound isolation.

Finally, a 2010 JAMA article based on NHANES for 1988 to 1994 and 2005 to 2006 found that there has been an increase in the prevalence of hearing loss for those participants aged 12 to 19 years from 14.9% in 1988 to 1994 to 19.5% in 2005 to 2006 ($P = 0.02$) (1). In addition, the hearing loss was more prevalent in males (both time periods) and was more frequently unilateral and high frequency in 2005 to 2006. Because the NHANES is cross sectional, associations with particular risk factors cannot be ascertained. However, the increasing use of personal listening devices and exposure to other loud noise sources certainly suggests that these may be factors in the recent increase in hearing loss in young people; further work is needed to see if this increase change is statistically related to noise exposure. In addition, the exposure to noise in the setting of other risk factors for hearing loss, such as systemic aminoglycosides, chemotherapy, and genetic factors, needs to be studied.

Ototoxicity

Several groups of drugs are well-recognized causes of SNHL, including aminoglycoside antibiotics, systemic chemotherapy (especially cisplatin), macrolides, and loop diuretics. The effects of these drugs on inner ear physiology may be compounded by concurrent medical conditions, including renal failure, the use of ECMO, sepsis, extreme prematurity, diabetes, noise exposure, and genetic factors, all of which are independently related to an increased incidence of hearing loss. Hearing loss related to these drugs may occur both during and long after administration, especially for cisplatin. Radiation therapy involving the temporal bones and cisplatin given within the same time frame have been reported to have an increased incidence of SNHL over either one alone, with the hearing loss often presenting years after the therapy is completed. While the ototoxicity of the aminoglycosides is strongly related to drug levels (peaks and troughs) and cumulative dosage, mutations in mitochondrial genes, especially the homoplasmic 1555A>G and 1494C>T mutations in the mitochondrial 12S rRNA, provide increased susceptibility to aminoglycoside ototoxicity, with hearing loss occurring after even one dose in some cases in patients who have these mutations. Hearing loss after exposure to macrolides is often reversible when the drugs are discontinued (65–71).

Mutations in the 12S rRNA genes also are associated with nonsyndromic SNHL in the absence of aminoglycoside exposure. Although the incidence of these mutations varies widely between populations, screening of certain populations at risk for ototoxicity due to the medical management of their disease, such as adult patients with cystic fibrosis, may identity those who are at increased risk for aminoglycoside-related ototoxicity. This knowledge would potentially allow modification of their medical regimen, decreasing the possibility of hearing loss. In addition, there has been increasing interest in preventing or moderating ototoxicity in patients requiring ototoxic medications, including recent studies evaluating aspirin, amifostine, and melatonin and 17-β-estradiol. It is likely that these types of investigations will provide new insight into both prevention of hearing loss as well as mechanisms of the hearing loss itself.

Prevention of hearing loss due to noise and chemotherapy is desirable. Although avoidance of ototoxic exposures will always be the first step in the prevention of hearing loss, in situations where these exposures are not preventable, methods to ameliorate the ototoxic effects are important. For noise, the use of physical barriers, such as specialized head phones, turning down the volume, and decreased overall exposure, are effective. However, pharmacologic means to prevent hearing loss are also being investigated and include the experimental use of *N*-acetyl-cysteine, D-methionine, and salicylates.

Head Trauma

It is well known that temporal bone fractures are associated with SNHL. Much less well recognized is the incidence of hearing loss due to closed head trauma, such as concussion and traumatic brain injury, in the absence of

obvious temporal bone fractures. In a recent study of soldiers returning from Iraq and Afghanistan, over half of the subjects with traumatic brain injury had hearing impairment, and many had both visual impairment and hearing loss (72). These subjects exhibit both peripheral hearing loss as well as more subtle central auditory findings, potentially making rehabilitation more challenging. With an increasing recognition of the prevalence of cognitive and behavioral effects of sports-related concussion as well as traumatic brain injury, adding an auditory evaluation to the clinical care of these patients should be considered.

SUDDEN SNHL

Sudden SNHL is a well-reported occurrence in adults but little discussed in children, although several published series include children. Although the definition of idiopathic sudden SNHL includes unilateral onset, many subjects with sudden onset of SNHL have bilateral findings. The causes of sudden onset SNHL are often difficult to identify, but Hughes et al. (73) list viral, immunologic, traumatic, neoplastic, vascular, toxic, neurologic, and metabolic as potential etiologic factors. Other causes could include unwitnessed head trauma, barotraumas, sudden auditory manifestations of preexisting temporal bone abnormalities (e.g., EVA, eighth nerve tumors) Meniere's disease, progression of unrecognized congenital infections (such as CMV, toxoplasmosis, syphilis), Lyme disease, or an underappreciated manifestation of a previously existing disease, such as the hereditary periodic fever syndromes (73). Ioannis et al. (74) studied the records of 48 children with sudden hearing loss presenting to their department between 2002 and 2007. Twenty-six (54%) were found to have pseudohypacusis. Of these, 16 were girls and the mean age was 10.5 years, in good agreement with existing literature. Of the 22 cases (46%) with true organic hearing loss, 2 had EVA, one had multiple sclerosis, one had Herpes virus, 2 had acoustic trauma, and the remainder were considered idiopathic. Suggested treatments for sudden SNHL (without an obvious etiology) include systemic steroids, intratympanic steroids, and antivirals, although nearly all treatment series only include patients over 18 years of age (74). Systemic steroids have been studied the most, with generally modest to mild benefit reported if they are started soon after the SNHL is identified. Huang and Sataloff (75) reported on seven children with autoimmune inner ear disease, with both systemic steroids and cytotoxic medications having some efficacy. In terms of antivirals, a study by Tucci et al. (76) looked at hearing improvement in patients over 18 years of age with idiopathic SNHL treated with systemic prednisone with or without valacyclovir (antiviral) therapy. No additional benefit over steroids alone was noted in the valacyclovir patients in this trial, or in two other trials using antivirals (76). Intratympanic steroids, as first or salvage treatment, have also recently been studied. Most studies have small numbers, are retrospective, are limited to case series, do not include a natural history group, and do not include large numbers of (or any) children. The efficacy of intratympanic steroids therefore remains unclear. Other therapies mentioned in the literature, including hyperbaric oxygen, volume expanders, vasodilators, herbal remedies, anticoagulants, and zinc, have not been studied in a rigorous fashion in any age group for sudden SNHL (77).

Hearing Loss in Babies Who Require Newborn Intensive Care Unit Management

It is well recognized that NICU infants, especially those with very low birth weight (VLBW; below 1,500 g), have a higher incidence of hearing loss than term infants in the well-baby nursery. The incidence of SNHL in VLBW babies varies between studies, but overall the incidence seems to be decreasing. Three studies between 2000 and 2006 found an incidence of possible hearing loss of 12.8% to 31.6% using OAE screening, but only 2% subsequently had hearing loss based on diagnostic ABR testing. During a similar time period, multiple studies found an incidence of newborn hearing loss in several general populations of 0.11% to 0.9%. Risk factors associated with permanent congenital, delayed onset, or progressive hearing losses are listed in the JCIH 2007 guidelines. A NICU stay of more than 5 days or the presence of any of the following raise the level of concern: ECMO, assisted ventilation, ototoxic drug exposure, loop diuretics (furosemide), and hyperbilirubinemia requiring exchange transfusion. A 2009 study by Robertson et al. studied 1,279 survivors born at a birth weight of ≤1,250 g and a gestational age of ≤28 weeks between 1979 and 2003 in Alberta, Canada. Although there was a marked improvement in the degree surviving over time (26% survived in 1974 to 1976 compared to 88% in 2001 to 2003), the percentage with hearing loss at age 3 years did not change. The overall rate of hearing loss of any degree was 3.1%, with a 1.9% rate of severe to profound hearing loss. One child was found to have auditory dyssynchrony, 4 (10%) had delayed onset of bilateral hearing loss, and 11 children (28%) had progressive hearing loss. They found prolonged use of supplemental oxygen beyond 36 weeks to have the strongest association with all degrees of hearing loss. Several additional factors they included that were markers for hearing loss were the need for gastrointestinal surgery, (colonostomy, ileostomy, or resection associated with necrotizing enterocolitis), patent ductus arteriosus ligation, and lower socioeconomic status. Additional studies have shown a statistical association between hearing loss and severe hypoxic/ischemic encephalopathy, prolonged mechanical ventilation, persistent pulmonary hypertension, higher serum bilirubin, intraventricular hemorrhage and meningitis, and high-frequency ventilation. Whether some of these are related directly to the hearing loss or occur as a result of factors that may also lead to hearing loss remains unclear (78–81). In some studies, aminoglycoside

use, long suspected of being a major risk factor for NICU-related hearing loss, is found to be only slightly statistically associated. This could be due to better monitoring of peak and trough levels or better management of NICU babies with decreased need for prolonged aminoglycoside courses. The use of loop diuretics (furosemide and ethacrynic acid) is associated with hearing loss in newborns. Of particular concern is that they potentiate the rate of aminoglycoside-induced hearing loss and may also be more likely to cause hearing loss in the presence of sepsis. Finally, noise in the NICU, generated by the presence of life support equipment, has been shown to be a contributing factor to hearing loss in NICU infants. Li and Steyger (82) and Li et al. (83) have recently suggested a mechanism for the synergistic effects on hearing of aminoglycosides and noise in humans and note that subdamaging doses of aminoglycosides may make the cochlea more likely to be damaged by noise. They cite a study by Rees (84) that showed that preterm infants born at less than 27 weeks who received aminoglycosides for 7 days or more while exposed to noise levels of greater than 80 dB for greater than 30 minutes produced by mechanical ventilation had a high probability (68%) of developing hearing loss (85). This clearly requires further study.

Hyperbilirubinemia is a well-recognized cause of hearing loss in newborns, and more recently it has been associated with auditory dyssynchrony. The 2007 JCIH guidelines list hyperbilirubinemia that requires exchange transfusion as a risk factor for the development of hearing loss. However, a study by Oh et al. (86) suggested that in VLBW infants even a moderate elevation of bilirubin may be related to poorer neurodevelopmental outcomes and hearing loss (86). A subsequent NEJM study by Morris et al. (87) assessing aggressive versus conservative phototherapy in VLBW infants showed that infants with even modestly elevated levels of bilirubin had less hearing loss when aggressive phototherapy was utilized, and in fact the aggressively managed group had better overall neurodevelopmental outcome (87). This raises the question of what level of bilirubin (bound or unbound, conjugated or unconjugated) should be considered a risk factor for the development of hearing loss, especially in relation to gestational age and weight, the presence or absence of sepsis or hypoxia, and other contributing factors.

Auditory neuropathy spectrum disorder (auditory dyssynchrony) is being increasingly identified in newborns who fail their hearing screening. A high percentage of these babies have a history of VLBW, early gestational age, hyperbilirubinemia, and sepsis. Because many of the studies assessing hearing loss in the NICU are observational, it is difficult to assign cause and effect. However, a recent study by Saluja et al. (88) found auditory dyssynchrony as the only manifestation of acute bilirubin-induced neurotoxicity in late preterm and term infants. The level of hyperbilirubinemia and the optimal management, especially in VLBW babies with complicated clinical pictures, remains uncertain (88).

Middle and Inner Ear Structural Anomalies

Although this chapter focuses primarily on inner ear pathology related to hearing loss, it is important to recognize that structural anomalies resulting in hearing loss can occur at any stage in the embryogenesis of these structures, with a resulting hearing loss that is conductive, mixed, or sensorineural. External auditory canal atresia is usually associated with various degrees of microtia and middle-ear abnormalities, and with improved imaging, an increasing number of these patients are also found to have inner ear anomalies. Congenital stapes disorders are often related to aberrant facial nerve development. During the crucial time period of 6 weeks postfertilization, if the facial nerve is displaced anteriorly, the stapes will be prevented from coming in contact with the otic capsule, resulting in a malformed stapes. Vrabec and Lin (89) reported a 13% incidence of facial palsy and a 22% incidence of inner ear anomalies in 118 pediatric patients with aural atresia. All of the facial paralysis patients also had inner ear abnormalities, with some children having unilateral facial palsy but bilateral inner ear anomalies (89).

Hundreds of syndromes have hearing loss associated with middle and/or inner ear anomalies as one of the features. Many of the patients will present with mixed, or occasionally purely conductive, hearing loss. Mutations in the X-linked POU3F4 gene are associated with dilatation of the internal auditory canal and a range of temporal bone anomalies that include stapes fixation and dysplasia of the cochlea and semicircular canals (SCCs). These patients, who are otherwise nonsyndromic, present with a congenital and subsequently progressive mixed hearing loss. The surgeon may encounter a fixed stapes and perilymphatic gusher at the time of cochlear implant or other middle-ear surgery (90).

Although hundreds of syndromes have both middle and inner ear anomalies, two syndromes for which the hearing loss is a defining feature include CHARGE and branchio-oto-renal (BOR) syndromes. Seventy percent of CHARGE patients have mutations in the CHD7 gene, with a much smaller number having mutations in the SEMA3E gene, while BOR patients have mutations in the EYA1 and SIX5 genes, and mutations in SIX1 in patients with branchio-otic syndrome. Both syndromes have characteristic middle and inner ear anomalies and may present with conductive, sensorineural, or mixed hearing losses. Findings in BOR include a hypoplastic apical turn of the cochlea; facial nerve canal deviated to the medial side of the cochlea; a funnel-shaped internal auditory canal; a patulous eustachian tube; hypoplasia of the horizontal, superior, and posterior SCCs; and hypoplasia/dysplasia of the malleus and incus (91,92). In 2006, Morimoto et al. reported temporal bone imaging in 13 patients (26 ears) with a clinical diagnosis of CHARGE association; none had testing for CHD7 mutations. Middle-ear findings included 21/26 ears with small middle-ear cavities and 23/26 with dysplastic

ossicles. All cases demonstrated absent SCCs. Twenty of twenty-six (77%) ears demonstrated cochlear aperture atresia; four were found to lack a cochlear nerve on MRI. Twenty-one of twenty-six (81%) had cochlear dysplasia, six had round window aplasia, and three had round window hypoplasia. Twenty-one of twenty-six (81%) had oval window atresia or aplasia, and fifteen had hypoplastic or dysplastic vestibules. Additional findings included enlarged or anomalous vestibular aqueducts, and 23/26 facial nerve canals had an anomalous course (93).

Congenital perilymphatic fistula (PLF) has been associated with a Mondini deformity of the cochlea (94). Sites of fistula include the oval window, fundus of the modiolus, fissulae ante fenestrum, and round window. Patients with congenital PLF are at increased risk for bacterial meningitis (95). Symptoms of PLF include fluctuating or progressive SNHL or mixed hearing loss and intermittent unsteadiness or vertigo.

Anomalies of the Inner Ear

In patients with unilateral or bilateral SNHL or mixed hearing loss, inner ear anomalies are demonstrated by either CT and/or MRI of the temporal bones 20% to 39% of the time (96). Histopathologically, the hearing losses can involve the membranous and/or bony components of the labyrinth. The membranous labyrinth consists of the cochlear duct, semicircular ducts, utricle, saccule and endolymphatic duct, and sac. The bony labyrinth envelopes the membranous labyrinth and consists of the cochlea, the three SCCs, the vestibule, and the vestibular aqueduct.

Currently, the most common classification system of labyrinthine malformations is that introduced by Jackler et al. (97) in 1987. This system proposed classification of inner ear anomalies based on their likely occurrence in embryogenesis. Based on radiographic and histologic studies, the most significant events in embryologic development of the labyrinth were noted to occur between the fourth and eighth weeks of gestation with further maturation occurring up until birth and possibly beyond. Most inner ear malformations resemble histologic sections of the inner ear taken at different points in development, leading Jackler et al. (97) to conclude that malformations arise as a result of arrest in development at a specific point in embryogenesis. Malformations are divided into either membranous alone or both membranous and osseous anomalies. While their development occurs during the same time period, the development of the SCCs and cochlea are dependent on many genes, several of which are specific for either the cochlea or the vestibular apparatus. Therefore, isolated arrest in the development of each of these structures can occur. While the Jackler classification system cannot account for the entire constellation of inner ear anomalies, it provides a framework when relating anomalies to embryogenesis. Further information will be obtained as imaging techniques improve and the molecular biology of the cochlear and vestibular systems is elucidated.

As the ability to radiographically evaluate patients with SNHL has improved, the classification of inner ear anomalies has been modified. Incomplete partition of the cochlea (*Mondini malformation*) is the most common cochlear malformation seen on imaging, accounting for up to one half of all bony cochlear anomalies. It is frequently associated with the presence of an EVA. In 1791, Mondini described a specific cochlear malformation of incomplete cochlear partition (hypoplastic modiolus); short cochlear duct with a flat cochlea; auditory and vestibular organs that were immature; a dilated vestibule; SCCs that were wide, small, or missing; an endolymphatic sac that was bulbous; and a large vestibular aqueduct (LVA). Instead of its usual 2½ turns, the cochlea has 1½ turns with an absent interscalar septum between the middle and apical turn. Embryologically, this corresponds to arrest in development during the seventh week of gestation. The "pseudo-Mondini" malformation likely occurs earlier in the seventh week than the more developed Mondini malformation.

With the advent of widespread newborn hearing screening and routine recommendations for cochlear implantation, hearing aid usage, bone-anchored hearing aids, and early intervention services for language and speech, the need for better definition of inner ear anatomy for planning and prognosis has increased. Additionally, routine use of high-resolution CT and MRI temporal bone imaging has shown increasingly detailed anatomy of both the bony and membranous labyrinth. A new classification, published by Sennaroglu and Saatci (98) in 2002, further classified the Mondini abnormality into two distinct entities. The intracochlear partition type II (IP-II, "Mondini") cochlea has 1.5 turns (in which the middle and apical turns coalesce to form a cystic apex) accompanied by a dilated vestibule and EVA. The intracochlear partition type I (IP-1) malformation has an empty, cystic cochlea and vestibule without an EVA. The degree of hearing loss in the true Mondini malformation is typically less severe than in the cystic cochleovestibular malformation (98,99).

Stapes footplate anomalies and modiolar defects have also been found in association with Mondini malformation, predisposing these patients to the risk of PLF and meningitis. Seventh nerve anomalies are typically found when stapes anomalies are present, with displacement of the second genu anteriorly and inferiorly (100). Mondini malformations have been associated with several syndromes including Waardenburg, DiGeorge, and Pendred. Pendrin gene defects have also been seen in nonsyndromic SNHL cases associated with EVA (DFNB4) (101).

Similar to Mondini's description of EVA, other inner ear anomalies were first described in temporal bone specimens. The Michel anomaly, complete aplasia of all inner ear structures, reflects arrest of inner ear development prior to the fourth week of gestation. Corresponding CT imaging shows an absence of inner ear structures. Rarely,

complete aplasia can be confused with labyrinthitis ossificans, although a combination of CT and MRI should be able to differentiate one from the other (102). Clinically, Michel aplasia has been associated with thalidomide exposure, anencephaly, and Klippel-Feil syndrome. As expected, patients with Michel anomaly present with profound SNHL. Although these patients are not candidates for cochlear implantation, they may be candidates for brain stem implantation in the future (103).

Failure of the cochlear and vestibular apparatus to develop early in the fourth week of gestation results in a common cavity deformity, where the membranous labyrinth is poorly differentiated and situated in a large common cavity (104). The labyrinthine segment of the facial nerve can be displaced anteromedially. Hearing loss in patients with a common cavity is generally in the severe to profound range. Although cochlear implantation has been successfully performed on these patients, results vary depending on degree of membranous and neural development, including auditory nerve development. Surgically, cerebrospinal fluid (CSF) or perilymphatic leaks are common and need to be addressed with the patient and parents preoperatively (100).

Failure in labyrinth development in the fifth week of gestation results in cochlear aplasia. This is a rare anomaly where the cochlea fails to develop and the vestibule and SCCs are present although abnormal. These patients present with profound SNHL and implantation may be precluded by lack of an auditory nerve (105).

Arrest of development in the sixth week of gestation results in cochlear hypoplasia. On CT imaging, the cochlea may appear round and undeveloped, usually measuring 6 mm in height compared to a normal cochlea of 10 to 12 mm. In severe cases, the labyrinthine segment of the facial nerve can be displaced anteromedially. These patients present with various degrees of hearing loss depending on the exact time of arrest within the sixth week. Patients who have greater differentiation of the membranous labyrinth and more neuroepithelial elements have better hearing. Hearing results following cochlear implantation also depend on the degree of membranous differentiation.

The LVA, also known as EVA is the most common inner ear anomaly seen on temporal bone imaging in patients with SNHL or mixed hearing loss. While it is agreed to be the most common radiographic finding, the radiographic definition of EVA is evolving. Using fresh temporal bone specimens and tomography, it was described by Valvassori and Clemis (106) as an aqueduct that measures 1.5 mm or greater at the midpoint between its internal and external aperture. They also noted an enlarged vestibule, enlarged vestibule and SCC, enlarged vestibule and hypoplastic cochlea, or hypoplastic cochlea in many of the specimens. They further suspected that there were probably other abnormalities below the level of resolution of the tomography (106).

Harnsberger et al. (107), in 1995, suggested that 0.1 to 1.4 mm at the midpoint of the endolymphatic duct was normal on CT. Other authors have defined it as a diameter greater than 2 mm, with the measurement taken at its widest point or at the external aperture (108,109). Further refinement of these measurements was published by Vijayasekaran et al. (110), in 2007, using ≥1.0 mm at the midpoint and ≥2.0 mm at the operculum. A large endolymphatic sac, with or without the presence of LVA, is also associated with hearing loss. While LVA can be detected with both CT and MRI, the entire endolymphatic sac can only be seen with MRI (111).

LVA is found in association with cochlear anomalies, most commonly incomplete partition. Cases of EVA in isolation have been reported (112). One argument in favor of the isolated LVA is based on the embryogenesis of the vestibular aqueduct. A histologic study by Pyle (109) demonstrated progressive growth of the aqueduct throughout gestation while growth of the remaining labyrinth was virtually complete by the second trimester. Therefore, an isolated LVA could occur following normal development of the cochlea and SCCs. However, opposing arguments have been raised, proposing developmental arrest at 5 weeks as the etiology of LVA (100).

LVA is often associated with Pendred syndrome. Pendred syndrome, characterized by goiter and SNHL, is the most common syndrome with associated SNHL, accounting for 10% of patients with syndromic hearing loss. Mutations in the Pendrin gene (PDS, SLC26A4) cause Pendred syndrome but are also responsible for a nonsyndromic form of recessive SNHL, DFNB4. In the nonsyndromic form, the patients have temporal bone anomalies without associated thyroid goiter or detectable abnormalities of thyroid function. The findings of LVA can also be found in other syndromes, including X-linked mixed deafness with gusher (DFN3, POU3F4), BOR syndrome (associated with mutations in the EYA1 and SIX1 genes), and Waardenburg syndrome (113). In each syndrome, associated cochlear malformations are common.

The clinical presentation of the hearing loss in patients with EVA is variable. The hearing loss may be sensorineural, mixed, or occasionally purely conductive. Not infrequently, patients have normal hearing at birth and experience progressive or fluctuating hearing loss. Sudden hearing loss is also seen, either spontaneously or with even mild head trauma. Approximately 30% to 50% of patients will experience worsening and/or fluctuation of their hearing over time. Proposed mechanisms for hearing loss include membrane rupture causing a change in electrolyte homeostasis versus increased pressure forcing CSF through the cochlear duct (114).

Hearing preservation procedures in patients with EVA have been attempted through endolymphatic sac shunts, occlusion, or decompression. However, the results were disappointing with 50% to 100% of the patients developing worse hearing loss following the procedure (115). As a result, surgical intervention is not recommended. Currently, patients are advised to avoid activities that have high risk for head trauma or pressure changes, such as

flying or diving, although the actual incidence of a permanent change in the hearing from these activities remains unknown.

Vestibular Anomalies

The most common abnormality of the vestibular apparatus is aplasia or dysplasia of the lateral SCC. Lateral SCC dysplasia is reported by some authors to be the second most common osseous inner ear anomaly after LVA (116,117). The lateral SCC is more often involved due to its later development during embryonic development than the superior and posterior canals. Vestibular malformations frequently present in association with cochlear malformations and LVAs as their development occurs during the same weeks of gestation.

Patients with lateral SCC dysplasia may present with sensorineural, mixed, or conductive hearing loss. It occurs in isolation or associated with a syndrome. A commonly associated syndrome is CHARGE syndrome. CHARGE syndrome has characteristic inner ear findings including SCC aplasia in association with a stenotic cochlear aperture, underdeveloped vestibule, and incomplete partition of the cochlea. Children with trisomy 21 often have abnormal middle and inner ear structures, notably abnormalities of the SCC and a small bony island of the lateral SCC, smaller middle-ear space, and ossicular abnormalities (118).

Membranous Anomalies

Membranous labyrinthine anomalies occur in isolation and in combination with all bony labyrinthine anomalies. They account for a large percentage of patients with SNHL but because of limitations in imaging can only be inferred without histologic sectioning. As previously mentioned, the membranous labyrinth is divided into two components, the pars superior and the pars inferior. The pars superior forms the SCCs, endolymphatic duct, and utricle, and the pars inferior becomes the saccule and cochlear duct. Anomalies can involve an isolated portion of the membranous labyrinth, one division, or the entire labyrinth.

Bing-Siebenmann Malformation (Cochleosaccular Dysplasia)

The Bing-Siebenmann malformation is an isolated membranous malformation characterized by membranous labyrinthine aplasia or dysplasia with a well-formed bony capsule. On histopathologic section, the cochlear duct has a poorly developed organ of Corti with an abnormal stria vascularis and collapse of Reissner membrane. The saccule and macula are also poorly developed. Clinically, patients with Bing-Siebenmann malformation have profound SNHL. This malformation has been seen in patients diagnosed with Usher syndrome and Jervell and Lange-Nielsen.

Scheibe Malformation

Scheibe malformation is the most common membranous inner ear malformation. It results from a defect in the development of the pars inferior resulting in a malformed organ of Corti and saccule. Histologically, there is a partial or complete aplasia of the organ of Corti and collapse of the cochlear duct. Clinically, the Scheibe malformation presents with severe to profound SNHL. It is most often associated with Usher syndrome but is also seen with Jervell and Lange-Nielsen, Refsum disease, Waardenburg syndrome, and trisomy 18. Inheritance in an autosomal recessive fashion with a gene defect on chromosome 1q32 has also been demonstrated.

Alexander Malformation

The least severe membranous malformation was described by Alexander in 1904. It involves an otherwise normal labyrinth with the exception of a dysplastic basal turn of the cochlea. The Alexander malformation is found in association with hereditary high-frequency SNHL.

The Overall Evaluation of Neonatal and Childhood Onset Hearing Loss

The diagnostic evaluation of hearing loss in newborns and young children is in rapid evolution, and several algorithms have been proposed for this purpose. Which diagnostic tests and in which order they are obtained depends on the age of the child, history and physical examination, family history, the degree and laterality of hearing loss, what the most likely etiologies are given the patient's presentation, and what the proposed interventions might be. In addition, insurance coverage for certain studies, parental understanding (especially of any proposed genetic studies), whether sedation is needed, and which studies are available locally versus away from the hometown or institution may all play a role in the diagnostic evaluation. Lin et al. (119) recently reported on the diagnostic yield of several studies in 270 children with severe to profound SNHL evaluated between 2002 and 2009. They reviewed temporal bone MRI and CT, renal ultrasound, electrocardiogram (ECG), fluorescent treponemal antibody absorption test for syphilis (FTA), connexin 26 sequencing, genetic consultation, and ophthalmologic evaluation. MRI revealed abnormalities in 24% of the children, CT in 18%, and biallelic connexin 26 (GJB2) mutations were present in 15%. The yield of the other tests was renal ultrasound (4%), ECG (long QT in 1%), FTA (0.5%), genetics evaluation (25%), and ophthalmologic consultation (8%). Nearly all the children with biallelic GJB2 mutations had nonsyndromic SNHL, and several had passed a newborn hearing screen. Although the percentage yield for CT and MRI was similar, they did not always find the same abnormalities; EVA was occasionally picked up by MRI and not by CT, and vice versa. MRI of the brain found brain malformations and indications of congenital infections (e.g., CMV),

which CT of the temporal bones did not. Ophthalmology evaluations revealed myopia, coloboma (in children with CHARGE association), and two with retinitis pigmentosa eventually found to have Usher syndrome. All children with hearing loss are visual learners, so even finding out that they need eyeglasses is useful information, and if they have less common but other important findings that may yield an additional diagnosis that obviously benefits the patient.

The diagnostic yield for specific tests in the Lin et al. (119) study is in good agreement with others, including Preciado et al. (120). Testing for diagnoses that are treatable, such as congenital CMV, or dangerous if missed, such as long QT in children with bilateral severe to profound SNHL, should always be considered. Many studies commonly performed in the past to diagnose genetic causes may now be better evaluated using actual genetic testing. An example of this are mutations in the SLC26A4 (PDS) gene associated with bilateral EVA (nonsyndromic EVA, DFNB4) and, in some cases, thyroid dysfunction (the full Pendred syndrome). A second is Usher syndrome, where genetic testing may be positive in the presence of a normal routine eye examination, especially in young children (121,122). CMV was not routinely tested in the Lin et al. (119) or most other studies. However, since congenital CMV and toxoplasmosis are treatable, testing for CMV in infants would be a reasonable place to start in neonates and very young infants (123). In addition, although CS is uncommon, it is another treatable cause, so testing would be justified if clinically suspected. In addition, patients with biallelic GJB2 mutations seldom have anatomic inner ear abnormalities, so if initial imaging is normal, then mutations in GJB2 would be a stronger consideration, while if the imaging is abnormal, GJB2 would be less likely. For some of the more common causes, very occasionally, there may be overlap in the same patient. For example, babies with congenital CMV may also have EVA or GJB2 mutations. Therefore, if the presentation does not completely fit the initial diagnosis, especially as the patient is followed over time, further evaluation for additional causes of hearing loss should be considered. The overall diagnostic yield for these studies taken together (especially imaging, genetics, and CMV) is 50% to 60% and is likely to improve with better genetic testing, higher-resolution imaging, and increased awareness of the incidence of congenital CMV.

SUMMARY

Pediatric hearing loss is common and, with the advent of newborn hearing screening, diagnosed at increasingly younger ages. The identification of a definite etiology can aid in prognosis and management. The yield of diagnostic studies has increased given accurate testing for, and awareness of the frequency of, congenital CMV, anatomic anomalies of the inner ear, and genetic causes. A methodical approach to diagnostic studies, based on laterality and degree of hearing loss, history and physical examination, family history, and overall clinical presentation, will frequently yield an etiology.

HIGHLIGHTS

- Hearing loss is the most common congenital sensory impairment.
- Even if an infant passes a newborn hearing screen, it does not always mean the baby does not have a hearing loss or will not develop hearing loss. If hearing loss is later confirmed, it may be because the hearing loss was mild, and the baby passed the screen, or in a frequency range not picked up by the screen; the hearing loss has worsened; the baby had an OAE screen and has auditory dyssynchrony; or the screen was a false negative.
- According to a recent NHANES study, by the age of 12 to 19 years, the rate for any degree or laterality of hearing loss is 19.5%.
- Hearing screening should be performed in all newborns and may consist of ABR, OAE, or a combination of both
- The most common causes of congenital hearing loss in healthy term newborns are related to CMV, structural middle and inner ear abnormalities, and genetics.
- Later onset hearing loss may be due to worsening of a congenital cause, such as congenital CMV or preexisting structural abnormality such as EVA, or to a newly acquired cause, such as noise exposure, head trauma, chemotherapy or meningitis.
- Prenatal exposure to CMV is the most common congenital viral infection and currently the most common viral cause of congenital SNHL. The prevalence of congenital CMV infection is approximately 0.4% to 2.3% of all newborns. If the mother has a primary CMV infection during pregnancy, there is a 40% chance that the infant will become infected, and if she has a reactivation infection, there is about a 2% chance.
- In patients with unilateral or bilateral SNHL, mixed hearing loss, or uncommonly conductive hearing loss alone, inner ear anomalies are demonstrated by CT and/or MRI of the temporal bones 20% to 39% of the time. The most common anomalies seen include cochlear dysplasia, enlarged vestibular aqueduct/endolymphatic sac, cochlear stenosis, and lateral SCC dysplasia.
- Some structural anomalies are associated with certain genetic abnormalities or syndromes. These include Pendred syndrome, CHARGE association, BOR syndrome, and Waardenburg syndrome.

- Ophthalmology evaluations in children with hearing loss are very important, as all children are visual learners. However, a normal routine eye exam, especially in an infant or young child, does not rule out retinitis pigmentosa and Usher syndrome. If Usher syndrome is a serious consideration, evaluation of the retina, with ERG as the gold standard, should be considered. Clinical genetic testing for most Usher genes is also available, and a definite diagnosis of Usher syndrome can now be made even in early infancy.

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Genetic Hearing Loss

102

John Greinwald *Catherine Hart*

Hearing impairment is the most common sensory deficit. It occurs in 2 to 3 per 1,000 live births and affects approximately 28 million Americans (1). It can be congenital or acquired, developing any time during infancy, childhood, or adulthood. Of children younger than 18 years of age, 5% have a hearing impairment, and that incidence increases to 40% to 50% by age 75. Among school-aged children, 2% have a hearing loss that interferes with educational achievement.

Most cases of hearing loss are attributed to nongenetic causes (e.g., middle-ear fluid). Advances in technology and mass screening programs, however, have resulted in an ongoing increase in the identification of specific heritable forms of deafness, most of which are expressed as sensorineural losses. Heritable hearing loss can be transmitted through various patterns of inheritance. Most authors attribute 75% to 80% of genetic deafness to autosomal recessive patterns and 18% to 20% to autosomal dominant patterns. The remainder are classified as X-linked or mitochondrial. Additionally, deafness can present as an isolated finding (nonsyndromic) or can be associated with other pathologic findings (syndromic) such as craniofacial anomalies.

This chapter presents an overview of heritable hearing loss within the framework of these basic genetic principles. We discuss a number of genes that are linked to a wide spectrum of hearing disorders and briefly describe the relevance of genetic advances to case management.

BASIC GENETIC PRINCIPLES

Human genes are molecular codes for inherited factors. Genes are arranged linearly on 23 pairs of chromosomes. These chromosomes consist of 22 pairs of autosomes and 1 pair of sex chromosomes, comprising a total of 46 chromosomes. Males have an X and a Y pair of sex chromosomes, whereas females have two X chromosomes. The location of a gene on a chromosome is termed a locus. Each chromosome pair carries a distinctive set of gene loci, and a given gene can have several alternative codes, which are referred to as alleles. The actual genetic code (genotype) for a specific trait consists of either two identical alleles (homozygous) or two disparate alleles (heterozygous). The physical manifestation of a trait, referred to as the phenotype, is determined by which alleles are present and how they interact. An allele is considered dominant if its presence results in a specific phenotype. It is considered autosomal recessive if both alleles are required for the expression of its phenotype. An X-linked recessive gene is present in only one allele (hemizygous) in males because the Y chromosome does not carry an allele complementary to the X chromosome. A specific DNA base pair change at a specific allele is considered a truncating or nontruncating mutation.

A nontruncating (or missense) mutation alters the codon resulting in an altered amino acid product. A truncating (or nonsense) mutation results in a nonfunctional protein due to premature termination of transcription. Truncating mutations can also occur due to mutations at the exon splice sites, which result in nonfunctional protein production.

Dominant traits are transmitted in a vertical fashion from one generation to another. A 50% chance exists that an affected heterozygous individual will transmit the abnormal gene to offspring. Penetrance is the ability of a gene to manifest any of the phenotypic characteristics related to that gene. In some dominant disorders, not all persons carrying the affected gene display the disease phenotype. This occurrence is called incomplete penetrance. Dominant disorders also can have variable expressivity, whereby family members present with different manifestations of the affected gene. It is thus presumed that environmental influences or interaction with other genes can modify phenotypic expression.

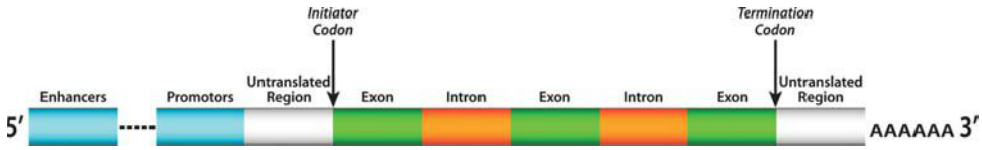


Figure 102.1 Basic gene structure.

In the absence of consanguinity, an autosomal recessive trait is usually seen in an offspring in small nuclear families. The offspring of heterozygous (i.e., carrier) parents have a 25% risk of being affected. Occasionally, being heterozygous for two different genes (double heterozygous) can cause a condition. An X-linked recessive trait can lack phenotypic expression if it is carried by a heterozygous female, but male offspring of this female would have a 50% chance of inheriting the gene. Expression of the gene would then occur because of the absence of a second X chromosome. A female offspring of an X-linked female carrier has a 50% risk of being a carrier of such a trait. Because males inherit their father's Y chromosome and not his X-linked recessive gene, they are unaffected and do not become carriers. In contrast, females inherit their father's X-linked recessive trait and, as such, do become carriers of the affected gene.

Heritable disorders that are caused by abnormalities at the chromosomal level and involve extra or absent chromosomal material are characterized by developmental delays and varied congenital anomalies, except when they involve the sex chromosomes. The nature and severity of the resultant disorders depend on the quantity and origin of the chromosomal material involved. In persons with trisomy, three copies of an entire chromosome are present. Trisomy 21 (Down syndrome) is the least severe autosomal trisomy. Trisomy 13 (Patau syndrome) and trisomy 18 (Edwards syndrome) are less common but more severe. Other autosomal types of trisomy usually are lethal. In the condition known as monosomy, which is also lethal, only one chromosome rather than a pair is present. Embryos with sex chromosome abnormalities are quite viable, with the exception of a conceptus with only a Y chromosome. Persons with one extra X or Y chromosome or with only one X chromosome have mild clinical features such as seen in Klinefelter syndrome (47,XYY or 47,XXY) and Turner syndrome (45,X).

It is known that disparate genotypes can produce a similar phenotype. This phenomenon, which is referred to as genetic heterogeneity, often makes it difficult to identify causative genes. In nonsyndromic hearing loss, gene identification is difficult in that there is a high degree of heterogeneity and an absence of features that clearly define clinical subtypes. In syndromic hearing loss, however, distinct subtypes as well as interfamilial differences assist in the identification of these genes. The identification of autosomal recessive nonsyndromic hearing loss genes is facilitated through the study of both inbred and isolated populations, which reduce genetic heterogeneity. Studies of large families (kindreds) can facilitate the identification of autosomal dominant hearing loss genes.

A detailed description of the process involved in gene identification is beyond the scope of this chapter. In brief, however, this process entails the following three steps: A gene is first localized to a specific chromosomal region. Physical mapping techniques are then used to isolate DNA from that region. Through the efforts of the Human Genome Project, nearly all of the 30,000 human genes have been mapped, thereby allowing for the bioinformatic identification of candidate genes. Step three involves sequencing analysis of candidate genes to identify the specific mutation associated with a particular disease.

Each gene generally consists of DNA that codes for (a) the actual protein(s) (exons); (b) interspersed areas between exons, which are called introns; and (c) untranslated regulatory regions before and after the exons, which are respectively referred to as upstream and downstream (Fig. 102.1). The upstream untranslated region has specific areas of DNA that are bound by regulatory proteins. These areas regulate the function of the gene, and this region is called the promoter. Occasionally, one common promoter may exist for several genes, which is called a locus control region.

AUTOSOMAL RECESSIVE DISORDERS

Most genetic hearing disorders are transmitted by an autosomal recessive mode of inheritance, and of the hearing disorders presenting in childhood, approximately 80% are inherited recessively. In most patients, hearing loss is nonsyndromic, but 10% to 20% of patients display syndromic disorders. The identification of recessive syndromes involving hearing loss, thus, necessitates a diligent search for other syndromic components. Because of the asymptomatic status of heterozygous carriers of a recessive gene and the 25% inheritance risk, it is often difficult to distinguish between nongenetic disorders and those that are recessively inherited. In both clinical situations, a single affected child generally presents in a family with no known history of hearing loss.

Nonsyndromic Recessive Disorders

To date, linkage studies have identified at least 85 loci for autosomal recessive nonsyndromic hearing loss (ARNSHL) (2). These loci are given the prefix DFNB; DFN signifies deafness, whereas B signifies a recessive mode of inheritance. Thirty seven causative ARNSHL genes have been identified (Table 102.1). DFNB1 accounts for about one half of all ARNSHL and, as such, is among the most active areas of clinical research. As implied by its designation,

TABLE 102.1 SELECTED GENETIC DEFECTS ASSOCIATED WITH HEARING IMPAIRMENT

Gene (Protein)	Locus	Mode of Inheritance or Syndrome	Phenotype
CDH23(cadherin 23)	DFNB12	ARNSHL	SNHL
	Usher 1C	AR syndromic	Congenital hearing loss, retinitis pigmentosa, and variable vestibular areflexia
COCH (cochlin)	DFNA9	ADNSHL	Onset of hearing loss occurs between ages 20–30; profound at high frequencies and variable progression to anacusis by age 40–50. Variable vestibular dysfunction
COL2A1 (collagen 2A1)	Stickler type 1	AD syndromic	Robin sequence, myopia, joint degeneration, variable degree of hearing loss
COL11A1(collagen 11A1)	Stickler type 2		
COLL11A2(collagen 11A2)	Stickler type 3		Stickler type 1 phenotype without ocular problems
COL4A3(collagen 4A3)	Alport	X-linked	Progressive high-frequency SNHL, nephritis
COL4A4 (collagen 4A4)		AR syndromic	
COL4A5 (collagen 4A5)		AD syndromic	
GJB2 (connexin 26)	DFNA3A	ADNSHL	Severe to profound SNHL
	DFNB1A	ARNSHL	Mild to profound SNHL
GJB6 (connexin 30)	DFNB1B	ARNSHL	Severe to profound SNHL
	DFNA3B	ADNSHL	High frequency to profound SNHL
DDP (deafness or dystonia peptide)	DDP (previously called DFN1)	X-linked syndromic	Early onset deafness with mental retardation
DIAPH1 (diaphanous)	DFNA1	ADNSHL	Fully penetrant progressive, low-frequency SNHL
EDNRB (endothelin receptor)	Waardenburg type 4	AR syndromic	WS with Hirschsprung disease
EYA1 (eyes absent 1)	Branchio-oto-renal	AD syndromic	Conductive, sensorineural, or mixed hearing loss with branchial remnants and renal anomalies
KVLQT1 (potassium-gated voltage channels)	Jervell and Lange-Nielsen	AR syndromic	Severe to profound SNHL, syncope, prolonged QT
KCNE1 (potassium channel voltage-gated, risk-related subfamily member 1)			
MITF (microphthalmia-associated transcription factor)	Waardenburg type 2	AD syndromic	Same as type 1 without dystopia canthorum
MYO7A (myosin 7A)	DFNB2	ARNSHL	Progressive SNHL with variable vestibular and ocular findings
	DFNA11	ADNSHL	Moderate SNHL
	Usher 1B	AR syndromic	Profound congenital deafness, vestibular areflexia, and progressive retinitis pigmentosa
NDP (norrin)	Norrie	X-linked syndromic	Ocular symptoms, progressive SNHL, and mental retardation
OTOF (otoferlin)	DFNB9	ARNSHL	Severe to profound SNHL
PAX3 (paired box gene 3)	Waardenburg type 1	AD syndromic	White forelock, heterochromia iridis, SNHL, and dystopia canthorum
SLC26A4 (pendrin)	DFNB4	ARNSHL	Enlarged vestibular aqueduct, euthyroid goiter
	Pendred	AR syndromic	Mondini dysplasia and SNHL
POU3F4 (POU domain 3, transcription factor 4)	DFN 3	X-linked	Stapes fixation
POU4F3 (POU domain 4, transcription factor 3)	DFNA15	ADNSHL	Progressive hearing loss
TCOF1 (treacle)	Treacher Collins	AD syndromic	Lower eyelid coloboma, micrognathia, microglossia, zygomatic arch hypoplasia, macrostomia, hearing loss
TECTA (α-tectorin)	DFNA8/12	ADNSHL	Prelingual severe to profound SNHL
	DFNB21	ARNSHL	
USH1C (USH1C)	Usher 1C	AR syndromic	Profound congenital deafness, vestibular areflexia, and progressive retinitis pigmentosa
USH2A (USH2A)	Usher2A	AR syndromic	Congenital sloping hearing loss, normal vestibular function, and progressive retinitis pigmentosa
MTRNR1	12rRNA	mitochondrial	Mild to severe hearing loss, usually associated with aminoglycoside
MTTS1	$tRNA^{ser\ (UCN)}$	mitochondrial	Mild to severe hearing loss, can be progressive

AD syndromic, autosomal dominant syndromic; ADNSHL, autosomal dominant nonsyndromic hearing loss; AR syndromic; autosomal recessive syndromic; ARNSHL, autosomal recessive nonsyndromic hearing loss; SNHL, sensorineural hearing loss.
Adapted from Van Camp G, Smith RJH. Hereditary Hearing Loss Homepage. Hereditaryhearingloss.org. For a comprehensive and current list of genes related to hearing impairment, please refer to this website.

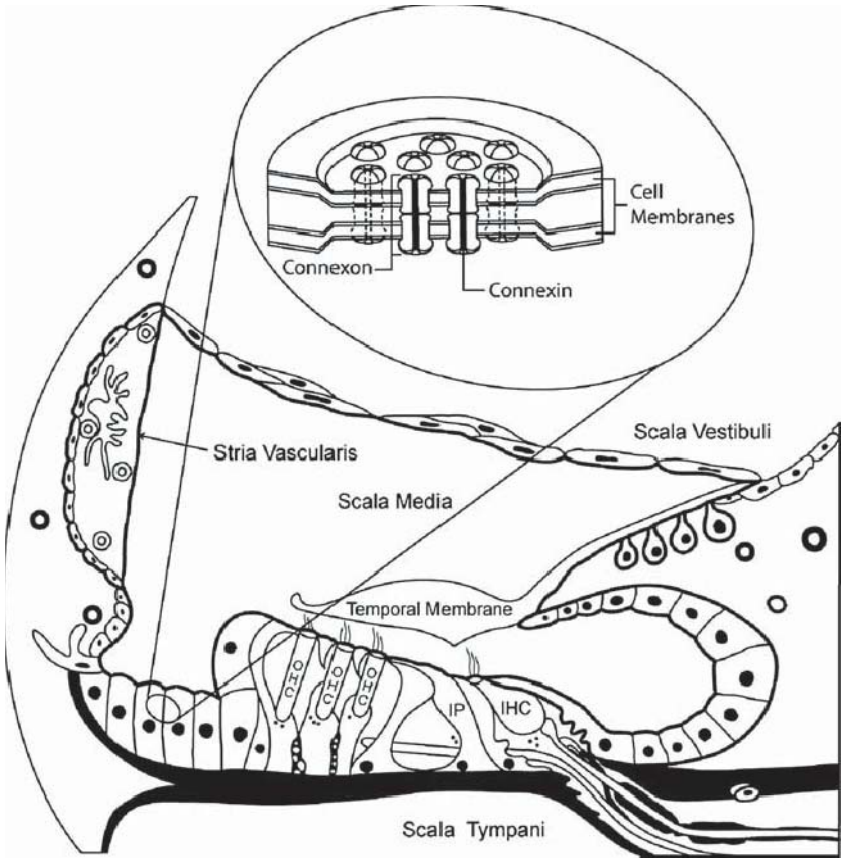


Figure 102.2 Location of gap junctions within the supporting cells of the organ of Corti. Six connexins comprise a connexon. Connexons form gap junctions, which function as intracellular channels.

DFNB1 was the earliest autosomal recessive gene locus to be successfully mapped and characterized. The gene at the DFNB1 locus is gap junction beta 2 (*GJB2*), which produces a protein called connexin 26 (1). Connexins comprise a family of gap junction proteins that function as intercellular channels. These channels allow ions and low molecular weight molecules to travel from cell to cell (Fig. 102.2). The supporting cells of the organ of Corti express several gap junction proteins, including connexin 26. Although the function of connexin 26 in the inner ear has not been conclusively determined, it is thought to be involved in potassium recycling. In the normal ear, a sound stimulus causes depolarization of hair cells, which is mediated by the influx of potassium ions. These ions are thought to transverse through connexin molecules back to the stria vascularis. From the stria vascularis, ions are actively pumped back into the endolymph to reset its electrical gradient (Fig. 102.2).

DFNB1 is estimated to cause up to 50% of all ARNSHL in many populations. Of patients presenting with hearing impairment of 70 dB or greater, nearly 40% have DFNB1; of those with a mild to moderate hearing loss, only 10% to 15% have this gene (3,4). *GJB2* mutations have been found in patients from many different ethnic backgrounds, and specific mutations vary with patient ethnicity. The deletion of a guanine at nucleotide position 35 of the gene (35delG) is one of the most common mutations that results in autosomal recessive hearing impairment, particularly in patients of European descent. The carrier frequency for the 35delG deletion in Europe is 1 in 50. A deletion of a thymine at position 167 (167delT) is often present in the Ashkenazi Jewish population, with a carrier frequency of 1 in 25. A 235delC mutation occurs more frequently in Asians. Among the white population in the United States, the frequency of heterozygous carriers of mutations in *GJB2* is approximately 1 in 40. This carrier frequency is almost as common as that in cystic fibrosis, which has a carrier frequency of approximately 1 in 24. The high frequency of mutations and the small size of this gene make screening and molecular genetic diagnosis feasible.

Additionally, a unique genetic mutation has been found in the *GJB6* gene. This mutation appears to present in carriers of *GJB2* mutations (double heterozygote state). A large deletion (170 to 340 kilobases [kb]) upstream and including the 5′ portion of the *GJB6* gene has been found to cause severe hearing loss (5). Interestingly, *GJB2* and *GJB6* are located in close proximity on chromosome 13, and this deletion may interfere with a common promoter element for the two genes (locus control region). Approximately 10% of patients with hearing loss who have one abnormal *GJB2* allele also have the *GJB6* deletion (6).

GJB2 mutations can create altered protein expression, subcellular localization, or abnormal functionality of the connexin complex. *GJB2* mutations cause a wide range of

hearing loss phenotypes, ranging from mild to profound hearing impairment. These mutations can be nontruncating or truncating. The type of mutation can produce varying levels of hearing loss. For example, a biallelic truncating mutation produces a severe to profound hearing loss in nearly all patients (e.g., 35delG/35delG). In contrast, the presence of one nontruncating mutation (e.g., V37I) commonly causes a milder form of hearing impairment (2).

The clinical significance of DFNB1 mutations lies in diagnostic evaluation and case management. Genetic testing is now routinely part of the algorithm in the evaluation of hearing loss (7). Genetic testing should be the first line of evaluation of children with bilateral ARNSHL of 60 dB or greater (Fig. 102.3). For those with unilateral or mild bilateral hearing impairment, genetic testing should be considered after temporal bone imaging is performed. If the imaging study is normal, genetic testing is then appropriate. If the imaging study demonstrates enlarged vestibular aqueduct or Mondini deformity, *SLC26A4* (Pendred) testing should be performed. New genetic platforms will allow rapid screening for multiple genes at one time (e.g., "Ear-gene," Cincinnati Children's Hospital Medical Center, Cincinnati, OH). Recent data have shown that gene chip platforms are highly accurate and will likely become instrumental in diagnostic evaluation of sensorineural hearing loss (SNHL) (8).

The prognosis for children with hearing loss related to *GJB2* is variable and has been shown to correlate with the genotype. This is particularly important in light of new hearing screening programs that are increasingly detecting hearing loss in very young children. Genetic information can assist in predicting the actual hearing phenotype, which is valuable considering the emphasis on early (age 12 months) cochlear implantation. For example, if a nontruncating mutation is present, a child would be more likely to have mild hearing loss. Conversely, the presence of biallelic truncating mutations in a child in whom an auditory brainstem response (ABR) test at 1 month of age showed severe hearing loss would lead the practitioners to recommend early aggressive treatment. A high likelihood would exist of recommending cochlear implantation to ensure the child's ability to communicate verbally. Interestingly, research indicates that patients with DFNB1-related hearing loss who meet criteria for cochlear implantation have better outcomes than those with congenital hearing loss from other causes (9). Such findings emphasize that genotype can have clinical significance, and further study aimed at elucidating this particular association is ongoing.

Most other ARNSHL genes have been identified from isolated consanguineous families, and the prevalence of mutations in these genes in the general population has yet to be determined. A technology now being developed (resequencing microarray), however, will enable the rapid reading of a large amount of DNA.

Another ARNSHL gene worthy of note is otoferlin (*OTOF*). This gene was originally found to be the cause of hearing loss in several isolated families (DFNB9) (Table 102.1). Although the function of *OTOF* is not certain, it is hypothesized that this gene is a calcium sensor involved in hair cell exocytosis (10,11). Research has shown that in some patients, *OTOF* is also responsible for auditory neuropathy (AN) (12). AN is a unique form

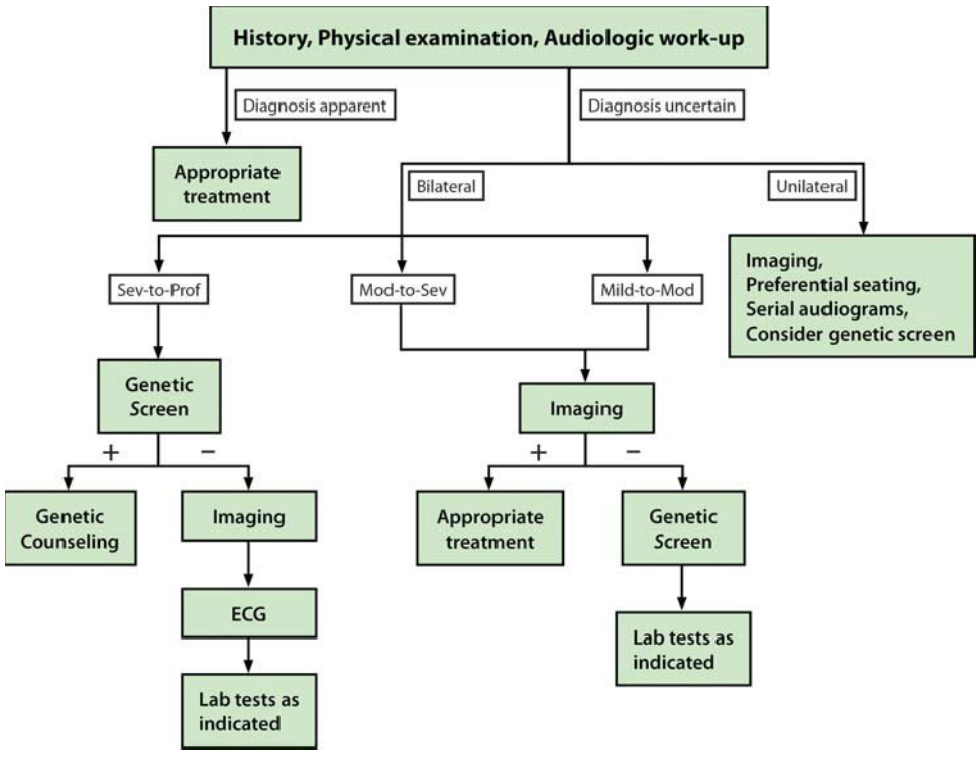


Figure 102.3 Algorithm for the diagnosis of genetic hearing disorders.

of SNHL characterized by absent ABR waveforms, present otoacoustic emissions, and variable behavioral thresholds. The prevalence of AN in patients with SNHL ranges from 0.5% to 15%. The etiology of AN is quite heterogenous with approximately 40% of cases having a genetic basis. It can be autosomal recessive, as in *OTOF*; autosomal dominant; X-linked; or syndromic. Some patients with AN also have other peripheral neuropathies or central nervous system disease. The treatment of AN can be challenging, involving the judicious use of FM devices and hearing aids as well as cochlear implantation. A better understanding of the molecular basis of this disease will allow for more accurate diagnosis and a more individualized treatment approach.

Syndromic Recessive Disorders

Jervell and Lange-Nielsen Syndrome

Jervell and Lange-Nielsen (JLN) syndrome is a congenital disorder associated prolonged QT interval leading to episodes of arrhythmias and syncope that occur as early as the second or third year of life. These episodes are caused by a cardiac conduction defect and can lead to sudden death. Beta-adrenergic blockers (e.g., propranolol) and implantable cardioverter defibrillators have proved effective in managing the cardiac component of the syndrome.

The degree of hearing loss can vary, but it is almost always severe to profound. Clinicians should consider this diagnosis in children with hearing loss and unexplained syncope or in cases of a family history of syncope or sudden death. Patients suspected of having JLN syndrome should have an electrocardiogram; results will show large T waves and prolongation of the QT interval.

One form of JLN has been attributed to homozygosity for mutations of a potassium channel gene called *KVLQT1* (13) (Table 102.1). Other mutations in this gene cause the dominantly inherited long QT syndrome (Romano-Ward syndrome), which does not include hearing loss in the phenotype. Not all families with JLN syndrome map to this gene, clearly indicating genetic heterogeneity. Mutations also have been found in another potassium channel gene, *KCNE1* (14). In some families, heterozygous carriers of JLN syndrome show a prolonged QT interval but are otherwise asymptomatic.

Pendred Syndrome and Enlarged Vestibular Aqueduct Syndrome

First described in 1896, Pendred syndrome is a disorder in which hearing impairment is associated with abnormal iodine metabolism; the typical result is a euthyroid goiter. The gene that causes Pendred syndrome has been identified and is named *SLC26A4* (or *PDS*) (15) (Table 102.1). This gene produces a protein called pendrin, which is responsible for iodine and chloride ion transport. For known families with the full phenotype of Pendred syndrome (hearing loss and goiter), little evidence indicates genetic heterogeneity.

Hearing loss can be profound at birth or can progress with age. Radiologic studies demonstrate that most patients have severe cochlear dysplasia (Mondini deformity), enlarged vestibular aqueduct, or both. Although in the past the diagnosis of Pendred syndrome rested on a perchlorate discharge test indicating abnormal organification of nonorganic iodine, this test is not specific for Pendred syndrome and its sensitivity is not known. Thyroid function tests should also be obtained in these patients. Although the goiter is sometimes detected at birth, it usually does not become clinically evident until 8 years of age. Administration of exogenous thyroid hormone is the best therapy. Surgical extirpation of the thyroid gland has proved ineffective and is not recommended. Of cases of severe to profound congenital hearing loss, 1% to 2% are attributed to Pendred syndrome.

Enlarged vestibular aqueduct syndrome (EVAS) is similar to Pendred syndrome in that patients have hearing loss and inner ear dysplasia and either an isolated, enlarged vestibular aqueduct; incomplete partitioning of the cochlea; or both, but they lack thyroid pathology (Fig. 102.4) (16). Single *SLC26A4* mutations have been found in 15% to 20% of patients with EVAS. More recently, mutations have been identified in *FOXI1*, which compromise the transcription of *SLC26A4*, resulting in the phenotype found in EVAS (17).

Unlike patients with Pendred syndrome, those with EVAS have normal thyroid function. The degree of hearing loss can be variable, ranging from mild to profound, and the audiometric configuration is commonly either flat or downsloping. Hearing loss is either sensorineural or mixed, with a lower frequency conductive component and a mid- to high-frequency sensorineural component. Children with bilateral EVA and any *SLC26A4* mutation are more likely to have greater aqueduct enlargement and are more likely to experience more

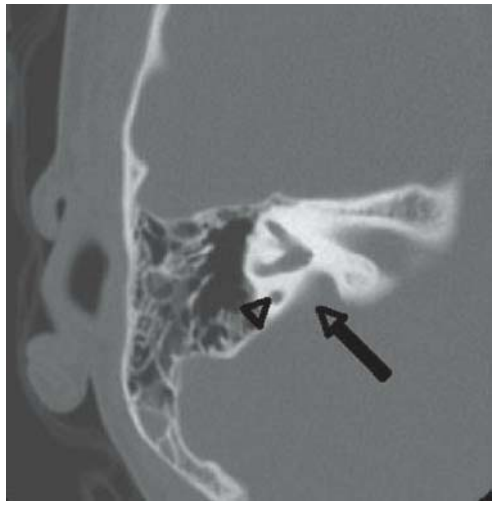


Figure 102.4 Enlarge vestibular aqueduct of the right ear. The vestibular aqueduct is grossly enlarged (*arrow*). The normal size should be less than 1.5 mm, about the size of the posterior canal (*arrowhead*).

significant progression of hearing loss (18). The cause of the conductive loss in patients with EVAS is unknown, and surgical correction of the ossicles is not recommended. Vestibular abnormalities occur in 5% to10% of cases, and they rarely occur without hearing loss. About 25% to 30% of patients with EVAS display hearing loss progression. There is an association between sudden hearing loss and head trauma in all patients with EVAS. Most patients, therefore, are counseled to avoid physical activities (e.g., contact football), which could cause such trauma. Molecular genetic testing for *SLC26A4* is available at select laboratories.

Usher Syndrome

Usher syndrome, characterized by hearing loss and retinitis pigmentosa, affects approximately one half of the 16,000 deaf and blind persons in the United States. The syndrome occurs in approximately 4.4 per 100,000 persons in the United States and in 3.0 cases per 100,000 persons in Scandinavia. Although Usher syndrome was initially recognized by Von Graefe (1858), it was named for Usher (1935), who emphasized its hereditary nature. Estimates of the prevalence of Usher syndrome among populations of deaf persons range from 0.6% to 28%, depending on the study population. Genetic linkage studies have shown this disorder to be genetically heterogeneous, with three clinically distinct subtypes that can be differentiated by the severity or progression of the hearing loss and the extent of vestibular system involvement (19). Patients with Usher syndrome type 1 (USH1) have congenital bilateral profound hearing loss and absent vestibular function. Those with Usher syndrome type 2 (USH2) have moderate hearing loss and normal vestibular function. Usher syndrome type 3 (USH3), which occurs primarily in Norwegians, involves progressive hearing loss and variable vestibular dysfunction. Although early studies estimated that USH1 accounted for nearly 90% of all cases of Usher syndrome and that USH2 represented only 10% or fewer cases, it is now recognized that these studies underestimated the prevalence of USH2 because patients with moderate hearing losses are not typically educated in schools for the deaf. Large series from both Scandinavia and the Unites States currently reflect a nearly equal number of cases of USH1 and USH2.

Genetic heterogeneity occurs both within and between these subtypes. Linkage analysis studies have revealed at least seven different causative genes for USH1 and at least three for USH2 (Table 102.1). In contrast, USH3 appears to have only one causative gene. To date, nine causative genes for Usher syndrome have been fully mapped. USH1 is most commonly caused by mutations in the myosin VII gene (*MYO7A*). All of the USH1 proteins have been found to be in a common molecular pathway in the hair cell stereocilia. This pathway appears to be involved with stereocilia or tip-link construction, maintenance, and function. The most common gene causing USH2 is *USH2A*, which produces a protein called usherin (20). The function of this protein is unknown, but it shares homology with laminin and fibronectin proteins and it is likely involved in extracellular matrix function.

An ophthalmologic evaluation is integral to the diagnosis of Usher syndrome. Results of electroretinographic studies have been reported to be subnormal in patients 2 to 3 years of age, before functional or fundoscopic abnormalities can be detected. Early diagnosis of Usher syndrome can have important implications on the rehabilitation of an affected child and on educational planning.

Autosomal Dominant Disorders

Identification of an autosomal dominant syndrome is facilitated by a family history that reflects a classic dominant inheritance pattern and a recognizable phenotype. In reality, variation in expressivity of dominant genes frequently leads to the presence of different phenotypic characteristics in various affected members of the same family. Decreased penetrance also is common with dominant genes, so an obligate carrier of the gene may not have any detectable phenotypic expression. When a new mutation occurs, an individual with no family history of the trait can actually have a disorder transmitted to offspring in a dominant manner.

As with recessive disease, advances in molecular genetics have greatly increased our understanding of the causes and mechanisms of autosomal dominant disorders. To date, 24 genes with an autosomal dominant nonsyndromic phenotype have been identified (21). Many of the common dominant syndromic phenotypes have been identified. This explosion of molecularly based knowledge brings the hope of a greater understanding of the intra- and interfamilial phenotypic variations seen in affected persons.

Nonsyndromic Dominant Disorders

Autosomal dominant nonsyndromic hearing loss (ADNSHL) is genetically heterogeneous. To date, 54 distinct loci have been identified through genetic linkage analysis of extended pedigrees. These loci are termed DFNA (DFN referring to deafness; A referring to dominant pattern of inheritance) followed by a number representing the order of discovery (e.g., DFNA1). The common clinical pattern of ADNSHL is that of postlingual progressive hearing loss, with onset in the second or third decade of life. Exceptions are DFNA2B, 10, 25, and 51, which, as with presbycusis, may not become clinically apparent until later in life. Additional exceptions are DFNA3, 6/14/38, 8/12, and 23, which cause prelingual deafness. The degree of progression and the audiometric frequency initially involved varies greatly with ADNSHL, depending on the genetic locus. Hearing loss progression in ADNSHL usually is incomplete, and most patients respond well to amplification. Some patients (i.e., DFNA1), however, do progress to complete hearing loss. As such, they are potential candidates for cochlear implantation.

Molecular genetic studies have elucidated the specific genetic abnormality in nearly half of the ADNSHL loci identified to date (Table 102.1). Examples of these genes include (a) membrane pores involved in signal transduction, such as the *KCNQ4* gene, which is a voltage-gated potassium channel at the DFNA2 locus; (b) connexins 26, 30, and 31, which are gap junction proteins at the DFNA3, DFNB1, and DFNA2 loci; (c) structural proteins, such as myosin VIIa, which causes DFNA11, DFNB2, and USH1B; (d) *COCH*, which causes DFNA9 and is a structural binding protein; (e) *TECTA*, a structural gene of the tectorial membrane, which causes DFNA12; (f) *COL11A2*, a collagen gene responsible for DFNA13; (g) developmental regulators, such as *POU4F3*, a transcription factor that causes DFNA15; (h) *HDIA1*, a gene with homology to the diaphanous gene in Drosophila, which causes DFNA1; and (i) several genes with unknown function (e.g., DFNA5).

Two genes with autosomal dominant inheritance have been linked to AN, *AUNA1*, and *PCDH9*. Starr et al. initially reported an extended large family with an auditory phenotype compatible with AN, segregating in a dominant fashion (22). Most affected patients had at least moderate SNHL, and many had a profound loss. These patients exhibited no other signs of neuropathies. Kim et al. subsequently identified the responsible gene as *AUNA1*, which is located on chromosome 13q14-21 (23). A recent study has identified two Italian families with AN but no mutations in the *AUNA1* gene. This group was found to have a mutation in protocadherin-9 (*PCDH9*), which is likely responsible for their AN (24).

Mutations in the *COCH* gene were found to be the cause of hearing loss in several large pedigrees (25). The hearing loss is present in the high frequencies during the second to fourth decades of life but progresses to profound in many patients by the fifth decade. Interestingly, many patients experience recurring bouts of vertigo similar to those seen in patients with Meniere disease. Usami et al. (26) found that *COCH* mutations were common in a significant proportion of Japanese patients with ADNSHL and vestibular symptoms, but *COCH* mutations were not identified in patients with classic Ménière disease. More recent work has identified a single region on chromosome 12p12 in three Swedish families, which may be responsible for Meniere disease in these patients (27).

Syndromic Dominant Disorders

Branchiootorenal Syndrome

Branchiootorenal (BOR) syndrome (also called Melnick-Fraser syndrome) is composed of conductive, sensorineural, or mixed hearing loss in association with abnormalities of branchial-derived structures (e.g., ear pits or tags, cervical fistulae) and renal anomalies that range from minor dysplasia, which usually is asymptomatic, to agenesis and renal failure. Cochlear dysplasia also is present in about 40% of patients, and its severity ranges from complete aplasia to a slightly smaller cochlea. BOR syndrome affects as many as 2% of children in schools for the deaf, thus emphasizing the importance of evaluating the renal status of any child with a hearing loss and an ear pit or branchial cleft anomaly (28) (Table 102.2).

TABLE 102.2 CLINICAL CRITERIA FOR BOR SYNDROME

Major Criteria	Minor Criteria
Branchial anomalies	*External ear anomalies*
Deafness	*Middle-ear anomalies*
Preauricular pits	*Inner ear anomalies*
Renal anomalies	*Preauricular tags*
	Other: facial asymmetry, palate abnormalities

The *EYA1* gene on chromosome 8q13 is the human homolog of the developmental Drosophila gene eyeless (Table 102.1). In 1997, Abdelhak et al. (29) first demonstrated that *EYA1* mutations were causal in BOR syndrome. *EYA1* encodes a transcript variant encoding 16 exons that span 159 kb of genomic DNA, translating into a protein of 559 amino acids. The putative function of the *EYA1* gene is that of a transcription factor involved in the morphogenesis of the ear, branchial structures, and kidney.

Based on historical data and loosely applied criteria for the diagnosis of BOR syndrome, only about 15% of affected persons had mutations in the *EYA1* gene. Based on more stringent contemporary criteria (Table 102.2), however, nearly 40% of patients have mutations in this gene. According to these criteria, BOR syndrome is defined as the presence of (a) three major criteria, (b) two major criteria and two minor criteria, or (c) one major criteria and an affected first-degree relative (30). Genetic testing for the *EYA1* gene is available in select laboratories.

Neurofibromatosis

Neurofibromatosis (NF) is a genetically heterogeneous disorder with two distinct forms, referred to as NF1 (classic neurofibromatosis) and NF2 (central neurofibromatosis). Both forms are associated with café au lait spots (light brown, variable-sized pigmented spots) and multiple fibromas; however, patients with NF2 have a lower prevalence of both of these cutaneous features. Both NF1 and NF2 have high penetrance but variable expressivity. Also, both have high mutation rates. NF1 is caused by a nerve growth factor gene (*neurofibromin*) on chromosome 17q11 (Table 102.1). NF2 is caused by the mutation of a tumor suppressor gene (*schwannomin*) on chromosome 22q12.

NF1 (also called von Recklinghausen disease) is diagnosed in approximately 1 of 3,000 persons per year. It is associated with a large number of café au lait spots and cutaneous neurofibromas, as well as plexiform neuromas, pseudoarthrosis

(particularly of the tibia), Lisch nodules of the iris, and optic gliomas. Although cutaneous tumors are the most common feature, also seen is involvement of the central nervous system, peripheral nerves, and viscera. The phenotype can be limited to a few café au lait spots or be expressed as multiple disfiguring tumors. Central nervous system lesions can produce mental retardation, blindness, or hearing loss, but these complications are uncommon. Although hearing impairment can be caused by a neurofibroma encroaching on the middle or inner ear, marked deafness is rare. True acoustic neuroma, which typically is unilateral, occurs in only 5% of patients. Children with this disorder require mandatory longitudinal audiologic follow-up evaluations.

NF2 is characterized by bilateral acoustic neuromas (vestibular schwannomas). These lesions usually grow slowly and are asymptomatic until young adulthood, when tinnitus and vestibular dysfunction often present. NF2 is associated with a higher risk of tumors of the central nervous system and spinal cord, but Lisch nodules and optic glioma are not present in affected patients. Genetic testing of the NF2 gene, which is available for presymptomatic family members who are at risk, facilitates early diagnosis and treatment.

Stickler Syndrome

Stickler syndrome is a relatively common genetic disorder characterized by typical facial characteristics (e.g., Robin sequence), hypermobility and enlargement of joints associated with the onset of arthritis in early adulthood, myopia severe enough to involve retinal detachment or cataracts, and occasionally spondyloepiphyseal dysplasia. Some degree of hearing loss occurs in as many as 80% of patients, and substantial sensorineural or mixed hearing loss, often progressive, is present in approximately 15%. The variation in expressivity that occurs with Stickler syndrome can be attributed to both allelic and genetic heterogeneity, which complicates diagnosis of the disorder.

Multiple types of Stickler syndrome are seen, each attributed to mutations in a different gene:

- Stickler syndrome type 1 (STL1) is the classic phenotype. It is associated with mutations in the *COL2A1* gene, a fibrillar collagen that is arrayed in quarterstaggered fashion to form fibers (Table 102.1). The STL1 phenotype includes cleft palate deformity, progressive myopia, vitreoretinal degeneration, premature joint degeneration with abnormal epiphyseal development, midface hypoplasia, irregularities of the vertebral bodies, and variable degrees of hearing loss. Different mutations of the same gene produce similar but more severe conditions, namely, Kniest syndrome and spondyloepiphyseal dysplasia congenita, both of which also include progressive SNHL (31).
- Stickler syndrome type 2 (STL2) is caused by mutations in the *COL11A1* gene. Persons with STL2 have the characteristic ocular, auditory, and orofacial features of STL1.
- STL3 is caused by mutations in the *COL11A2* gene, which result in a disease characterized by the typical facial features associated with STL1 together with hearing impairment. Cleft palate and mild arthropathy can also occur; however, ocular abnormalities (e.g., high myopia, vitreoretinal degeneration, and retinal detachment) are absent. The phenotypic differences between STL1 and 2 and STL3 can be explained by the absence of *COL11A2* in the vitreous (31).
- A fourth gene, *COL9A1*, can cause Stickler syndrome that is inherited in an autosomal recessive fashion (32).

Treacher Collins Syndrome

Treacher Collins syndrome (mandibulofacial dysostosis) is a craniofacial disorder with manifestations that include microtia, aural meatal atresia, and conductive hearing loss caused by ossicular chain malformations; the latter occurs in approximately 30% of patients. SNHL and vestibular dysfunction also can be present.

The hearing loss varies, depending on the degree of severity of the malformation of the ear, and ranges from mild to severe. As such, hearing reconstructive procedures are technically challenging. The usual facial findings are malar hypoplasia, including underdeveloped zygomatic arches with resultant downward slanting palpebral fissures, coloboma of the lower eyelids, and a hypoplastic mandible. Symmetric facies and bilateral eyelid coloboma differentiate this syndrome from Goldenhar spectrum and other oculoauricular vertebral syndromes that include similar but unilateral microtia and craniofacial abnormalities.

Penetrance is high and the oculoauriculovertebral spectrum is sporadic and thought to be multifactorial. The syndrome is often caused by an abnormality in the *TCOF1* gene, which functions in early craniofacial development. In as many as 60% of affected individuals, however, the disorder is caused by new mutations. The resulting protein has been named treacle (Table 102.1). Although no evidence indicates genetic heterogeneity, considerable inter- and intrafamilial variability are seen, indicating that other genes can modify the expression of the treacle protein (33).

Waardenburg Syndrome

Waardenburg syndrome (WS) exemplifies a syndrome with variable expressivity. This syndrome is characterized by varying degrees of unilateral or bilateral SNHL and various pigmentary anomalies (e.g., white forelock, heterochromia iridis, premature graying, and vitiligo) and variable craniofacial features (e.g., dystopia canthorum, broad nasal root, and synophrys). The white forelock is present in only 20% to 30% of cases, with a variable age of first appearance. Recent data have shown that enlarged vestibular aqueducts also are present in as many as 50% of patients (34).

There are four types of WS, with the most common being type 1 (WS1) and type 2 (WS2). These clinical types are distinguished on the basis of the presence of dystopia canthorum (WS1) or its absence (WS2). Hearing loss occurs

in approximately 20% of individuals with WS1 and more than 50% of those with WS2. Lateral displacement of the medial canthi may not be immediately apparent, and indices based on objective measures of the distances between anatomic landmarks (e.g., the inner canthi, pupils, and outer canthi) are helpful in making a determination. If only one or a few characteristics are present in each family member, definitive diagnosis of WS can be difficult. WS3 (Klein-Waardenburg syndrome) includes the features of WS1 and skeletal malformations, particularly of the hands and forearms. WS4 (Waardenburg-Shah syndrome) differs from the other three types in that it is a heterogeneous disorder with either autosomal recessive or autosomal dominant inheritance. Phenotypic features are similar to those of WS2; however, it occurs in association with Hirschsprung disease. The importance of obtaining a complete history of the extended family in questionable cases cannot be overemphasized. Audiologic screening of family members can help identify previously unsuspected unilateral hearing loss.

Six different genes for WS have been identified and located: *PAX3*, *MITF*, *SNAI2*, *EDNRB*, *EDN3*, and *SOX10*. Mutations in the *PAX3* gene cause WS1 and WS3 (35). This gene is located on chromosome 2q37 (Table 102.1) and controls some aspects of the development of the face and inner ear. Mutation of the mouse homolog of this gene produces a condition called splotch, which includes pigmentary and ocular abnormalities in the heterozygote (36). Only the homozygote has hearing loss, however, and has far more severe neural tube defects. Approximately 20% of cases of WS2 are attributable to a mutation of the microphthalmia-associated transcription factor (*MITF*) gene on chromosome 3p12-14. Again, a mouse homolog with mutation of the same gene is known, but these animals are not deaf in the heterozygous state. Recently, a second WS2 gene called *SNAI2* was identified on chromosome 8q11. Experimental evidence has shown that *MITF* activates the promoter of *SNAI2*, thereby linking these genes in the neural crest developmental pathway. WS4 can be caused by mutations in the endothelin-B receptor gene (*EDNRB*), endothelin 3 (*EDN3*), or *SOX-10*.

X-Linked Disorders

Sex-linked disorders are caused by genes on the X or Y chromosome. Because no known hearing loss genes are found on the Y chromosome, the disorders discussed in this chapter are all X-linked. This pattern of inheritance is uncommon in hearing disorders, accounting for only 1% to 2% of cases. It is, however, associated with up to 5% of nonsyndromic profound hearing loss in males.

Nonsyndromic X-Linked Disorders

Five loci on the X chromosome for nonsyndromic hearing loss are known. The most well-characterized phenotype is related to X-linked stapes fixation with perilymphatic gusher. This has been localized to the DFN3 locus, which encodes the *POU3F4* transcription factor, and is associated with progressive mixed hearing impairment. Females can have mild expression of this gene. The *POU3F4* gene is located close to a gene that causes choroideremia, which is a condition characterized by progressive vision loss secondary to atrophy of cells within the retina and choroid. Deletion of these genes produces the contiguous gene syndrome of choroideremia, hearing loss, and mental retardation. Preoperative temporal bone CT scanning can be used to detect predictive findings, such as an enlarged internal auditory canal with thinning or absence of bone at the base of the cochlea. Because of the high risk of a gusher, stapes surgery should be considered cautiously for any young male patient, particularly one with an X-linked family history or with choroideremia.

Syndromic X-Linked Disorders

Norrie Disease

Norrie disease is a rare congenital neurodevelopmental disorder characterized by rapidly progressive blindness with bilateral pseudoglioma and exudative vitreoretinopathy, opacification, and ocular degeneration that results in microphthalmia. Progressive SNHL, with onset in the second or third decade, affects approximately one-third of patients. In some families, progressive mental deterioration also occurs. The gene responsible for Norrie disease, *NDP*, produces a protein called norrin and appears to be a growth factor similar to transforming growth factor β, which is responsible for vasculogenesis. Some families have variable deletions in this chromosomal region, and deletions involving contiguous genes, particularly the monoamine oxidase genes, may account for the variable finding of mental deficiency. On the other hand, mutations entirely within the *NDP* gene also have produced progressive mental retardation (37).

Otopalatodigital Syndrome

Otopalatodigital syndrome consists of hypertelorism, craniofacial deformity involving the supraorbital area, flat midface, small nose, and cleft palate. Affected persons are short, have broad fingers and toes that vary in length, and have an extremely wide space between the first and second toes. Conductive hearing loss usually is caused by an ossicular malformation, which may be amenable to surgical intervention. Female carriers can have mild manifestations of the disorder. The gene has been mapped to Xq28 (38).

Wildervanck Syndrome

Wildervanck syndrome comprises the Klippel-Feil malformation involving fused cervical vertebrae, sensorineural or mixed hearing loss related to bony malformation of the inner ear, and paralysis of the sixth cranial nerve, which causes retraction of the eye on lateral gaze (Duane retraction syndrome). Hearing loss in Wildervanck syndrome almost always occurs in females, raising the possibility of X-linked

dominant inheritance or polygenic inheritance with lethality in males. Isolated Klippel-Feil sequence includes hearing loss in approximately one-third of cases, but it is rarely familial. Hearing loss also can be associated with Duane retraction syndrome in a small percentage (less than 10%) of cases (39).

Alport Syndrome

Alport syndrome is characterized by varying degrees of progressive SNHL and with progressive glomerulonephritis that leads to end-stage renal disease. Hearing loss may not become manifest until the second decade of life. Renal disease, which can manifest as hematuria in infancy ("red diaper"), usually remains asymptomatic for several years before its onset. This component is especially severe in males, often causing death from uremia before 30 years of age. Early diagnosis of this syndrome is essential to facilitate management of the renal disease. Alport syndrome is genetically heterogeneous, with X-linked inheritance accounting for 85% of cases, caused by mutation of a type 4 collagen gene (*COL4A5*) (40). Mutations of *COL4A3* and *COL4A4* produce an autosomal recessive form of Alport syndrome, but expression still is more severe in males. Fechtner syndrome is a similar autosomal dominant disorder, which is associated with progressive hearing loss, renal disease, and macrothrombocytopenia.

Deafness Dystonia Optic Atrophy Syndrome

Deafness dystonia optic atrophy syndrome (Mohr-Tranebjaerg syndrome) is a rare neurodegenerative syndrome characterized by progressive SNHL, vision loss, dystonia, fractures, and mental deterioration. It is caused by a mutation of *TIMM8A* (initially named *DDP*, Deafness Dystonia Peptide), which is involved in the translocation of proteins across the inner mitochondrial membrane into the mitochondrial matrix (41,42).

MITOCHONDRIAL DISORDERS

Mitochondria are cytoplasmic organelles that contain small pieces of nonnuclear DNA in a ring form. Each mitochondrion contains two to ten copies of the mitochondrial genome. Each copy is composed of approximately 16 kb, which contain the genes for messenger, ribosomal, and transfer RNA needed for the synthesis of mitochondrial proteins. These proteins interact with proteins encoded by the nuclear chromosomes to facilitate energy production through synthesis of adenosine triphosphate and oxidative phosphorylation. Mutations in the mitochondrial genome can affect this energy production. As a result, tissues that require high levels of energy (e.g., muscle) are disproportionately affected. The mutation rate of mitochondrial DNA exceeds that of nuclear DNA because the DNA repair mechanisms in the mitochondria are less effective.

Mitochondrial inheritance is distinctly different from the inheritance pattern of nuclear genes. Because sperm transmit few or no mitochondria, nearly the entire contribution is from the egg. The result is matrilineal inheritance that affects male and female offspring equally. If a mother is homoplasmic for a mitochondrial mutation, all of the offspring are affected. Among hundreds of mitochondria in each cell, only a small fraction can contain a specific mutation, a condition known as heteroplasmy, and different percentages of mutated mitochondria can be present in different tissues.

Mitochondrial Nonsyndromic Hearing Loss

Recently, progress has been made in understanding the association of mitochondrial mutations with nonsyndromic hearing loss and ototoxicity. Several mutations in the 12S rRNA and the $tRNA^{ser}$ genes have been genetically and biochemically linked to hearing loss. Of particular clinical relevance, patients with 12S rRNA mutations have been found to have a genetic predisposition to aminoglycoside-induced hearing loss. Milder hearing loss can be expressed among family members with these mutations who have not been exposed to aminoglycosides (Fig. 102.5). The 961, 1,494, and 1,555 loci are linked to the genetic predisposition to aminoglycoside-induced hearing loss. The A1555G mutation is the one most reported, but a variety of mutations at the 961 loci may prove to be more prevalent. It is estimated that 1,555 mutations are present in about 2% of the hearing loss population and about 0.5% of the general population in the United States. Mitochondrial mutations that predispose patients to aminoglycoside ototoxicity may be present in 1% to 2% of newborns. The relatively high prevalence of these mutations would render 12S rRNA genetic screening valuable to neonatologists. The mechanism of this ototoxic effect may be related to these mutations, making the12S rRNA structurally similar to the 16S rRNA found in bacteria. The bacteriocidal effect of aminoglycosides has been found to occur in the16S rRNA (43).

Because gradual accumulation of mitochondrial mutations in affected tissues can worsen the phenotype over time, some authors have postulated a mitochondrial role in presbycusis. As yet, however, no definitive evidence exists. Additionally, a few families reportedly have nonsyndromic hearing loss because of the combination of a mitochondrial mutation and a recessive mutation in the nuclear gene.

Mitochondrial Syndromic Disorders

Mitochondrial diseases typically involve progressive neuromuscular degeneration with ataxia, ophthalmoplegia, and progressive hearing loss. Syndromes involving SNHL include the following:

- Mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS). Hearing loss occurs in approximately 30% of patients. Findings are highly variable and can include intermittent vomiting, limb weakness, and stroke-like episodes, which can result in hemiparesis and cortical blindness. It is often associated with short stature.

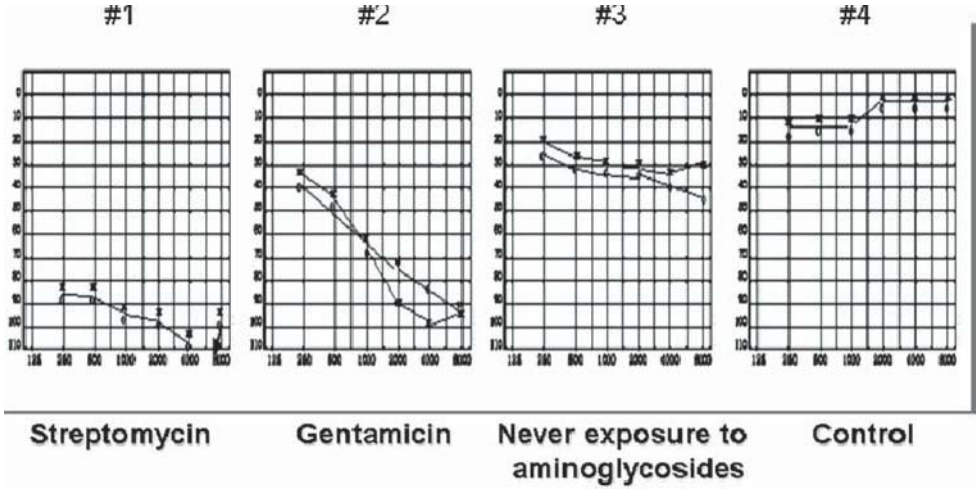


Figure 102.5 Representative audiograms of a family with #1 to 3 having a mutation in the 12SrRNA gene while #4 in unaffected. #1 and #2 received aminoglycoside antibiotics and develop significant hearing loss. Patient #3 only had a mild hearing loss phenotype from the mutation.

- Maternally inherited diabetes and deafness (MIDD). This condition has been attributed to a unique mitochondrial mutation in the same $tRNA^{lys}$ gene that causes MELAS. Additionally, cases of MIDD have been linked to large deletions, insertions, and point mutations in the $tRNA^{glu}$ gene (44).
- Kearns-Sayre syndrome. In addition to SNHL, findings include ataxia, heart block, progressive ophthalmoplegia, and retinopathy.
- Myoclonic epilepsy with ragged red fibers. In addition to variable degrees of SNHL, findings include ataxia, epilepsy, myoclonus with dementia, and optic atrophy occurring in some cases.

CHROMOSOMAL SYNDROMES

Down Syndrome

Middle-ear and mastoid disease are often seen in children with Down syndrome (Trisomy 21), but SNHL may also be present. Careful audiologic and tympanometric follow-up evaluation are essential. Trisomy 13 is often lethal in the newborn period, but survivors can have marked SNHL.

Turner Syndrome

Turner syndrome, monosomic for all or part of one X chromosome, generally presents in females as gonadal dysgenesis, short stature, and often a webbed neck or shield chest. Sensorineural, conductive, or mixed hearing loss can be present. Hearing loss can be progressive and can constitute the first evidence of the syndrome in prepubescent girls.

MULTIFACTORIAL GENETIC DISORDERS

Some genetic disorders cannot be attributed to the action of a single gene but are caused by the interaction of genetic factors and environmental influences. Clefting syndromes that are associated with conductive hearing loss and the Goldenhar spectrum are both examples of this type of inheritance. In the latter, a positive family history can be found in approximately 6% of cases, but different aspects of the spectrum can occur even within the same family. Findings include preauricular tags or pits, vertebral anomalies (e.g., hypoplastic vertebrae or hemivertebrae in the cervical region), epibulbar dermoids, and coloboma of the upper lid. The Goldenhar spectrum (also called oculoauriculovertebral dysplasia) has been described in some families as being inherited in an autosomal dominant pattern but clustering in a single family. Other conditions thought to represent multifactorial inheritance are the increased susceptibility to hearing loss that is associated with diabetes and hyperlipidemia.

Otosclerosis

Clinical otosclerosis has a reported prevalence of 0.2% to 1% among white adults, making it the single most common cause of hearing impairment in this population. The mean age of onset is in the third decade of life, and 90% of affected persons are younger than 50 years of age at the time of diagnosis. A preponderance of women are affected, suggesting a possible hormonal influence. This disorder is characterized by isolated sclerosis of the endochondral bone of the inner ear. Conductive hearing loss develops when otosclerotic foci invade the stapediovestibular joint (oval window) and interfere with the free motion of the stapes. SNHL also may be present. Histopathologic examination shows measles virus particles within the bony overgrowth, indicating the possibility of an interaction with the viral genome.

Although in most patients the cause of otosclerosis is unknown, studies of large families with this disorder indicate an autosomal dominant inheritance pattern with incomplete penetrance. Penetrance rates ranging from 25% to 40% have been estimated. Genetic heterogeneity is likely, and some genes are more penetrant than others. Although no specific genes have been identified, seven loci have been mapped in these families.

HEARING LOSS EVALUATION AND GENETIC COUNSELING

Great strides have been made in identifying hearing-impaired infants. Early detection and hearing intervention (EDHI) programs are currently ongoing in a large number of centers throughout the United States. These programs are based on what is referred to as the "one-three-six rule" (45). Hearing screening is carried out before 1 month of age, definitive audiometric evaluation is performed before 3 months of age, and enrollment in rehabilitation programs is accomplished by 6 months of age. To date, 42 states have legislated EDHI programs. In the remaining states, many medical centers have initiated voluntary newborn screening programs.

When faced with pediatric patients with an identified hearing loss, clinicians must carefully review the prenatal, perinatal, and postnatal medical history. They should assemble a detailed family history, including a pedigree chart that includes third-degree relatives. Queries should be directed toward determining the health and hearing status of other family members who may have subtle manifestations (e.g., ear pits) that could represent variable phenotypic expressing of a hearing loss syndrome. Previous audiologic data from the patient and other family members should also be reviewed to validate the history and determine whether familial progressive hearing loss is involved. Also, a thorough physical examination should be performed to detect subtle signs of a possible genetic syndrome. Depending on the history and physical findings, other clinical consultations (e.g., genetics, ophthalmology), radiographic imaging, and laboratory studies may be needed.

In the past, a simultaneously conducted, comprehensive diagnostic evaluation was advocated for pediatric patients with SNHL. Recently, however, data have shown that a stepwise evaluation is a far more prudent and cost-effective paradigm (46). Children with bilateral severe-to-profound SNHL should undergo genetic screening as the initial step, whereas children with milder types of SNHL or unilateral SNHL should undergo imaging first (46). Additional genetic testing for mitochondrial mutations, *GJB6* and *SLC26A4*, are also available for select patients.

Genetic counseling provides parents with information regarding the cause of their child's hearing loss and the expected pattern of inheritance of a genetic disorder. Counselors, as well as other members of the otologic team, must realize that a number of unique clinical and genetic situations can arise. First, they may encounter couples who are deaf. These couples may not view having a deaf child as a burden. Rather, they may be proud of their heritage, their language (American Sign Language), and the accomplishments of deaf persons throughout history. Sensitivity to this perspective is essential, as is the availability of an interpreter who can communicate genetic terminology (47). Even in marriages in which both persons are deaf, unless the partners have an identical genetic cause of the hearing loss, the actual risk of having an affected child is slight. Second, all professionals should be aware that mitochondrial disorders have a unique inheritance pattern that is often missed. The risk of a mitochondrial disorder depends on whether the mother is homoplasmic or heteroplasmic and whether other genetic or nongenetic factors are necessary for expression. Offspring of a man with a mitochondrial disorder are not at risk. Lastly, a problem commonly encountered with nonsyndromic hearing loss is the presence of phenocopies, which are two distinct causes having the same phenotype. For example, a clinician may be faced with a patient who has an infection-related or environment-related hearing loss. This patient may belong to a family with a history of genetic hearing loss. These phenocopies would make gene identification studies and the clinical prediction of recurrence risk very difficult.

In sum, rapid advances in molecular genetics have had a direct impact on clinical practice, and it is essential that clinicians responsible for the management of pediatric patients with heritable hearing loss become familiar with these advances. The future holds the promise of effective strategies to accurately screen for, diagnose, prevent, and ameliorate these losses.

HIGHLIGHTS

- Several population studies have estimated that 50% of cases of childhood hearing loss are caused by genetic factors. Of these, 75% to 80% involve autosomal recessive genes; the remainder are dominant, X-linked, mitochondrial, and chromosomal.
- Genetic hearing loss can be congenital or delayed in onset, progressive or nonprogressive, unilateral or bilateral, and syndromic or nonsyndromic. Genetic hearing loss syndromes are commonly classified according to the other systems involved. Nonsyndromic hearing disorders are classified according to audiologic characteristics, age at onset, presence or absence of progression, and mode of inheritance.
- Human genes are arranged linearly on 23 pairs of chromosomes, composed of 22 pairs of autosomes and 1 pair of sex chromosomes. A gene can have several alternative codes or alleles. The genotype for a specific trait can consist of two identical alleles (hemizygous) or two different alleles (heterozygous).
- Phenotype is determined by which alleles are present and how they interact. A dominant allele is expressed in the homozygous or heterozygous state, whereas an autosomal recessive allele is expressed only in homozygotes. Recessive X-linked genes are expressed in males but usually not in female carriers. Certain dominant genes have variable

penetrance and expressivity, even within the same family. Heritable disorders also can be caused by abnormalities at the chromosomal level.

- Autosomal dominant disorders associated with hearing loss include WS, Stickler syndrome, BOR syndrome, Treacher Collins syndrome, NF, otosclerosis, and at least four forms of nonsyndromic hearing loss.
- Autosomal recessive disorders associated with hearing loss include Usher syndrome, Pendred syndrome, JLN syndrome, and at least three subtypes of nonsyndromic hearing loss. Mutations of the *GJB2* gene account for the cause of hearing loss in up to 50% of all patients presenting with autosomal recessive SNHL.
- Major X-linked disorders that include hearing loss are Norrie disease, otopalatodigital syndrome, Wildervanck syndrome, Alport syndrome, and several types of nonsyndromic congenital severe SNHL. Examples of multifactorial inheritance are clefting syndromes and the Goldenhar spectrum.
- Mitochondrial-related hearing loss accounts for about 2% of cases of SNHL. Some cases have multisystem involvement, but most are thought to be nonsyndromic. Of particular clinical relevance, specific mutations in the 12S rRNA gene are related to aminoglycoside ototoxicity.
- Counseling about genetic hearing loss is complex because family histories often involve a number of marriages between deaf persons with hearing losses of uncertain causation. A sequential evaluation paradigm is warranted, with genetic testing being the cornerstone of the evaluation.

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103 Comprehensive Cleft Care

Alexander J. Davit III *Todd Otteson* *Joseph E. Losee*

Despite the numerous advances in caring for patients affected with cleft lip and/or palate (CL/P), parents who learn their child is affected can often feel considerable anxiety and confusion over the significance of this diagnosis. In order to better care for cleft patients and their families, treatment protocols have evolved that utilize a multidisciplinary team-based approach, incorporating skills offered by several subspecialties, including otolaryngology, plastic surgery, orthodontics, pediatric dentistry, speech pathology, audiology, psychology, and social services. Each discipline is focused on delivering coordinated, comprehensive care to the cleft patient.

Numerous authors have written extensively on this challenging subject; this chapter is intended to serve as a detailed outline for the evaluation and treatment of patients affected with CL/P, focusing on the salient points of comprehensive cleft care. At the Children's Hospital of Pittsburgh of UPMC, our cleft team focuses on every stage in each patient's development where intervention may be considered to benefit the patient. It is important to recognize that caring for the child with a cleft is a long-term process, extending from infancy into early adulthood, and is a journey with several important "stops" along the way. During the child's first year of life, the primary focus of care is in promoting proper nutrition and growth, while also performing the initial soft tissue reconstructions. Repairing the CL/P in a skilled manner is of utmost importance, thereby laying the foundation for the patient's future facial appearance, but it is hardly the final procedure for most patients today. After infancy, a major focus is on speech outcomes, when selected patients may benefit from revisional speech surgery to address velopharyngeal insufficiency. During the period of mixed dentition, the patient is evaluated for alveolar bone grafting and "touch up" revisional soft tissue procedures to the lip and nose. In late adolescence, patients are considered for orthognathic surgery and definitive rhinoplasty to refine the patient's "final result." During this entire process, the cleft team routinely follows patients in order to assess their individual needs with regard to appearance, psychosocial development, speech, hearing, orthodonture, and dentistry. Comprehensive team care of the cleft patient can be a clinically gratifying endeavor, one that necessitates a multidisciplinary approach to deliver reproducible, high-quality results for the patient.

EPIDEMIOLOGY: INCIDENCE AND GENETIC FACTORS

CL/P is one of the most common congenital anomalies: the prevalence in North America is currently 0.2 to 2.3 cases per 1,000 population, while the prevalence of isolated cleft palate (CPO) is 0.1 to 1.1 cases per 1,000 (1,2). For CL/P, these rates vary between ethnic subgroups: 3.6 per 1,000 in Native Americans, 2.1 per 1,000 in Asians, 1 in 1,000 in Caucasians, and 0.41 per 1,000 in African Americans (1,3,4). CPO has a relatively stable incidence across ethnic subgroups (1). The male to female ratio for CL/P is 1.5 to 2.0:1 (2). For CPO, the converse is true; females are more commonly affected, with a male to female ratio of 1:2 (2).

Development of CL/P or CPO is believed to be a complex, multifactorial process involving multiple risk factors, genetic mutations, family history of orofacial clefting (OFC), maternal diseases and behaviors, fetal exposure to teratogenic medications, and nutritional deficiencies or excesses. A positive family history of OFC has long been recognized as a strong risk factor and was first studied in 1942, when Fogh-Anderson began to apply statistical analysis to familial inheritance patterns of CL/P (1). Genetic studies in both humans and mice have identified transforming growth factor beta 3 (TGFβ3) and msh homeobox 1 (MSX1) as genes that play an important part in the development of CL/P (1).

While most cases of CL/P and CPO are nonsyndromic, there are a multitude of genetic syndromes that may be associated with CL/P and CPO. The most common syndrome associated with CL/P is Van der Woude syndrome, an autosomal dominant syndrome characterized by blind lower lip pits in addition to CL/P (5). The most common syndromic diagnoses associated with CPO are the autosomal dominant syndromes caused by microdeletions or additions of chromosome 22q11.2: DiGeorge syndrome, conotruncal anomaly face syndrome, and velocardiofacial syndrome; these have an incidence rate of 1:4,000 live births (5,6). Other syndromes associated with CPO include Stickler syndrome, popliteal pterygium syndrome, and ectrodactyly ectodermal cleft syndrome (5).

Environmental factors are also believed to play a pivotal role in the development of CL/P. These factors can be grouped into several categories: maternal health, teratogenic substances, and nutritional factors. The association between birth defects and maternal illnesses such as diabetes mellitus and gestational diabetes has been studied extensively; an increased incidence of congenital malformations is notably higher in patients with diabetes mellitus, but not gestational diabetes (2). Maternal obesity has also been studied as a risk factor for CL/P and CPO, and women with a BMI greater than 29 kg/m^2 have been shown to have a 1.3 times higher risk of having a child with a cleft when compared to women with nonobese BMI values (2). Teratogenic medications associated with development of CL/P include valproic acid, phenytoin, retinoic acid, dioxin, and thalidomide (1). Maternal tobacco smoking has been implicated in the development of OFC: CL/P and CPO are approximately 1.2 times more likely than in the general population (2). Although the children of women who consume heavy amounts of alcohol during pregnancy are known to be at increased risk for congenital malformations, the specific relationship between the development of OFC and maternal alcohol consumption remains unknown (2). Based on previous animal studies, maternal folic acid supplementation has frequently been considered to have a protective effect with regard to CL/P, although in a case–control study in the United Kingdom, higher maternal folic acid intakes were not associated with a lower incidence of OFC (7).

EMBRYOLOGY

Embryologic formation of the nose and upper lip begins during the fourth week of gestation, when the bilaminar prechordal plate containing ectodermal and endodermal elements is formed. This structure gives rise to the stomodeum, or primitive mouth, about which five facial prominences develop: the frontonasal prominence, paired maxillary prominences, and paired mandibular prominences (8).

Development of the upper lip and nose is controlled by several developmental pathways, including sonic hedgehog (SHH), wingless type (Wnt), bone morphogenic protein (BMP), and fibroblast growth factor (FGF) (9). Fusion of the frontonasal and maxillary processes begins to evolve in the anterior face at approximately 32 days' gestation, when the ventrolateral aspects of the frontonasal prominence undergo cellular proliferation to form the nasal placodes, which in turn give rise to the medial and lateral nasal processes (9). During this process, the maxillary processes also undergo rapid mesenchymal growth, and at the 38th day of gestation, fusion commences between these processes and the lateral and medial nasal prominences, approximating the distal tips of the medial and lateral nasal processes, eventually causing contact and fusion between them (9,10) (Fig. 103.1). Further development of the upper lip and nose follows, with the continued growth of the maxillary processes causing anteromedial positioning of the nasal pits, which undergo further maturation into the nasal ducts (9). Upper lip development is typically complete by the 48th day of gestation, once the interposed epithelial elements have undergone apoptosis and the remaining mesenchymal elements undergo final fusion between the maxillary and medial nasal prominences, to be followed by anteroposterior formation of the primary and secondary palate (9).

Palatal anatomy is subdivided into the primary and secondary palates, with the primary palate being formed by the frontonasal prominence and the secondary palate being formed by the paired lateral maxillary prominences (8). In the eighth week of normal embryologic development, the tongue begins to be withdrawn from its position between the lateral maxillary prominences, and they begin to shift from a vertical to horizontal orientation, ultimately undergoing fusion in the normal fetus (8). Several different mechanisms are believed to contribute to this vertical migration, including increased mesenchymal proliferation, increased tissue fluid content, and multiple signaling pathways, including platelet-derived growth factor, FGF10, SHH, and TGFβ3 (8). Once the palatal shelves meet in the midline, the line of fusion forms in the midpoint of the hard palate, later progressing both anteriorly and posteriorly from this point (8).

PRENATAL DIAGNOSIS AND COUNSELING

Prenatal diagnosis of CL/P, along with other developmental anomalies, has become more common with the widespread use of screening ultrasonography. It is important to recognize that approximately 50% of children with cleft lip and alveolus have other anomalies as well; 22% have an abnormal karyotype (11). In several large studies, it was possible to identify an isolated cleft lip deformity by ultrasound approximately 30% to 55% of the time at 24 weeks' gestation (11,12). The high variability in detection rates is believed to be due to differences in each center's ultrasonographic examination protocols (12). The ability to identify CPO on ultrasound is significantly lower,

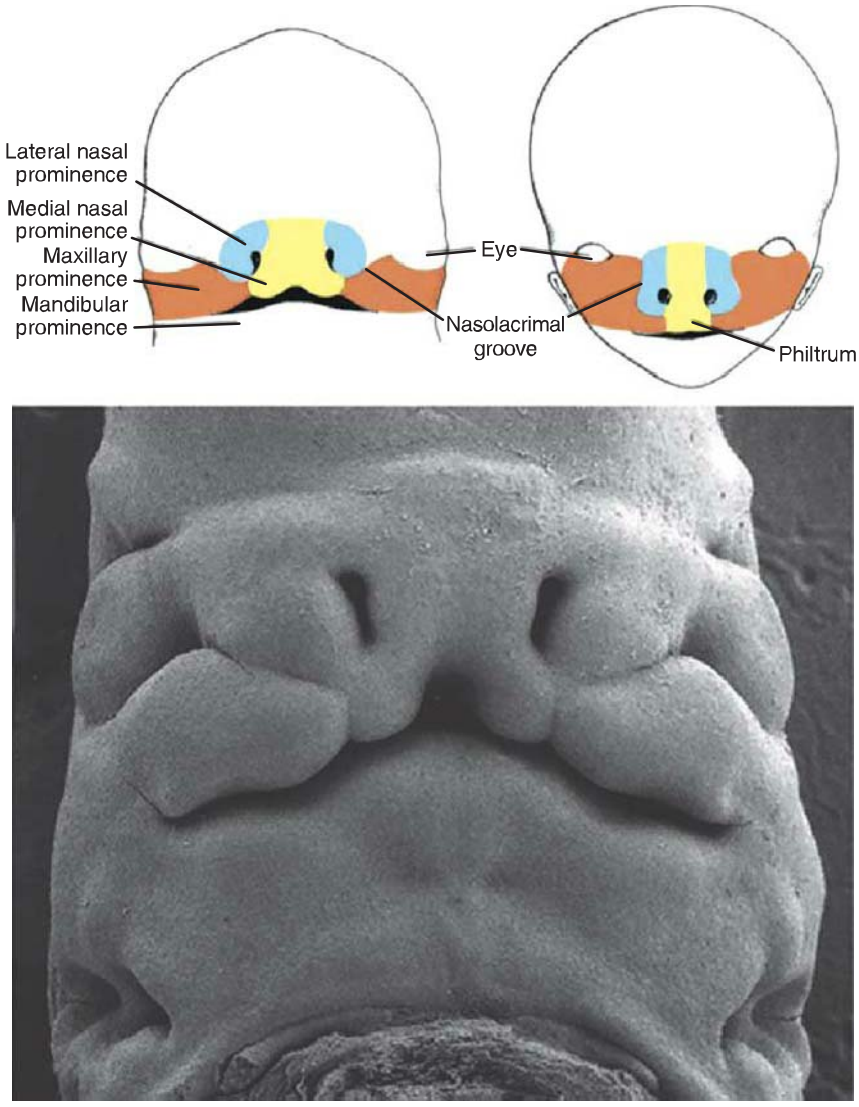


Figure 103.1 Facial development in the embryo. Note the development of the upper lip, philtrum, and nose from the maxillary, medial nasal, and lateral nasal prominences. (From van Aalst J, Kolappa KK, Sadove M. Nonsyndromic cleft palate. *Plast Reconstr Surg* 2008;121(1):1–14, with permission.)

with a rate of 1.4% in the Eurofetus study (11). Detection rates with newer imaging modalities, such as 3-D ultrasound and MRI, have yet to be fully elucidated at this time.

The goal of detecting OFC in the prenatal period is to allow parents to obtain appropriate genetic counseling, emotional support, and treatment planning. In counseling parents with regard to CL/P, it is important to discuss the potential recurrence risk, so informed choices with future family planning may be made. Population studies have determined the statistical risk of having a second child with CL/P or CPO. In first-degree relatives of patients with a nonsyndromic OFC, the risk of having a child with CL/P is approximately 3% to 4% (13). For patients affected with CPO, the risk for first-degree relatives is approximately 1.8% (13). For an affected parent with CL/P who already has one affected child, the recurrence risk is approximately 10% to 17% (5,8). For an affected parent with CPO who already has one affected child, the risk is slightly lower, 8% to 15% (13) (Table 103.1).

TABLE 103.1 FAMILIAL RISKS FOR NONSYNDROMIC CLEFT LIP AND PALATE

Family History	Cleft Lip ± Cleft Palate	Cleft Palate
No family history of cleft lip or cleft palate	0.1%	0.04%
Unaffected patients with		
One previously affected child	4%	2%
Two previously affected children	9%	1%
One affected parent	4%	6%
One affected parent and one previously affected child	17%	15%

± = with or without

From Kirschner RE, LaRossa DD. Cleft lip and palate. *Otolaryngol Clin North Am* 2000;33(6):1191–1215, with permission.

FEEDING THE CLEFT PATIENT

Establishing a reliable oral feeding strategy is critical for patients born with OFC. Patients with wide, complete clefts often have significant initial challenges with oral feeding, since the cleft prevents them from making an adequate seal on the bottle or breast (14). This can lead to inefficient suckling, resulting in the infant tiring more readily. Because of the ineffectual seal, patients often swallow a significant amount of air during feeds and require more aggressive burping during and after feeding. Most cleft patients will be able to feed well orally with the assistance of bottles with softer nipples and/or a valve flow control system. In addition, modified positioning that places the infant's head in a more vertical position helps to avoid significant reflux and air swallowing in many patients (14). Specialized nipple and bottle kits used for feeding cleft patients include the Mead-Johnson Cleft Palate Feeder, the Pigeon Cleft Palate Nipple and Bottle, and the Special Needs Feeder (Haberman Feeder). These special bottles can be made available and demonstrated to the cleft patient's parents well in advance of their due date—during their prenatal educational appointment (14). Prenatal counseling regarding the use of these techniques is important for families to be well prepared for the challenges of feeding the cleft patient. Cleft patients without other medical issues requiring hospitalization are discharged home once able to ingest appropriate quantities of breast milk or formula to prevent malnutrition and dehydration, and the family is instructed to follow up in the cleft clinic in the week after discharge. Patients should return to their birth weight by their 2-week postnatal examination and should thereafter gain approximately 0.5 to 1 oz./day (14). Frequent reevaluations early in the patient's life ensure that the patient is monitored for any signs or symptoms of malnutrition or dehydration, which may require medical intervention.

ANATOMY AND CLASSIFICATION OF THE CLEFT DEFORMITY

Unilateral Cleft Lip Anatomy

The anatomy of the upper lip and nose is complex and involves several important structures: the nasal alae, the columella, the nasal septum, the philtrum of the upper lip, the wet and dry vermillion, the orbicularis oris muscles, and the oral commissures. These structures are affected differently in patients with unilateral and bilateral clefts. In the unilateral cleft, there is an imbalance of the lip/nasal morphology, causing the medial premaxillary segment to rotate externally and upward, while also causing internal and posterior rotation of the lateral minor maxillary segment (5). The orbicularis oris muscle is abnormally inserted into the anterior nasal spine at the base of the columella on the nonclefted side and the nasal alar base on the clefted side (5). The clefted side's lower lateral cartilage is typically flattened and displaced posterolaterally, and the middle crus (dome) of the lower lateral cartilage is separated from the noncleft middle crus (5). The caudal septum is frequently dislocated from the vomerine groove and displaced into the nonclefted nostril (5).

Bilateral Cleft Lip Anatomy

In patients with a complete bilateral cleft lip, the premaxillary segment is positioned more anteriorly than in nonclefted patients, due to its lack of fusion with the lateral maxillary segments. The prolabium does not contain orbicularis oris muscle, and the vermilion and white roll are significantly deficient. The nasal deformity is fairly uniform and consists of flared nasal alar bases, a wide and flat nasal tip, and a short columella (5). Incomplete bilateral clefts have similar features, although the protrusion of the premaxillary segment is less severe than that of patients with a complete deformity.

Palatal Anatomy

The palate may be divided into the primary palate and the secondary palate; the primary palate (premaxilla) is located anterior to the incisive foramen, and the secondary palate located posterior to the incisive foramen (15). The secondary palate is further subdivided into the hard palate posterior to the incisive foramen and the velum, or soft palate. The velum contains five paired muscles: the muscularis uvulae, the palatoglossus, the palatopharyngeus, the levator veli palatini (LVP), and the tensor veli palatini (TVP) (16). The muscularis uvulae originates anteriorly on the tensor aponeurosis in the midline and extends posteriorly in the midline to the uvula (16). The palatoglossus muscle originates from the dorsolateral aspect of the tongue and extends within the anterior tonsillar pillar to insert into the velum (15,16). The palatopharyngeus muscle originates from the superior pharyngeal constrictor and extends within the posterior tonsillar pillar to insert into the velum, dividing into a superior oral head and an inferior nasal head, both enveloping the LVP muscle within the velum (16). The TVP originates from the eustachian tube (ET) and greater wing of the sphenoid, coursing anteriorly around the hook of the hamulus and inserting medially upon the tensor aponeurosis (15). In Huang's anatomic dissection of the paratubal muscles, the LVP was found to originate from the junction of the bony and cartilaginous portions of the eustachian tube, rather than the quadrate region of the petrous temporal bone as previously described (17).

Clefts of the soft palate alter the ability of the velum to obturate the nasopharyngeal port and have a relatively predictable anatomic structure. Rather than coursing medially to coalesce in the midline of the middle third of the velum,

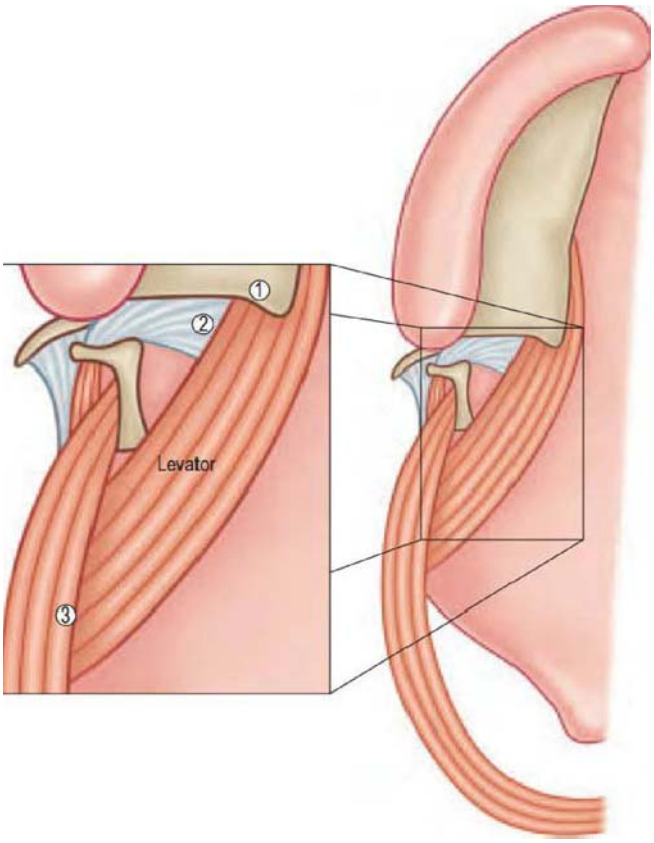


Figure 103.2 The three abnormal insertion points of the levator palatini muscle—*1.* posterior edge of the hard palate, *2.* TVP aponeurosis, *3.* superior pharyngeal constrictor muscle. (From Losee JE, Smith D. Cleft palate repair. In: Butler CE, ed. *Head and neck reconstruction.* Philadelphia, PA: Saunders Elsevier, 2009:275, with permission.)

the paired LVP muscles follow a more anterior direction to insert upon the posterior edge of the hard palate. In patients with cleft palate, the LVP has three abnormal attachments: the superior pharyngeal constrictor, the tensor aponeurosis, and the posterior edge of the hard palate (15) (Fig. 103.2).

Anatomical Classification Systems

Multiple classification systems for CL/P have been proposed; each has its own merits and limitations. These systems range from simple lettering systems, such as Kriens' LAHSHAL system, to Millard's modification of Kernahan "striped-Y" (18). At our institution, we prefer to use the LAHSHAL system for clefts of the lip and alveolus, given its simplicity and ability to address complete, incomplete, and submucous cleft anatomy. The LAHSHAL descriptive system represents the patients Lip, Alveolus, Hard palate, Soft palate, Hard palate, Alveolus, Lip anatomically from right to left. It is convenient in that it allows the clinician to categorize the cleft with the use of capital letters to signify a complete cleft, small letters to signify an incomplete cleft, an asterisk to signify a submucous or microform cleft, and an "X" to signify a normal structure. Hence, a left-sided complete cleft of the lip, alveolus, hard palate, and soft palate would be: "XXXSHAL." An incomplete right-sided lip and cleft of the soft palate would be: "lXXsXXX" (Fig. 103.3). For similar reasons, we utilize the Veau classification system for clefts affecting only the palate. The Veau classification system for cleft palate deformities is also simple and convenient: Veau I clefts involve only the soft palate; Veau II clefts involve the hard and soft palate; Veau III clefts are unilateral complete clefts of the alveolus, hard, and soft palate; and Veau IV clefts are bilateral complete clefts of the alveolus, hard, and soft palate. Often the Veau III and IV clefts are associated with clefts of the lip (15).

SURGICAL MANAGEMENT OF THE PRIMARY DEFORMITY: SEQUENCING AND TIMING

There is no "cookbook" approach to cleft care, and each patient requires an individualized treatment plan. As an example, patients presenting to large cleft centers may live several hours away. This distance may present a logistical barrier to the use of innovative presurgical treatments, like presurgical infant orthopedics (PSIO), that often require weekly visits for up to several months. If this is the reality, then prior to definitive surgery for the lip and nose, a lip adhesion procedure may be considered as an alternative to PSIO. While there is a general "timeline" for the overall surgical care of these patients, an individualized approach is preferred, taking into consideration the patient's and family's particular needs.

Presurgical Infant Orthopedics

Presurgical infant orthopedics (PSIO) is a treatment started early in a cleft patient's life. The goal of PSIO is to realign the clefted maxillary shelves, bring the widely separated lip margins together, and reshape the nose, "setting-up" and facilitating the surgical reconstruction. PSIO modalities include active techniques such as the Latham appliances or passive techniques such as lip taping or nasoalveolar molding (NAM). NAM, a passive form of PSIO, has gained popularity among cleft centers and is generally started in patients with complete unilateral or bilateral clefts at approximately 1 week of age. Weekly evaluations with modification of the NAM device to mold the lip, alveolus, and nasal ala are continued until the patient is 3 to 4 months of age, immediately prior to definitive repair of the cleft lip/nose deformity. In patients with complete clefts who are not candidates for NAM, lip adhesion surgery may be performed at approximately 1 to 2 months of age. Originally described in 1960 by Johansson and Olson (1960), staged lip repair with lip adhesion as the initial procedure has been utilized in patients with wide complete clefts in order to convert

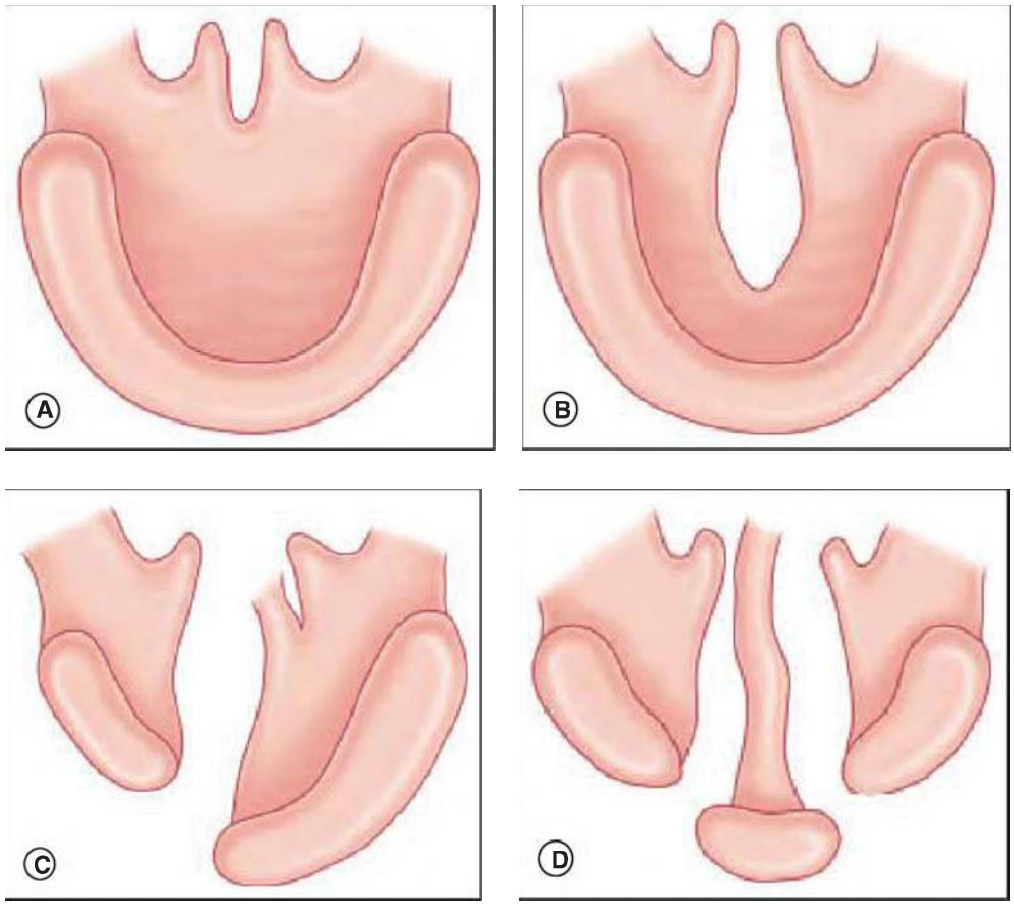


Figure 103.3 Veau classification system for cleft palate. **A:** Veau I cleft of soft palate. **B:** Veau II cleft of soft and hard palates. **C:** Veau III cleft of unilateral hard and soft palates. **D:** Veau IV bilateral cleft of hard and soft palates. (From Losee JE, Smith D. Cleft palate repair. In: Butler CE, ed. *Head and neck reconstruction.* Philadelphia, PA: Saunders Elsevier, 2009:276, with permission.)

these defects into a more easily managed "incomplete" defect (19). Lip adhesion places the soft tissue elements of the cleft in a more normal position and allows the lip to exert guiding forces along the major and minor maxillary segments, thereby reducing the size of the cleft and improving alignment. Patients undergoing staged cleft lip repair typically undergo definitive cleft lip/nose repair at 4 to 6 months, in order to allow the lip adhesion to mature, and for the tension from the adhesion to passively bring the major and minor cleft maxillary segments together.

Cleft Lip and Nose Repair

At our institution, the primary repair of a unilateral or bilateral cleft lip is performed in otherwise healthy infants at approximately 3 to 6 months of age, when the infant has grown enough to make surgical repair safer for the patient. In the past, many surgeons have used the "rule of 10s" as a guideline for the timing of primary repair—10 lb, 10 g/dL hemoglobin concentration, and 10 weeks of age (20). At the time of cleft lip repair, the child should be healthy and well nourished, without signs of active illness, in order to safely undergo anesthesia.

Cleft Palate Repair

Primary repair of the cleft palate deformity is generally undertaken at 9 to 12 months. As the development of normal speech is the primary outcome of palatoplasty, delaying palatal repair beyond 15 to 18 months of age is generally not recommended unless the patient has other developmental or medical concerns.

Speech Surgery

Speech surgery to address velopharyngeal insufficiency (VPI) may be carried out at any time following cleft palate repair, once the diagnosis has been confidently made by an experienced speech pathologist on the cleft team. The speech pathologist periodically monitors the patient's speech for the development of VPI and then makes the

appropriate recommendations for secondary speech surgery for patients with VPI before compensatory changes make speech improvement challenging.

Secondary Surgery

At each cleft team visit, an assessment of the repaired lip and nose is made to categorize any secondary deformity. Secondary, "touch up" surgical procedures are common, being the "rule" and not the "exception." Typically, they are first considered prior to the patient entering kindergarten. Pulsed-dye laser therapy may also be of benefit for scars that remain overly hyperemic. Later lip revisions and definitive septorhinoplasty may be entertained in adolescence. Both the patient and family, in consultation with the surgeon, guide the timing and appropriateness of these secondary procedures.

Alveolar Bone Grafting

Alveolar bone grafting is typically performed in mixed dentition just prior to eruption of the permanent maxillary canines around 6 to 9 years of age. Oronasal fistula repair and alveolar bone grafting is performed before the eruption of the permanent canine in order to provide stable alveolar bone for the tooth, thereby maximizing its chances for long-term retention.

Orthognathic Surgery

The correction of maxillomandibular discrepancies can be performed in the growing child if the class III malocclusion is severe and symptomatic; this is usually accomplished with distraction osteogenesis in this age group. Classic orthognathic surgery for the cleft patient is reserved for patients who have completed skeletal growth. Options for patients with significant maxillary retrusion include LeFort I osteotomy in patients with mild to moderate deformities and LeFort I osteotomy and maxillary distraction osteogenesis in patients with severe deformities without mandibular prognathism. In the unusual cleft patient with maxillary retrusion with concomitant mandibular prognathism, double jaw surgery with mandibular procedures such as bilateral sagittal split osteotomy (BSSO), may be indicated to restore a normal facial profile.

Cleft Rhinoplasty

The primary cleft lip–nasal deformity was historically treated only in a delayed fashion, avoiding any nasal surgery during primary lip repair (21). More recent experience has shown that concurrent primary lip and nasal repair is a safe and effective practice and is an approach utilized by most cleft surgeons today (21,22). Secondary cleft septorhinoplasty is typically performed in early adolescence or following orthognathic surgery.

SURGICAL MANAGEMENT OF THE PRIMARY DEFORMITY: TECHNIQUE

Presurgical Infant Orthopedics: Nasoalveolar Molding

Nasoalveolar molding (NAM) has been utilized for patients with both unilateral and bilateral cleft lip/nasal deformities with considerable success. Several studies by Grayson et al. have demonstrated the remarkable ability of this technique in facilitating both the approximation of the complete cleft lip deformity and improving the deformed cleft side lower lateral cartilage (23,24). In the New York University NAM protocol, patients with a complete cleft lip/nose deformity are treated with NAM for approximately 4 months, beginning at 1 week of age (23). Patients undergoing NAM treatment must have an impression taken of the alveolar segments, and a custom-made NAM splint is made from this mold. Patients must return to the office weekly for NAM device adjustment and to examine the child for any potential complications of treatment, including pressure sores, malalignment, or lack of progress. A nasal conformer is added to the device once the alveolar cleft measures less than 5 mm in width, and is used to mold the collapsed nasal ala (23). A 2008 anthropometric study by Grayson et al. demonstrated that patients who were treated with presurgical NAM demonstrated improved nasal tip projection, nasal alar symmetry, and decreased columellar deviation when compared to patients who underwent cleft repair without NAM (23).

Lip Adhesion

Lip adhesion surgery is typically performed in infants before 3 months of age. In patients with a unilateral cleft, the lip is marked with methylene blue as in unilateral cleft lip repair. By clearly marking these structures, the surgeon can place the incisions for the adhesion away from structures used in the definitive lip repair. "Book flap" incisions for the adhesion are placed within the mucosa of the lateral and medial lip elements, approximately 6 to 8 mm inferior to the nostril sill (19). A buccal sulcus incision on the lateral lip element is designed so that supraperiosteal dissection of the lateral lip element and alar base may adequately mobilize the lateral lip and ala. This incision is extended superiorly onto the inferior turbinate, along the pyriform aperture to release and advance the lateral lip and nose element (19). The lower lateral cartilage on the cleft side and nasal tip may be dissected through this incision if the surgeon desires to reposition the lower lateral cartilage at this stage. Once the incisions have been made and the lateral lip element mobilized, a horizontal mattress 3-0 polypropylene suture is placed across the cleft to bring the medial and lateral lip elements together (19). Muscle and mucosal sutures are placed to approximate the orbicularis oris muscle and lip margin mucosal flaps.

For patients with bilateral cleft lip and nose deformity, the adhesion procedure is carried out in a similar fashion as in a unilateral cleft lip and nose deformity, widely mobilizing the lateral lip elements and bringing them toward the midline with the 3-0 polypropylene horizontal mattress stitch. The lower lateral cartilages are dissected and mobilized through the buccal sulcus incision, and the mucosal flaps are then sutured to each other to complete the adhesion. In both unilateral and bilateral lip adhesion procedures, nasal conformers are placed to help support the repositioned lower lateral cartilages and are left in place until the time of definitive lip repair.

Unilateral Cleft Lip and Nose Repair

Several types of unilateral cleft lip and nose repair have been extensively described; however, variations on the classic Millard rotation–advancement technique are the most commonly utilized repair (25). Important landmarks of the upper lip–rotation flap are marked with methylene blue (Figs. 103.4 and 103.5):

1. The nadir of Cupid's bow
2. The peak of Cupid's bow on the noncleft side
3. The distance between 1 and 2 is measured with a Castroviejo caliper; this distance is then transposed to the proposed peak of Cupid's bow on the cleft side.



Figure 103.4 Key anatomic landmark points for marking a unilateral cleft lip repair. Note the principal anatomic points: *1.* the nadir of Cupid's bow; *2.* the peak of nonclefted side of Cupid's bow; *3.* the peak of clefted side of Cupid's bow; *4.* the desired point for the peak of Cupid's bow on the lateral lip element, where the white roll loses its fullness. (From Salyer KE, Cheng AM, Michenzi JW, Genecov E. Unilateral cleft lip/nose repair. In: Kischner RE, Losee JE, eds. *Comprehensive cleft care.* New York, NY: McGraw-Hill, 2009:310, with permission.)

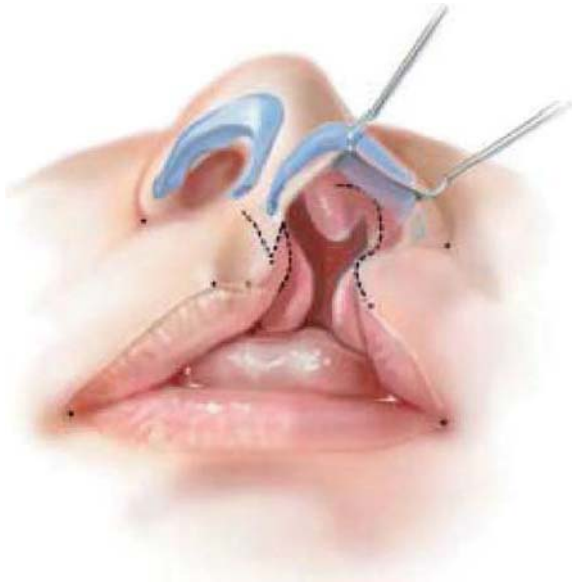


Figure 103.5 Incisions utilized for unilateral cleft lip repair. Note the incision along the new, desired philtral column and the creation of a C-flap. Note cleft side incision along margin of cleft, extending onto inferior turbinate, to allow for left nasal alar mobilization. (From Salyer KE, Cheng AM, Michenzi JW, Genecov E. Unilateral cleft lip/nose repair. In: Kischner RE, Losee JE, eds. *Comprehensive cleft care.* New York, NY: McGraw-Hill, 2009:311, with permission.)

The height of the philtral column on the noncleft side is measured with 26-gauge surgical wire and is then transposed to the cleft side's proposed philtral column. A small back cut from the apex of the philtrum down to the noncleft philtral column is marked. The lateral lip element–advancement flap markings are then made:

4. The vermilion–cutaneous junction of the desired peak of Cupid's bow where the white roll and lateral lip element begin to lose their fullness.
5. The surgical wire is used to mark distance for the medial incision of the advancement flap as it courses cephalad toward the nasal sill.

The red line separating wet and dry vermilion is marked on the medial and lateral upper lip elements, and the dry vermilion is measured with a Castroviejo caliper. If the medial lip element dry vermilion is deficient, a triangular flap of dry vermilion can be designed on the lateral lip element to augment this deficient height.

The medial lip element–rotation flap is incised, beginning at the apex of the philtrum, down along the philtral column marked on the cleft side, across the white roll and into the dry vermilion. The incision is continued vertically to the upper gingivobuccal sulcus. The orbicularis is dissected off its abnormal attachment to the anterior nasal spine, and the upper lip is mobilized in a supraperiosteal plane along the maxilla and pyriform aperture, allowing it to be rotated inferiorly, balancing Cupid's bow.

The lateral lip element–advancement flap incision is made in a similar fashion and is carried vertically into the

nose and onto the anterior surface of the inferior turbinate. Supraperiosteal dissection is continued laterally to the pyriform aperture, mobilizing the abnormally tethered alar base, allowing medial transposition of the nasal ala and lateral lip element–advancement flap. A buccal sulcus incision is made to further allow for medialization of the lateral lip element–advancement flap. The free cut edge of the orbicularis oris muscle is dissected free from the overlying skin and underlying mucosa and is sutured to the muscle of the medial lip element. Once the muscle has been repaired, the external skin of the upper lip is repaired. The tip of the lateral lip element advancement flap is inset into the back cut of the medial lip element–rotation flap.

Attention is turned to the nose, and a nasal rim incision is made on the cleft side, so the lower lateral cartilage may be completely mobilized from the overlying skin. This dissection is carried over the nasal dorsum and over to the contralateral side of the nose. Absorbable sutures are used to reapproximate the genua of the lower lateral cartilages and resuspend the cleft side lower lateral cartilage. Closure of the nasal floor completes the repair, and a silicone nasal conformer is placed.

Bilateral Cleft Lip and Nose Repair

Variations of the Mulliken repair are widely utilized in patients with a bilateral cleft lip and nose deformity (Fig. 103.6). First, the upper lip landmarks and proposed incisions are marked. The subnasale is marked, as is the desired nadir of the new Cupid's bow. The vertical distance between these two points in a 3-month-old infant is typically 6 to 8 mm. The base of the philtrum and the proposed peaks of Cupid's bow are then marked (26). The lateral lip elements are then marked where the fullness of

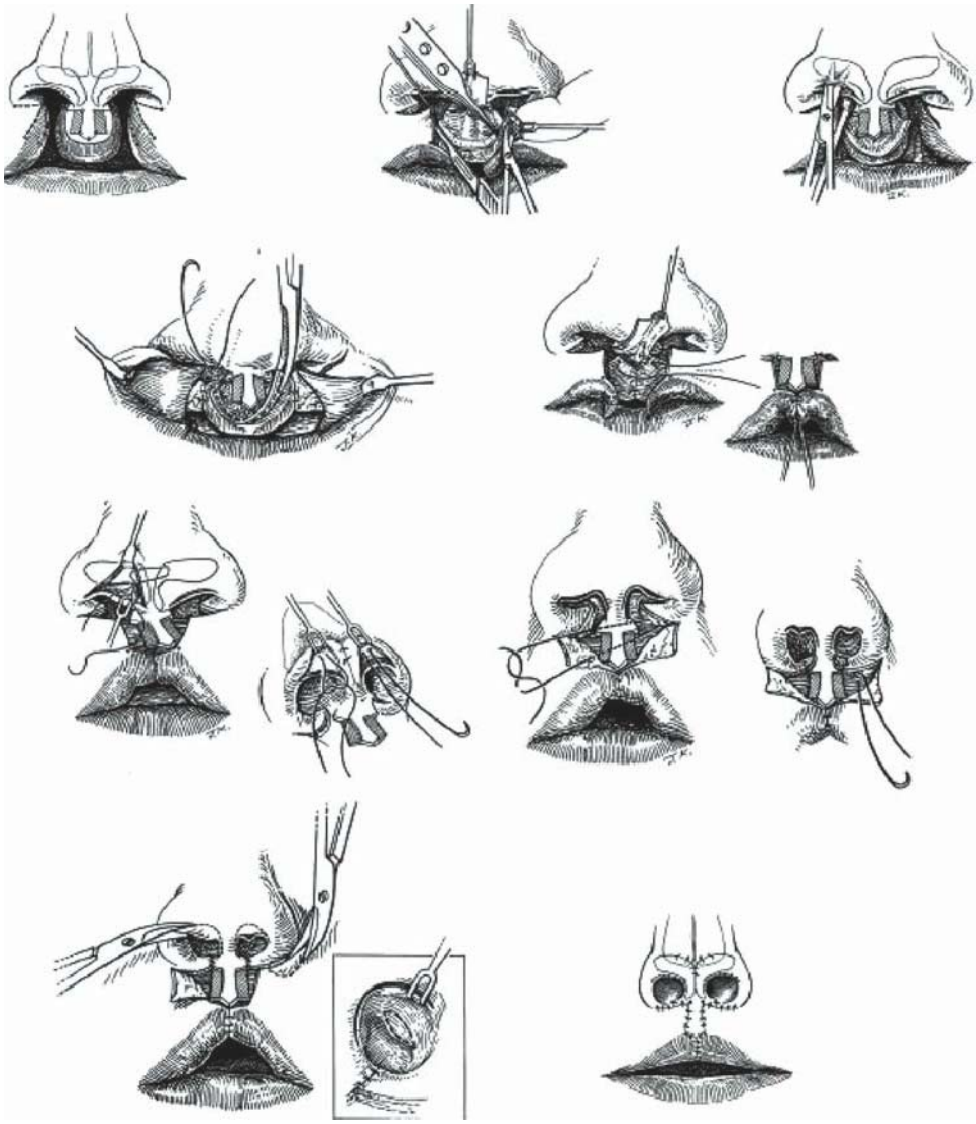


Figure 103.6 Mulliken method of single-stage bilateral nasolabial cleft repair, utilizing a semiopen approach to the nasal tip cartilages through bilateral nasal rim incisions. (From Mulliken JB. Primary repair of bilateral cleft lip and nasal deformity. *Plast Reconstr Surg* 2001;108(1):186, with permission.)

the white roll and lip begins to fade. As the white roll of the reconstructed Cupid's bow will come from the lateral lip elements, a distance of 2 mm is marked down each of the lateral lip elements (26). This incision will turn down a segment of white roll and vermilion to form Cupid's bow and the central tubercle of the upper lip.

Dissection begins on the prolabium, and the new philtrum is incised and raised in the subcutaneous space to the level of the subnasale. The vermilion of the premaxilla is placed beneath the elevated philtrum and on to the raw surface of the premaxilla. Next, the lateral lip element incisions are made, extending into the buccal sulcus, and dissection in the supraperiosteal plane is undertaken to mobilize the lateral lip element flaps. The buccal sulcus incisions are extending into the nose and onto the inferior turbinate, again allowing for complete mobilization of the abnormally tethered alar bases. The orbicularis oris muscle is then dissected free for several millimeters from the free edges of the skin and mucosal incisions.

Once dissection is complete, the mucosal closure of the lip is performed with absorbable sutures. This is followed by precise orbicularis oris repair to realign the pars peripheralis and pars marginalis in an anatomically correct position in the midline, posterior to the philtral flap, tacking the superior aspect of the muscular closure to the anterior nasal spine.

The tip of the nose is degloved through nasal rim incisions. Interdomal sutures to reapproximate the genua of the lower lateral cartilages are placed, narrowing the nasal tip. In order to correct the widened the nasal base, an alar base cinch stitch is placed through both alar bases and tightened to correct the distance between the alar bases. The nostril sills are then repaired. Judicious trimming of the soft triangles is required to remove excess tissue in this area and create a more round nostril aperture. These incisions are then repaired with fine absorbable suture (26).

Cleft Palate Repair

There are many different approaches to both hard and soft palate repair. Options for soft palate repair include both straight line and Z-plasty techniques with or without intravelar veloplasty. For repair of hard palate defects, unipedicled or bipedicled mucoperiosteal flaps are utilized (4). Patients typically undergo palatoplasty at 9 to 15 months of age, depending upon their physical status and other comorbidities.

Furlow Double Opposing Z-Plasty

The Dingman retractor is gently placed to hold the mouth open and retract the tongue (Fig. 103.7). The proposed lateral relaxing incisions are marked in the crease where the cheek sidewalls meet the velum laterally, extending around the posteromedial aspect of the maxillary tuberosity and

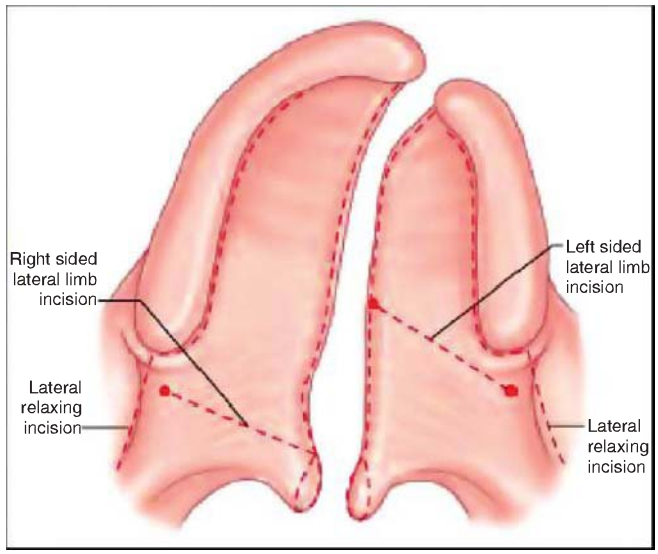


Figure 103.7 Standard incision markings for Furlow palatoplasty. (From Losee JE, Smith D. Cleft palate repair. In: Butler CE, ed. *Head and neck reconstruction.* Philadelphia, PA: Saunders Elsevier, 2009:279, with permission.)

onto the lingual surface of the hard palate. The hamulus is then palpated and marked, lying posterior to the maxillary tuberosity. Next, markings are placed at the hard/soft palate junction and base of the uvula. The medial aspects of the cleft margins are marked, extending from the hard–soft palate junction to the uvular bases, taking care to "cheat" onto the oral surface by 1 mm in order to recruit mucosa for nasal lining closure. The posteriorly based oral musculomucosal flap is marked on the patient's left side, from the hamulus to the junction of the hard and soft palate. The anteriorly based oral mucosal flap on the right side is marked from the uvular base to hamulus. Care is taken to leave an adequate mucosal bridge between these incisions and the relaxing incisions, to preserve vascularity to the flaps.

Next, the velum is infiltrated with dilute epinephrine, and the uvular halves are demucosalized with dissecting scissors. The left-sided posteriorly based musculomucosal flap is incised along the marked lines. Deeper dissection separates the soft palate musculature from the underlying nasal mucosa. Care must be taken to ensure that the three abnormal attachments of the levator are released: the posterior edge of the hard palate, the tensor aponeurosis, and the superior pharyngeal constrictor (15). These maneuvers allow the left-sided posteriorly based musculomucosal flap to be transposed from its anteroposterior orientation to a transversely oriented posterior position.

The right-sided anteriorly based oral mucosal flap is then incised along the cleft margin and then the uvular base to the hamulus. The underlying soft tissues are then retracted so that they may be divided with dissecting scissors until the aponeurosis of the palatopharyngeus

and palatoglossus muscles is identified and preserved. Submucosal dissection is continued laterally, taking care to include the subcutaneous fat and mucosal glands with the mucosal flap to preserve vascularity. The abnormal connection between the levator muscle and posterior edge of the hard palate is identified and then divided 2 to 3 mm posteriorly, to preserve a cuff of nasal mucosa along the posterior edge of the hard palate for nasal lining repair. This dissection is carried posterolaterally to the point where the levator exits the skull base beneath the superior constrictor muscle.

Bilateral relaxing incisions are made with a scalpel; scissors are then inserted into the posterior aspect of each relaxing incision with the tips oriented medially. These are gently spread in the space of Ernst to release the overlying mucosal bridge. Within these relaxing incisions, the tendon of the TVP muscle should be identified, isolated, and divided. The soft tissues medial to the hamulus and posterior to the hard palate are divided with dissecting scissors to complete the mobilization of the velar flaps.

The hard palate mucoperiosteal flaps are then incised and mobilized with a Blair elevator, taking care to identify and preserve the neurovascular pedicle as it exits the greater palatine foramen posterolaterally. Gentle stretching of the periosteum surrounding the pedicle is often necessary to fully mobilize the hard palate flaps. The nasal mucosa is dissected from the undersurface of the maxillary shelves along the medical bony edge of the cleft with a Woodson elevator. If necessary, vomerine mucoperiosteal flaps are used for nasal lining closure of the hard palate.

The soft palate nasal flaps are then made. The left-sided anteriorly based nasal mucosal flap is then designed and incised from the uvular base to the origin of the LVP posterolaterally as it exits the skull base. The right-sided posteriorly based nasal musculomucosal flap is incised at a point just posterior to the junction of the hard and soft palate, extending posterolaterally to the origin of the LVP as it exits the skull base, leaving a cuff of nasal lining along the posterior edge of the hard palate for nasal lining repair. The nasal lining flaps are transposed in a Z-plasty fashion and inset. In selected cases where nasal lining closure is tenuous or impossible, thin acellular dermal matrix as an onlay repair may be utilized (27). Care is taken to avoid suturing the graft to the levator sling; securing sutures are placed in the nasal lining, tensor aponeurosis, and posterior edge of the velum. Once the nasal lining repair is complete, repair of the uvula is performed. The oral flaps are then transposed in an opposing Z-plasty fashion, bringing the left-sided posteriorly based musculomucosal flap into transverse orientation, completing the velar reconstruction. The hard palate mucoperiosteal flaps are inset in the midline with absorbable suture and secured along the anterior edge of the lingual surface of the alveolar incisions (Fig. 103.8).

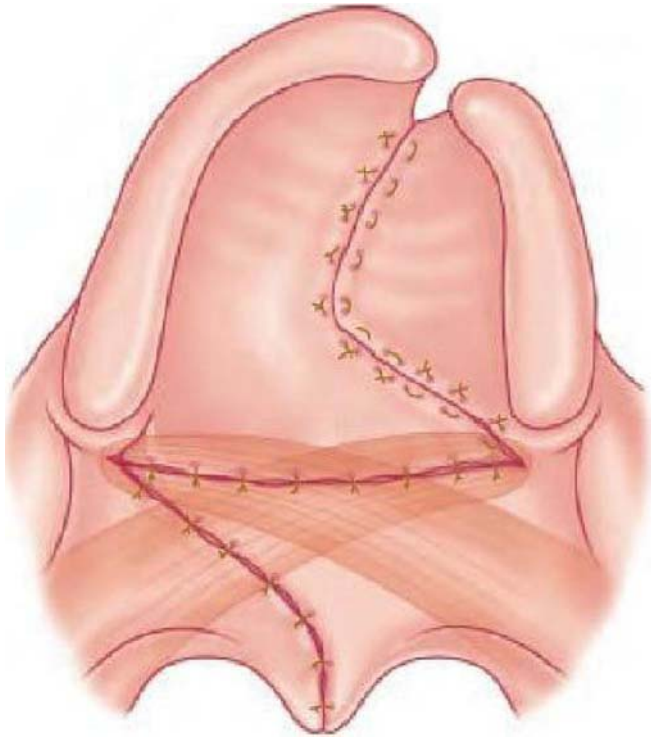


Figure 103.8 Palate repaired with Furlow technique. Note the transverse orientation of the LVP muscles. (From Losee JE, Smith D. Cleft palate repair. In: Butler CE, ed. *Head and neck reconstruction.* Philadelphia, PA: Saunders Elsevier, 2009:287, with permission.)

Straight-Line Repair with Intravelar Veloplasty

Straight-line cleft palate repair with intravelar veloplasty is a technique also utilized by many surgeons (Fig. 103.9). The principles of straight-line soft palate repair in intravelar veloplasty are similar to Furlow palatoplasty in that the crucial element of the procedure is to restore the levator sling musculature to a transverse orientation from an abnormal anteroposterior orientation in the unrepaired state.

The medial incisions are made along the cleft margin, beginning at the uvular base, extending anteriorly along the length of the cleft. Sharp dissection is performed in the submucosal plane, taking care to include the subcutaneous fat and mucosal glands in the oral mucosal flaps. The oral mucosal flaps are widely undermined to the lateral aspects of the velum in order to completely expose the levator muscles bilaterally. Wide dissection is then carried out between the levator muscles and the nasal lining, separating the velum into three distinct layers. The LVP muscles are then carefully released from their abnormal attachments: the posterior edge of the hard palate, the tensor aponeurosis, and the superior pharyngeal constrictor. The nasal lining along the cleft is repaired, utilizing acellular dermal matrix to augment the closure if there are any areas of tenuous closure or mucosal defects that cannot be primarily closed (27). Once the nasal mucosal layer has been

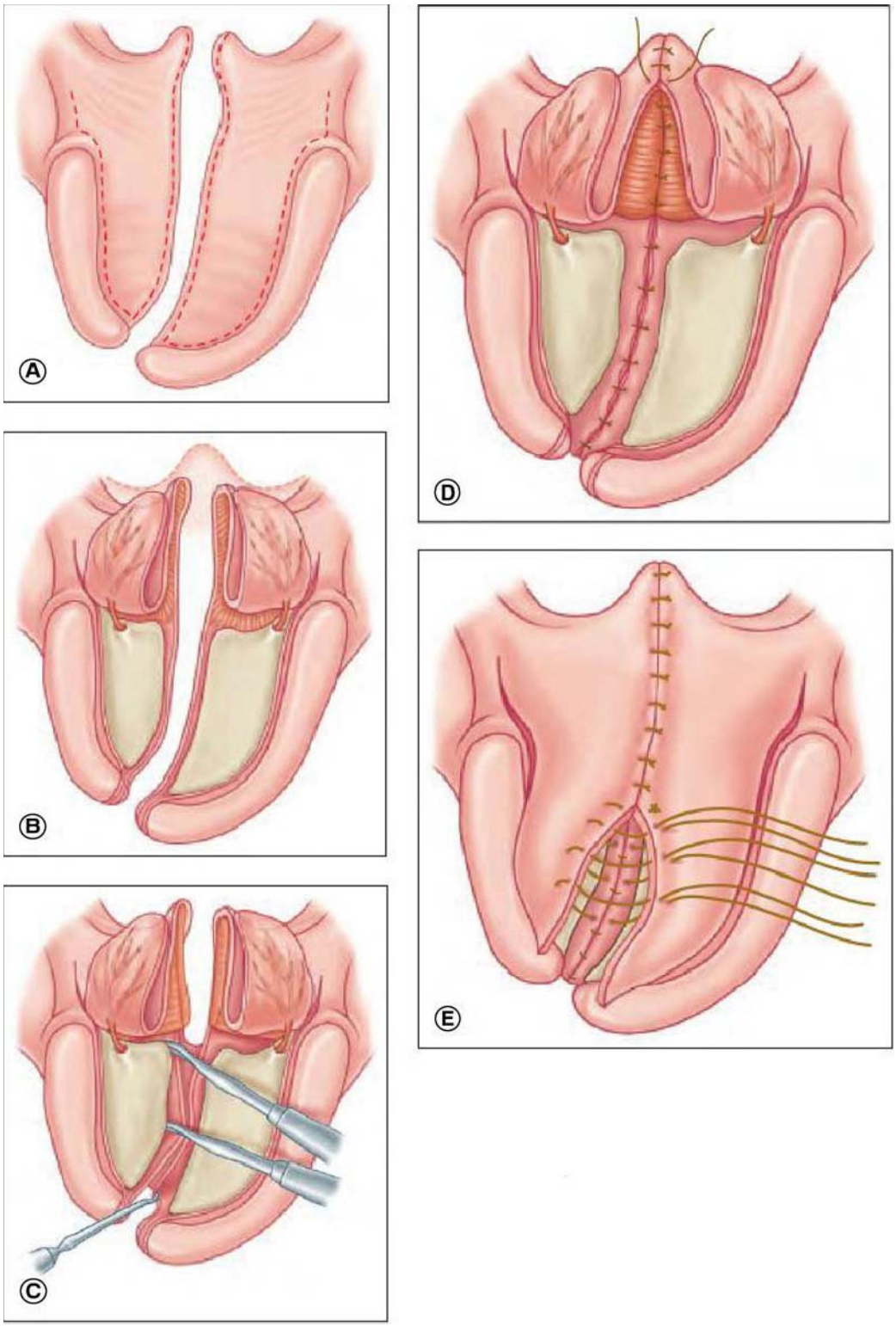


Figure 103.9 **A:** Design of bilateral unipedicled hard palate mucoperiosteal flaps. **B:** Dissection of bilateral unipedicled hard palate mucoperiosteal flaps, each containing the greater palatine artery on each side. **C:** Dissection of nasal lining from posterior edge of the hard palate. **D:** Repair of nasal lining along edges of hard and soft palate cleft. **E:** Repair of oral lining along edges of hard and soft palate cleft. (From Losee JE, Smith D. Cleft palate repair. In: Butler CE, ed. *Head and neck reconstruction.* Philadelphia, PA: Saunders Elsevier, 2009:288, with permission.)

repaired, the LVP muscles are transposed posteriorly into a posterior transverse orientation, where they are properly tensioned and sutured together in the midline. After levator muscle closure, the oral mucosa is closed with interrupted absorbable sutures.

Speech Surgery

Velopharyngeal insufficiency (VPI) after cleft palate repair is reported to occur in approximately 10% to 20% of patients (28). Many authors advocate the use of pharyngeal flap surgery in patients with poor palatal motion, a large central velopharyngeal port gap, and good lateral wall motion (29). Sphincter pharyngoplasty is typically used in patients with good palatal motion, a small central velopharyngeal gap, and poor lateral wall motion (28–31). Conversion to furlow palatoplasty has also gained favor as a technique utilized to correct VPI in patients who have previously undergone straight-line palatoplasty. Patients selected for secondary speech surgery often undergo tonsillectomy and adenoidectomy procedure 6 weeks in advance of their speech surgery in order to remove tissues that can cause significant obstruction of the velopharyngeal ports, decreasing the risk of hyponasality and possible obstructive sleep apnea (31).

For pharyngeal flap surgery, we prefer the modified Hogan technique. With this technique, the raw surface of the superiorly based pharyngeal flap is covered with nasal mucosal lining turndown flaps (32). The velum is incised in the midline, ending the incision just posterior to the junction of the hard and soft palate. Next, the nasal mucosa lining turndown flaps, pedicled on the posterior free edge of the velum, are incised and dissected free from the nasal side of the palatal musculature. A superiorly based posterior pharyngeal flap is developed on the posterior pharyngeal wall, setting the base of the flap superior to the level of estimated velopharyngeal closure and allowing for adequate lateral port size bilaterally. The pharyngeal flap is then elevated off the prevertebral fascia and inset into the velum with absorbable sutures. The nasal lining flaps are turned down to line the raw undersurface of the inset pharyngeal flap and are secured to the base of the elevated flap with absorbable sutures. Watertight mucosal closure proceeds from posterior to anterior, completing the procedure.

In patients undergoing sphincter pharyngoplasty, the posterior tonsillar pillars with underlying palatopharyngeus muscle are dissected to create superiorly based musculomucosal flaps. Once these flaps are elevated, they are transposed superomedially and inset transversely, high on the posterior pharyngeal wall at the estimated level of velopharyngeal closure, thereby creating a smaller velopharyngeal port (31).

Alveolar Bone Grafting

Reconstruction of the cleft maxillary and alveolar defect is of great importance in treating cleft patients. Approximately 20% to 30% of cleft patients develop significant dentofacial abnormalities, and may benefit from orthognathic surgery during late adolescence; the restoration of a one-piece maxilla with alveolar bone grafting greatly facilitates this process (33,34). In addition to facilitating orthognathic treatment, repair of the alveolar defect and oronasal fistula eliminates nasal fluid regurgitation and improves oral hygiene and provides bone support for the dentition.

Cleft patients are radiographically evaluated for dental development while in mixed dentition and undergo bone grafting of the maxillary and alveolar bone defect prior to the eruption of the permanent lateral incisor and canine (33). Patients benefit from presurgical orthodontic treatment to appropriately expand their maxillary dental arch and optimize the position of the teeth bordering the cleft.

Alveolar bone graft surgery begins by raising anterior gingival mucoperiosteal flaps on either side of the cleft. Wide subperiosteal dissection is performed to expose the edges of alveolar and maxillary defect. The oronasal fistula is taken down and repaired, creating a mucosal pocket, with its tip at the incisive foramen and its base at the anterior alveolus and maxilla. If there is a deficiency of nasal mucosa along the base of the defect, human acellular dermis may used to close the defect (27). A separate surgical setup is utilized to harvest iliac crest cancellous autograft, and the graft is packed densely into the cleft defect, and the gingival mucoperiosteal flaps are closed over the graft, completing the repair.

Orthognathic Surgery

Twenty to thirty percent of cleft patients will have severe maxillary retrusion and an angle class III dentofacial deformity unable to be corrected by standard orthodontic treatment (33). Subperiosteal dissection of the midface and restriction by postoperative scar tissue have been proposed as potential etiologies for this deformity, although in a caprine fetal model study by Weinzweig et al., animals that did not undergo cleft palate repair also demonstrated some degree of midface hypoplasia (35). It is important that a multidisciplinary cleft team routinely evaluates cleft patients with midface deformities in order to optimize select patients for orthognathic surgery.

Patients with a class III dentofacial deformity, but without mandibular prognathism, may benefit from a LeFort I osteotomy and advancement, which can be performed as a one-step operation in patients who require a small advancement or with distraction osteogenesis in patients who require advancement in excess of 7 mm. Kumar et al. demonstrated decreased relapse rates in patients with severe class III dentofacial abnormalities who underwent LeFort I osteotomy and distraction osteogenesis (15%) when compared to traditional one-step LeFort I osteotomy and advancement (63%) (34). Other patients with class III dentofacial deformities, in combination with prognathism, may require double jaw surgery—LeFort I with BSSO—to correct the problem.

In cleft patients being evaluated for dentofacial deformities, cephalometric evaluation and dental models should be obtained for preoperative planning. Presurgical orthodontic preparation for the orthognathic movement desired is often required. Once these preparations are complete, the patient may undergo surgical manipulation of the jaws.

Patients undergoing LeFort I osteotomy and advancement are nasotracheally intubated and access to the maxilla is obtained through upper gingivobuccal sulcus incisions (Fig. 103.10). It is important to recognize that the central area of the gingivobuccal sulcus may be the only blood supply to the premaxillary segment in bilateral cleft patients, and this mucosa should be preserved. Once the maxilla has been exposed, the pyriform aperture is dissected free of nasal mucosa, extending the dissection along the floor of the nose posteriorly. Lateral dissection of the maxilla is then performed until the pterygomaxillary fossa is encountered, allowing access to the pterygomaxillary junction. Once maxillary dissection is complete, a high osteotomy is designed bilaterally along the anterior maxilla from the zygomaticomaxillary buttress to the pyriform aperture, staying 5 mm below the infraorbital foramen and nerve (33). The maxillary osteotomies are then cut with a reciprocating saw, and the vomer and septum are separated with an osteotome. Finally, pterygomaxillary junction osteotomies are performed with a curved osteotome, aiming the osteotome inferoposteriorly to avoid injury to the maxillary artery within the pterygomaxillary fissure. The maxilla is down fractured and hemostasis is obtained by packing the defect, methodically exploring each side for bleeding vessels and controlling these with bipolar cautery. Any large nasal lining rents are sutured with absorbable suture, and the maxilla is freely mobilized on its pedicle—the posterior mucosal attachments of the soft palate. Bony interferences along the posterior aspects of the lateral and medial walls of the maxillary sinuses are removed with a rongeur, and the surgical splint is used to guide the maxillary dentition into appropriate occlusion prior to the placement of plate fixation. In select cases with significant inferior placement of the maxilla, or in multipiece advancements, bone grafting may be required to increase stability of the construct. In distraction cases, the maxilla is returned to its original position, and internal or external distraction devices are applied to the maxilla. A nasal alar base cinch stitch is performed to decrease nasal base width, and the intraoral incisions are closed with absorbable sutures.

If a BSSO is required, bilateral mandibular rami are exposed with intraoral incisions along the anterior aspect of each ramus. Subperiosteal dissection is utilized to obtain wide exposure of both mandibular rami anteriorly, medially, and laterally. Once the mandibular ramus has been dissected, the sagittal split osteotomy is designed, beginning medially at two-thirds the height of the ramus, inferior to the coronoid process, and extending mesially along the external oblique ridge to the inferior border of the mandible. The osteotomy is completed with osteotomes and a bone spreader (33). Once bilateral osteotomies have been completed, the mandibular condyles are seated, and the distal segment is guided into position with the surgical splint to orient the mandible into the correct occlusal relationship with the maxillary dentition. Both the distal and proximal segments are then secured with a clamp, and mandibulomaxillary temporary fixation is achieved by

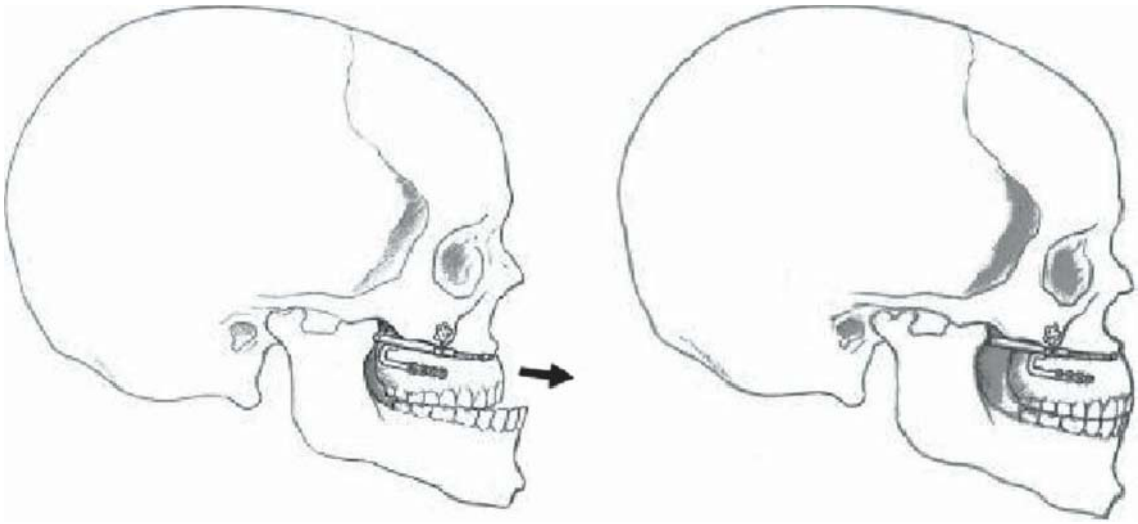


Figure 103.10 LeFort I maxillary advancement by distraction osteogenesis. (**Left**) Before distraction. (**Right**) After distraction of LeFort I segment. (From Kumar AR, Gabbay JS, et al. Improved outcomes in cleft patients with severe maxillary deficiency after LeFort I internal distraction. *Plast Reconstr Surg* 2006;117(5):1501, with permission.)

wiring of the jaws with the occlusal splint in place. Internal fixation is then performed to stabilize the mandibular construct, and the mandibulomaxillary fixation is released to confirm the occlusion.

Definitive Cleft Rhinoplasty

Repair of the cleft nose deformity presents a formidable surgical challenge, and surgical manipulation of the cleft nasal defect was frequently postponed until late adolescence. Recently, it has become standard for patients to undergo primary repair of the cleft nasal defect concurrently with cleft lip repair, understanding that many patients will still require definitive septorhinoplasty during adolescence. Patients wishing to improve nasal appearance and function must undergo complete facial analysis to determine their individualized functional and aesthetic goals. The nose is examined in detail to observe the specific deformities that may be present. In the unilateral cleft patient, these may include deviation of the columella to the noncleft side; inferior, posterior, and lateral displacement of the cleft side nasal ala; lateral displacement of the cleft side nasal alar base; nasal septal deviation toward the noncleft side; and hypertrophy of the inferior turbinate on the cleft side (21). Patients with a bilateral cleft deformity typically have a shortened columella, a broad and flat nasal tip, flat nasal alae, severely deformed lower lateral cartilages, and horizontally oriented nostrils (21).

Because of the amount of dissection required to address the asymmetries and contour abnormalities in cleft patients, many cleft rhinoplasties are performed using an open technique. While the surgical maneuvers required to correct each patient's deformity are individualized to the patient, most cleft patients will require submucous resection of the quadrangular cartilage of the septum, removal of abnormally situated portions of the vomer and perpendicular plate, reduction of a dorsal hump defect, nasal bone osteotomies, dorsal spreader grafts, a columellar strut cartilage graft for support, an alar rim graft on the cleft side in unilateral patients, and refinement of the nasal tip by repositioning the lower lateral cartilages (36). Internal and external nasal splints are placed to support the new nasal construct.

OTOLARYNGOLOGIC CONSIDERATIONS IN THE CARE OF THE CLEFT PATIENT

Ear Disease/Eustachian Tube Dysfunction

The relationship between middle-ear disease and a cleft palate is both structurally and physiologically tied to the ET. The ET connects the middle ear with the nasopharynx and depends on proper function of both the TVP and LVP musculature. A more detailed explanation of the anatomy and physiology of the ET is available elsewhere (37). Compared to adults, a noncleft child's ET has a larger bony component, is shorter, and is approximately 10 degrees off the horizontal hard palate. The orifice opening is oblique and both the lumen and the orifice opening of the ET are smaller (37).

The differences between the ET in a noncleft child compared to a child with a cleft palate have been well studied (37). The tube is shorter and there is a larger angle between the cartilage and the TVP. There are inherent changes to the cartilage and muscle as well. The cartilage is deformed and there is a greater cartilage cell density. There is less elastin at the hinge of the cartilage. Both the TVP and LVP muscles have less contractile tissue and more connective tissue (37). The relative position of the TVP causes baseline functional obstruction of the ET.

These differences in the anatomy and physiology of the ET are manifested clinically as chronic middle-ear disease. The theoretical "sequence" is that an unrepaired cleft causes obstruction at the nasopharyngeal end of the ET because of the baseline compression of the ET with impaired ability to open the ET due to abnormalities of its component parts described above. This obstruction induces negative middle-ear pressure, which leads to middle-ear mucosal swelling and eventual middle-ear fluid accumulation. The combination of the fluid accumulation and an obstructed isthmus leads to fluid stasis, increased fluid viscosity, and no clearance of the fluid. This sequence of events with the associated persistent middle-ear effusion (MEE) has been documented as early as the first month of life. Bluestone et al. studied 21 infants with an unrepaired cleft palate and found abnormal ET function to be ubiquitous (38). Fria et al. performed auditory brainstem response testing in a number of children with unrepaired cleft palate and found significant conductive hearing loss prior to tympanostomy tube (TT) placement, which was reversed after tube placement (39). Similarly, the relationship of abnormal middle-ear and ET function prior to cleft palate repair, which normalized after the palatoplasty, is borne out in an animal model. Eight monkeys with a surgically induced cleft palate had abnormal ET function. Once the palate was repaired, the ET function normalized (40).

The big question is what happens to the ET function in a child with a cleft palate after the cleft is repaired? Although the muscle sling was repaired, there is not an immediate improvement in ET function. There seems to be improved retrograde function and prograde clearance, but a functional obstruction still exists. Follow-up ET function testing after cleft repair suggests there is still difficulty at equilibrating negative pressures (37). Chronic otorrhea, which is often present in children with ear tube placement prior to their palatoplasty, improves significantly and fairly soon after the repair (41,42). Approximately 70% of children with a cleft palate obtain normal ET function 6 to 10 years after the repair.

The mantra for the treatment of ET dysfunction in a child with a cleft palate has long been the placement of TT "early and often." Increasingly though, there is debate about the appropriate timing of TT placement. At our institution, TTs are placed at the time of CL repair if there has been any history of acute otitis media, any documented physical examination with MEE, or any abnormal tympanometry or audiometry. If the infant has passed the newborn hearing screening examination and has been heretofore free of middle-ear disease, an examination of the ears while under anesthesia is performed. If the ear examination is normal, no TTs are placed. If there is a MEE, TTs are placed at that time. Regardless of the history or examination findings, TTs are placed at the time of the palate repair. After this initial set of TTs are placed either at the time of the palate repair or sometime prior to this, the ears are examined at intervals until the TTs extrude. An assessment is made at that time to determine if the sequelae of the ETD recur after the tube extrusion. Smith et al. reported an average of 3.1 sets of Armstrong tubes and 1.1 sets of T-tubes for a child after palate repair (43).

In addition to having an increased number of sets of TT, children with a cleft palate are more likely to have cholesteatoma. Dominguez determined that the prevalence of cholesteatoma in children with cleft palate was 9.2% compared to 6 per 100,000 for the noncleft population. The patients ranged in age from 6 to 15 years and each had many sets of TT placed. All had a prior retraction pocket (44). This increase in the cholesteatoma risk necessitates careful interval examinations and timely TT placement for any retraction pocket noted.

Airway Issues in the Cleft Palate Population

Airway Obstruction/Obstructive Sleep Apnea

Children who have a cleft palate are at higher risk for upper airway obstruction than their noncleft peers. Children with cleft palate as part of a syndrome such as Apert syndrome or Pierre Robin sequence (PRS) are even more likely to experience airway obstruction. This airway obstruction may be manifested in a variety of circumstances and in a range of severities. At birth, aside from concerns with feeding and swallowing, there may be signs of airway obstruction, particularly if there is any degree of retrognathia. This may be explained anatomically, since the possibility of airway obstruction at multiple levels exists: from nasal obstruction due to a deviated nasal septum to hypopharyngeal obstruction due to collapse of the epiglottis and base of tongue (EBT). Children with PRS are especially prone to this type of hypopharyngeal collapse as a sequela of the retrognathia present in this population. In general, the more severe the retrognathia, the more severe the EBT collapse. The airway obstruction symptom severity in this circumstance often coincides with the severity of the EBT collapse. Mild airway obstruction at birth may prompt only conservative measures such as prone positioning or a nasal or oral airway. A lower threshold to perform airway endoscopy should be employed in children with a syndrome. More severe airway obstruction that does not improve with conservative measures warrants a diagnostic endoscopy in the operating room consisting of at least a flexible nasolaryngoscopy and a direct rigid laryngobronchoscopy (DLB) that serves many purposes. The exact anatomic location of the airway obstruction may be determined. If the severity of the obstruction warrants it, or if multiple levels of obstruction are present, surgical intervention to improve the safety of the airway is indicated. The direct laryngoscopy also allows an assessment as to the ease of orotracheal intubation. If additional intervention is required, the patient may be intubated as part of the endoscopic procedure. The technique for DLB in children is described elsewhere. A DLB in an infant with PRS is more difficult technically because of the retrognathia and the position of the mandible relative to the anteriorly placed larynx.

Children may experience an increase in airway obstruction symptoms at the time of their palatoplasty. This may be due to a decrease in the functional airway space caused by closure of the palate. The tongue is acutely more swollen because of pressure applied by the Dingman retractor during the palatoplasty and closure of the palate decreases the available space that the tongue has previously occupied. Placement of nasal airways prior to the extubation after palatoplasty may alleviate some of the airway obstruction symptoms.

Other circumstances, which may make a child with cleft palate more susceptible to airway obstruction, include children with a syndrome causing generalized hypotonia, children who have undergone another procedure that may partially compromise airway patency (e.g., pharyngeal flap). An assessment of the severity of the airway obstruction with airway endoscopy may be required in this setting. Endoscopy may also be helpful when the severity of the symptoms of either airway obstruction or obstructive sleep apnea described by the caregiver does not correlate with physical examination findings.

One of the manifestations of airway obstruction is obstructive sleep apnea (OSA). OSA is defined as a "disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction that disrupts normal ventilation during sleep and normal sleep patterns" (45). The prevalence of OSA in the general pediatric population is approximately 2% to 3% (46) with 3% to 12% having primary snoring (47). Multiple studies have shown that children with a cleft palate are more likely to have sleep-disordered breathing with prevalence data ranging from 22% to 65% (48). Robison demonstrated a polysomnogram (PSG)-confirmed prevalence of OSA of 8.5%, approximately three times the healthy pediatric prevalence of 2% to 3%. In general, the younger patients were more prone to OSA, with decreasing prevalence as the population aged. One exception was a subset of patients who experienced an increase

in their OSA symptoms after surgical repair of their cleft palate or the performance of a pharyngeal flap for VPI (48). Children with PRS are at significantly higher risk of OSA, particularly with more severe airway obstruction symptoms early in infancy.

As noted, the airway management in infants with a syndrome or with PRS is difficult and has been a topic of much debate. In general, infants with nonsyndromic PRS improve with conservative measures such as prone positioning. They are also more likely to have symptomatic improvement after interventions such as mandibular distraction osteogenesis (MDO) or tongue lip adhesion (TLA). Children with syndromic PRS are more likely to need tracheostomy tube placement and/or gastrostomy tube placement and are more likely to fail other interventions such as MDO or TLA. Regardless of the chosen intervention, if the child with PRS has airway obstruction ± OSA that does not resolve with conservative measures, they should have an airway evaluation. At our institution, this evaluation consists of flexible fiberoptic nasolaryngoscopy to get a dynamic assessment of collapse of EBT, if present, and of laryngeal structure and function. A direct laryngoscopy and bronchoscopy is also performed with a twofold purpose: (a) to assess the ease or difficulty of orotracheal intubation and (b) to assess for other pathology in the distal airway. If the anatomic information gathered during the endoscopy warrants consideration for an MDO or TLA, the patient can be intubated at that time.

Each child with a cleft palate should be carefully monitored for history or examination findings that may suggest airway obstruction or OSA. There should be a low threshold for ordering a PSG with any treatment focused on the specific anatomic level of airway obstruction. If no surgical options exist for the treatment of OSA, a trial of bilevel positive airway pressure (BiPAP) should be considered.

Hoarseness

There have been conflicting data as to a higher prevalence of hoarseness and vocal cord pathology in children with a cleft palate compared to noncleft children. Previous reports indicate rates of dysphonia in the cleft palate population from 12% to 43% (49). There are many hypotheses to explain this possible increase in hoarseness. The most common is laryngeal compensation for abnormal velopharyngeal valving (50). If children with a cleft have any degree of VPI that persists after repair of the palate, the hypernasality that exists with articulation of specific consonants may prompt the utilization of compensatory mechanisms to overcome insufficient air pressure in the oral cavity. Some of these mechanisms include middorsum palatal stops, posterior nasal fricatives, velar fricatives, pharyngeal stops, pharyngeal fricatives, and glottal stops (51). Glottal stops, in particular, have been implicated in vocal cord abnormalities and voice disturbances such as hoarseness (51). Because of this tendency for vocal strain and dysphonia, a careful phonatory history plus a low threshold to administer a voice quality of life survey or perform a flexible nasolaryngoscopy, as indicated, is important. Additional investigation based on these findings may be necessary depending on the examination.

CONCLUSIONS

Providing care to patients with OFC is one of the most gratifying and technically challenging endeavors in surgery. The establishment of multidisciplinary cleft teams has allowed patients to receive truly comprehensive care throughout their infancy, childhood, and adolescence—optimizing aesthetic, speech, and functional outcomes for each patient. Continued clinical and basic science research is necessary in all fields pertaining to cleft care, as this clinical problem is widespread, persistent, and difficult for patients and their families alike.

HIGHLIGHTS

- Cleft lip and palate are the most common congenital malformations in the United States, affecting between 0.2 and 2.3 patients per 1,000 births, depending upon race.
- Isolated cleft palate has a higher association with genetic syndromes; Stickler syndrome and microdeletions of 22q being the most common.
- Repair of the cleft lip deformity in otherwise healthy patients is typically performed at 3 to 6 months of age, while repair of the cleft palate deformity is performed at 9 to 12 months of age.
- Care of the cleft patient should be a multidisciplinary endeavor, focusing on all aspects of the child's growth and development.

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104 Congenital Vascular Lesions

Ravindhra G. Elluru

In 1982, a seminal article authored by Mulliken and Glowacki (1) marked a turning point in the history of classifying and managing congenital vascular lesions, or more properly termed vascular anomalies. These authors developed a classification system in which vascular anomalies were designated as either vascular tumors or vascular malformations, based on their clinical appearance, histopathologic features, and biologic behavior (Fig. 104.1). Hemangiomas were identified as benign tumors that undergo a phase of active growth characterized by endothelial proliferation and hypercellularity, followed by gradual tumor regression that occurs over the first decade of life. In contrast, vascular malformations were described as structural congenital anomalies derived from capillaries, veins, lymphatic vessels, arteries, or a combination of these. Unlike vascular tumors, vascular malformations were shown to have normal levels of endothelial turnover and to grow proportionately with the child. In the chapter to follow, readers will be presented with a description of the most common types of vascular anomalies and available treatment modalities.

VASCULAR TUMORS

Infantile Hemangioma

The most commonly occurring vascular tumor is the infantile hemangioma, affecting 1 in 10 white infants in North America, though less commonly seen in children of African or Asian descent (2). These tumors are more common in females (3:1) and in infants with low birth weight (3). They are typically observed at birth or during the first several weeks of life. Lesions generally present cutaneously in the head and neck (60%), but can involve any anatomic site, including the extremities (15%), visceral organs, and brain (3).

Infantile hemangiomas are clinically characterized as superficial, deep, or combined, depending on their anatomic depth. Superficial lesions are typically soft, red, and raised, whereas deep lesions show a spectrum of appearance and consistency, ranging from soft and supple to raised and firmer warm masses with a bluish hue. Combined lesions have both a red epidermal coloration and a subcutaneous mass that is either blue or flesh colored.

Although most tumors present singularly, up to 20% of affected infants have multiple cutaneous lesions. When a patient has six or more cutaneous hemangiomas, there is an increased risk of having visceral hemangiomas, which in turn can give rise to serious or life-threatening conditions such as hepatomegaly, gastrointestinal bleeding, profound hypothyroidism, anemia, or congestive heart failure (4,5).

Hemangiomas of infancy generally follow a predetermined clinical course of active growth (proliferation) and later tumor regression (involution); however, there is wide variation in the rate, duration, and degree of growth and spontaneous tumor regression. Proliferation begins during the first few weeks of life and generally continues for 4 to 10 months, though deep lesions may proliferate until 2 years of age. The proliferative phase is followed by a period of quiescence during which the growth rate of the lesion stabilizes. Involution occurs at 12 to 18 months and can last up to 5 to 6 years. During this time, the color of the lesion fades, becoming grayish or dull purple (Fig. 104.2). Clinical studies show that maximum involution occurs in 50% of children by age 5 and in 90% by age 9 (6).

The cosmetic outcome after involution varies considerably and is generally unpredictable. In many patients, involution results in the restoration of normal skin. In others (20% to 40%), residual changes of the skin such as laxity, discoloration, telangiectasia, fibrofatty masses, or scarring are seen in the affected area. Given this unpredictability, for patients who are not at risk, clinical monitoring, parental education, and ongoing support are preferable to early intervention.

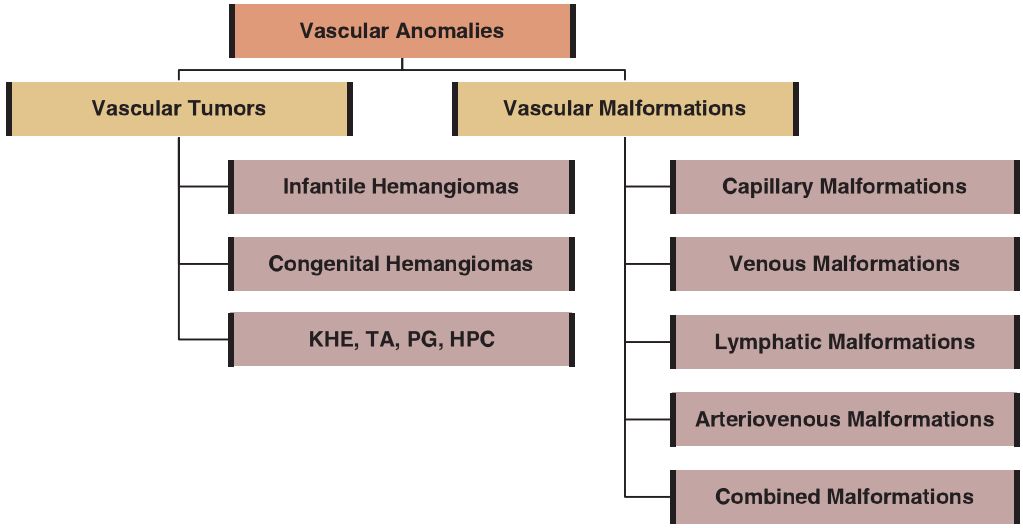


Figure 104.1 A schematic representation of the 1996 ISSVA classification of vascular anomalies. KHE, kaposiform hemangioendothelioma; TA, tufted angioma; PG, pyogenic granuloma; HPC, hemangiopericytoma.

In the growth phase, infantile hemangiomas are composed of proliferating endothelial cells and large numbers of pericytes, mast cells, and fibroblasts (7). As lesions regress, endothelial cell apoptosis increases and the vascular network is slowly replaced by fibrofatty tissue. Over the past two decades, many studies have investigated possible molecular factors that control this tumor life cycle, and considerable progress has been achieved in understanding the etiology of these lesions. To date, however, no single theory can explain key characteristics of hemangiomas, such as the predilection for females, usual occurrence after birth, spontaneous involution, and abnormal tissue architecture.

Proliferating hemangiomas have been shown to have increased expression of type IV collagenase, vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF) (8). In involuting hemangiomas, the high expression level of bFGF is maintained, whereas the level of expression of VEGF significantly decreases. Gene expression analysis comparing proliferating versus involuting hemangiomas demonstrates that insulin-like growth factor 2 (IGF-2) is highly expressed during proliferation but is significantly decreased during involution (9).

There is sound evidence that hemangiomas of infancy are related to placental endothelial cells. Four markers of hemangioma cells that are coexpressed in placental vessels have been identified: GLUT1 (a glucose transporter enzyme), merosin, Lewis Y antigen, and Fcγ-RIIb (10). GLUT1 is strongly expressed in infantile hemangiomas, placentas, and the blood–brain barrier; however, it is not expressed in normal surrounding vascular endothelium or in vascular malformations nor is it generally expressed in congenital hemangiomas (see discussion below). Because the positive expression of GLUT1 persists throughout all phases of the hemangioma life cycle, this histochemical marker is particularly useful in distinguishing hemangiomas of infancy from other vascular tumors and from vascular malformations.

Congenital Hemangiomas

Congenital hemangiomas are an uncommon variant of infantile hemangiomas. They differ from infantile hemangiomas in clinical behavior, appearance, and histopathology and are occasionally diagnosed *in utero*. Unlike infantile hemangiomas, congenital hemangiomas present at birth as fully grown lesions and do not undergo additional postnatal growth. Congenital hemangiomas fall into distinct subgroups: rapidly involuting congenital hemangiomas (RICHs) and noninvoluting congenital hemangiomas (NICHs) (11). RICHs typically involute by 12 to 14 months of age, leaving a residual patch of thin skin with prominent veins and little, if any, subcutaneous fat. NICHs do not undergo involution. Both tumor types have a predilection for the head or limbs. Both tumor types generally present as solitary violaceous lesions at birth and rarely coexist in a patient with a typical infantile hemangioma. Both are high-flow lesions that can be misdiagnosed as arteriovenous malformations (AVMs). In contrast to infantile hemangiomas, congenital hemangiomas are GLUT1 negative and comprise less than 3% of all hemangiomas seen in infancy (12).

Problematic Head and Neck Hemangiomas

Hemangiomas can occur anywhere in the head and neck region. Hemangiomas can occur singularly on the neck, cheek, nose, ears, forehead, or scalp, or multifocally at several of these sites. The head and neck can also be the site of segmental hemangiomas that occupy an entire developmental subunit (Fig. 104.3).



Figure 104.2 Infantile hemangiomas undergo a process of natural regression. The following series of photographs depict a young girl at **(A)** 2 months, **(B)** 6 months, **(C)** 18 months, and **(D)** 36 months of age. As the child grows older, the hemangioma changes from a bright red color to a grayish red color, and finally to the natural skin color. The mass of the lesion also decreases, leaving little evidence of the hemangioma over time.



Figure 104.3 A series of photographs of children with hemangiomas are presented demonstrating variations in morphology. **A:** Example of a child with an isolated focal hemangioma. **B:** Example of a child with multiple cutaneous hemangiomas. **C:** Example of a child with a facial segmental hemangioma occupying the periorbital, temporal, cheek, and chin areas of the face. Segmental hemangiomas are prone to ulceration as can be seen in this child around the left nasolabial crease.

Phaces

Hemangiomas that present in developmental segments are referred to as "segmental" lesions. These lesions are less common than focal lesions and have a higher risk of being life- or function-threatening and of having associated structural anomalies. Large cervicofacial segmental hemangiomas, particularly those on the forehead, temple, upper cheek, and around the periorbital area can be accompanied by a constellation of anomalies referred to as PHACES association (13). This association is far more common in females. Accompanying anomalies include *p*osterior fossa brain malformations (e.g., Dandy-Walker malformation), *h*emangiomas, *a*rterial abnormalities, *c*ardiac and aortic arch defects (e.g., aneurysms and congenital valvular aortic stenosis), *e*ye abnormalities (e.g., congenital cataract, microphthalmia, and abnormal retinal vessels), and *s*ternal clefts or supraumbilical raphes. More than 50% of patients are affected by neurologic sequelae, including seizures, stroke, developmental delay, and migraines (14).

Segmental hemangiomas are plaque-like in contour, typically undergo an extended proliferative period of 18 months, and unlike most hemangiomas of infancy, they do not completely regress. Furthermore, segmental hemangiomas are at a higher risk of ulceration and residual scarring (13). When there is an index of suspicion for PHACES association, referral should be made for an ophthalmologic and neurologic examination, screening echocardiogram, and possibly a magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA) of the head, neck, and chest. Patients in whom imaging reveals

a central nervous system abnormality should be closely monitored. The frequency of repeated imaging depends on symptom presentation and disease progression.

Hemangiomas in a Beard Distribution

Sixty-five percent of patients with hemangiomas that occur in a beard distribution (i.e., the chin, jawline, and preauricular areas) have associated airway involvement (15), and most airway hemangiomas are localized in the supraglottic or subglottic region. Patients must be closely followed and treatment should be initiated when airway involvement is suspected. Localized lesions are managed with laser ablation, intralesional steroids, surgical resection, or medical therapy (see below). Tracheotomy placement is used only in refractory cases or in cases in which the airway hemangioma is extensive. Hemangiomas that occur in the beard distribution often involve the parotid glands. Parotid gland hemangiomas typically occupy the entire gland and adjacent parapharyngeal space. They grow rapidly, causing extrinsic compression of the upper pharyngeal airway. These lesions frequently have a prolonged proliferative phase (12 to 16 months) and may require systemic therapy if the airway is compromised (16). Children with extensive hemangioma of the parotid region and pharyngeal area often have chronic recurrent otitis media, likely secondary to extrinsic compression of the eustachian tube.

Periocular Hemangiomas

Periocular hemangiomas can involve the upper lid, lower lid, and/or the retrobulbar space (Fig. 104.4). Pressure from the hemangioma on the globe may lead to astigmatism and amblyopia. Early ophthalmologic evaluation and treatment is indicated for all cases of periocular hemangiomas to avoid deprivation amblyopia, which can occur with as little as 1 week of deprivation during key developmental periods. Treatment options for vision-obstructing periocular hemangiomas include either medical therapy or surgical excision. Children older than age 1 who have gone untreated have rates of deprivation amblyopia as high as 75%.



Figure 104.4 An axial cut through the orbit of a child with a right pre- and postseptal orbital hemangioma.

Nose, Lip, and Ear Hemangiomas

Hemangiomas involving the nose occur in close to 16% of facial hemangiomas (17). Proliferation of lesions on the nasal tip often distort the anatomy of the nose, causing misalignment of the nasal cartilages and mild to severe nasal volume increase. Management approaches must consider the depth, location, rate of involution, and functional and cosmetic disturbance caused by the lesion. A multimodal approach combining serial observation, intralesional steroid injection, systemic steroid therapy, pulsed-dye laser (PDL) treatment, and surgical intervention is generally used (18). In view of possible complications such as severe cutaneous infiltration, the consequences on nasal growth, and the psychological impact of nasal distortion, surgical excision before school age is currently recommended. Various surgical techniques have been reported (19).

Lesions of the pinna of the ear can deform normal anatomic structures and result in ulceration with focal destruction of the auricle. Lesions obstructing the auditory canal can cause temporary conductive hearing loss. Lip lesions frequently involute slowly, sometimes leaving residual skin changes. Additionally, lip ulcerations can result in feeding difficulties, secondary infection, and significant scarring.

Subglottic Hemangiomas

Hemangiomas can occur anywhere within the tracheobronchial tree; however, they are most commonly seen in the subglottis (Fig. 104.5). As mentioned above, there is a close association of hemangiomas in a beard distribution with airway hemangiomas. However, airway hemangiomas can occur without associated cutaneous hemangiomas. In fact, only 50% of patients with airway hemangiomas have cutaneous hemangiomas (20). Presentation usually occurs within the first 6 months of life, and the earlier the presentation, the greater the likelihood that patients will require surgical intervention. Symptoms typically include progressive stridor and retractions. The diagnosis is made on rigid bronchoscopy, and though radiologic evaluation (MRI with contrast enhancement) is indicated, it rarely demonstrates extension of the lesion beyond the confines of the subglottis. Lesions are typically asymmetric and usually covered by a normal smooth mucosa.

Open surgical excision is an option in large focal hemangiomas of the subglottis and is accomplished through a vertical tracheotomy extending through the cricoid ring. Typically, a thyroid alar graft is needed to augment the concomitant narrow subglottis (20). Although many other treatment modalities (systemic steroids, intralesional steroids, prolonged intubation, CO_2 [carbon dioxide] and KTP [potassium–titanyl–phosphate] laser ablation, and microdebrider resection) have been used, these modalities carry a significant risk of inducing an acquired or congenital subglottic stenosis (20). Medical management as discussed below is also an option in selected cases.

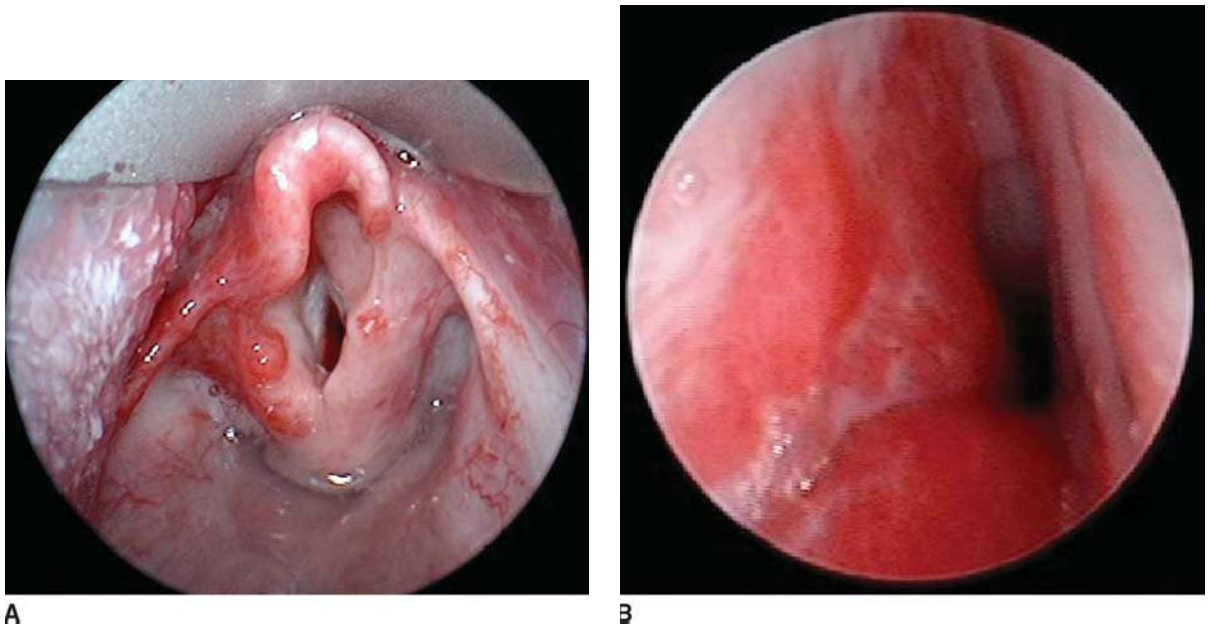


Figure 104.5 Endoscopic photographs of **(A)** a child with flat supraglottic hemangiomas occupying the left epiglottis and aryepiglottic fold and **(B)** a child with a large left subglottic hemangioma that severely narrows the subglottic lumen.

KASABACH-MERRITT PHENOMENON

Kasabach-Merritt phenomenon is a rare, life-threatening condition associated with two specific subtypes of vascular tumors, tufted angioma or kaposiform hemangioendothelioma. Kasabach-Merritt phenomenon is included in this section only to highlight the fact that it is not associated with infantile hemangiomas, as sometimes construed. In Kasabach-Merritt phenomenon, the tumor traps and destroys platelets. In addition to platelet trapping, there are also other associated coagulopathies. As the tumor grows, it causes more platelet trapping. No single treatment approach is effective and unfortunately, responses to various treatments are inconsistent. Initially, corticosteroids are given at varying doses. If this approach is not effective, chemotherapy with vincristine is started. If this regimen is not effective, other drugs such as interferon, Cytoxan, and Amicar are used. If the tumor does not respond to drug therapy, embolization, surgical removal, or both may be necessary. Blood products such as platelets and packed red blood cells are administered only if absolutely necessary. The lesion may take many years to decrease in size. Improvement in platelet counts initially occurs with a decrease in the size of the lesion.

DIAGNOSTIC EVALUATION OF INFANTILE HEMANGIOMAS

The diagnosis of infantile hemangiomas is generally established on the basis of clinical presentation, history, and physical examination. In patients with complex lesions that require surgical intervention, additional investigations can be helpful in determining the extent of involvement. Ultrasound (US) with color flow Doppler can be extremely useful in differentiating hemangiomas from vascular malformations that may have a similar appearance. On US, an infantile hemangioma appears hypoechoic, well defined, and heterogeneous in texture, with small cystic and sinusoidal spaces. In most proliferating hemangiomas, a characteristic fast-flow pattern is visualized by Doppler US. Typically, a quick upstroke and gradual down slope is seen (Fig. 104.6).

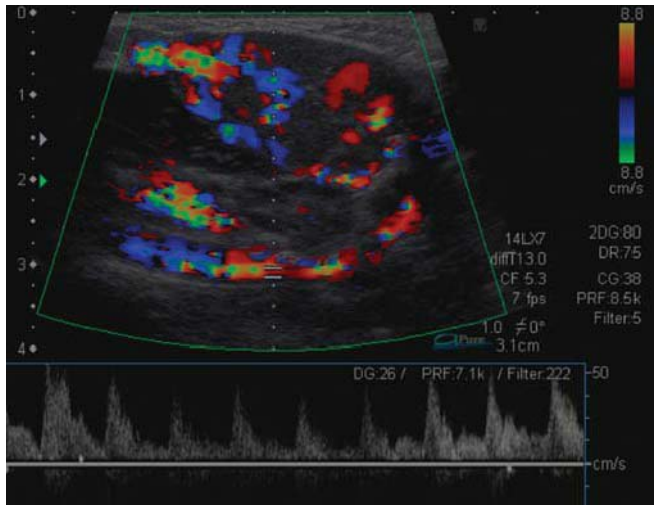


Figure 104.6 Color ultrasound Doppler image of an infantile hemangioma. Infantile hemangiomas are composed of small blood vessels conducting blood at high flow rates **(top panel)**. Doppler demonstrates that the blood flow in these small blood vessels is pulsatile, characterized by a rapid upstroke and a gradual down stroke in flow rates **(bottom panel)**.

TABLE 104.1 MRI CHARACTERISTICS OF VASCULAR ANOMALIES

Anomaly Type	T1-Weighted	T2-Weighted	Contrast	Gradient
Hemangioma	Soft tissue mass, isointense or hypointense, flow voids	Lobulated soft tissue mass, increased signal, flow voids	Uniform intense enhancement	High-flow vessels within and around soft tissue mass
Venous malformation	Isointense to muscle, possible high-signal thrombi	Septated soft tissue mass, high signal, signal voids (phleboliths)	Diffuse or inhomogeneous enhancement	No high-flow vessels
Lymphatic malformation	Septated soft tissue mass, low signal	Soft tissue mass, high signal, fluid levels	Rim enhancement or no enhancement	No high-flow vessels
Arteriovenous malformation	Soft tissue thickening, flow voids	Variable increased flow voids	Diffuse enhancement	High-flow vessels throughout abnormal tissue

Dubois J, Garel L. Imaging and therapeutic approach of hemangiomas and vascular malformations in the pediatric age group. *Pediatr Radiol* 1999;29(12):879–893.

MRI and computed tomography (CT) scans can delineate the extent and involvement of the hemangioma and can also be helpful in distinguishing hemangiomas from other malformations (21) (Table 104.1). In the proliferative phase, a hemangioma appears as a well-circumscribed tumor with homogeneous parenchymatous density and intense enhancement. In the involutive phase, it appears heterogeneous, with distinct lobular architecture and large draining veins in the center and the periphery. Through rarely used for the diagnosis of vascular anomalies, conventional angiography can provide information about the size of lesions and feeding vessels and can also distinguish between hemangiomas and other vascular malformations. Biopsy is indicated only when the diagnosis is uncertain or when the possibility of malignancy must be ruled out.

Treatment of Infantile Hemangiomas

Most uncomplicated focal hemangiomas involute spontaneously and do not require intervention. Nevertheless, rapidly proliferating lesions are sometimes problematic and can cause a wide array of complications, including ulceration, infection, hemorrhage, necrosis, airway obstruction, loss of vision, and cardiac failure. To ensure timely intervention should any of these complications occur, patients should be closely monitored during the proliferative phase. Optimally, management strategies for complex lesions should be planned by a multidisciplinary team of clinicians with expertise in treating vascular anomalies. Management decisions should consider the size and location of the lesion, the presence of complications at diagnosis, the age of the patient, and the rate of tumor growth. Large segmental hemangiomas and life- or function-threatening hemangiomas are likely to require immediate treatment. Immediate treatment is also essential in the presence of ulceration or secondary infection. Serious aesthetic concerns such as the possibility of permanent disfigurement or scarring warrant early intervention.

These patients almost always require multimodal therapy. Major therapies currently include pharmacotherapy, chemotherapy, laser therapy, and surgical excision. Recently, the dramatic effect of oral propranolol has been reported in several small case series (22–24), and prospective studies are underway at several major centers. Although research regarding propranolol is in its infancy, this medication has replaced steroids as the first line in medical management. Propranolol is discussed further below.

Ulceration is the most common complication of hemangiomas, often occurring in lesions involving the nose, lips, and periorbital region (25). Most ulcers develop during a phase of rapid growth. They are often painful and can lead to infection, anemia, scarring, and disfigurement. Treatment should focus on decreasing pain, preventing secondary infections, and promoting reepithelialization. Painful ulcerations may require oral medications such as acetaminophen or acetaminophen with codeine. Superficial ulcerations generally respond to supportive therapy such as gentle cleansing and the daily application of a topical antibiotic. Dressings that cover the ulceration such as DuoDERM or Mepilex can provide pain relief and promote healing. When an associated cellulitis occurs, oral systemic antibiotics are given. Ulcerations on localized cervicofacial lesions are amenable to surgical resection, which generally results in excellent cosmetic outcomes. When resection is not feasible or desirable, PDL is used to promote reepithelialization and decrease pain. This approach is particularly helpful in anatomic areas that are not amenable to resection, such as extensive facial lesions. Products such as imiquimod, which stimulates endogenous interferon production, and becaplermin gel, which appears to accelerate reepithelialization, have been used for treating refractory ulcerated hemangiomas but require further study.

Until recently, corticosteroids have remained the first line of therapy for the treatment of complicated hemangiomas (26). Currently, the two indications for the use of corticosteroids in the treatment of infantile hemangiomas are for

those patients who fail propranolol treatment and for intralesional injection in small focal hemangiomas (27). Local injection is especially effective in the periorbital region, nasal tip, and subglottic region. Some surgeons and ophthalmologists recommend using general anesthesia, whereas others perform the procedure on an outpatient basis using a topical anesthetic. A long-acting steroid (e.g., triamcinolone acetonide) and a short-acting steroid (e.g., betamethasone acetate) can be combined in a total volume that generally does not exceed 2.5 mL. The dose and volume are individualized according to the size of the lesion. A 25-gauge needle is used and injections are made directly into the hemangioma in different directions through the same needle hole. Following this, direct pressure is applied for 2 to 10 minutes to stop bleeding. In subglottic lesions, it is important to avoid direct injection of the cricoid plate, as cartilage resorption may occur. Although this approach is associated with a 70% to 90% response rate in periorbital hemangiomas, a known complication is the risk of retinal artery embolization and thrombosis, with resulting blindness (28). To lessen this risk, fundoscopic retinal examination should be performed as the lesion is slowly injected so to recognize early signs of retinal arterial flow interruption. Adrenal suppression and failure to thrive have also been reported following local injection for periocular hemangioma (27).

Propranolol, a nonselective beta-blocker, has recently been introduced as a novel modality for the treatment of proliferating hemangiomas. The dramatic effect of propranolol therapy on hemangiomas was first described in 2008 by Leaute-Labreze et al. (22). These authors serendipitously discovered that propranolol induced early regression of infantile hemangiomas during their proliferative phase. Their reported findings in a small series of infants sparked the enthusiasm of clinicians eager to identify appropriate uses for propranolol. Buckmiller et al. (24) reported the successful management of tracheal hemangiomas in a young patient with otherwise treatment-resistant airway lesions. Within 6 weeks of beginning oral propranolol (2 mg/kg/day), airway compromise was eliminated and the patient had complete resolution of endoscopically visible disease. No side effects occurred. Denoyelle et al. (23) reported the successful management of two infants with subglottic hemangiomas that were resistant to established medical treatments. Both patients' subglottic hemangiomas responded dramatically to propranolol, and no side effects were noted. The mechanisms of action are speculative, but may involve the downregulation of angiogenic factors and upregulation of apoptosis. In summary, early research illustrates that propranolol may be a safe and effective therapeutic strategy for both cutaneous and airway lesions. There is controversy as to the diagnostic testing needed prior to drug administration and the appropriate venue (inpatient or outpatient) for drug. Table 104.2 depicts an inpatient and outpatient algorithm developed

TABLE 104.2 PROTOCOL TO INITIATE PROPRANOLOL THERAPY

Inpatient propranolol algorithm

- Preadmission diagnostic testing—echocardiogram to rule out congenital anomalies in patients with a history of murmurs, failure to thrive, or other significant medical comorbidities; EKG to rule out cardiac arrhythmia
- Admit to telemetry unit with continuous heart rate and blood pressure monitoring
- Initiate propranolol at 0.5 mg/kg PO BID for 2 doses; increase to 1 mg/kg PO BID for 2 doses; finally increase to 2 mg/kg PO BID
- Propranolol is increased in this manner as long as the patient exhibits no adverse response to the administration of the medication
- Check blood glucose 2 h after each dose of propranolol
- Check EKG 24 h after initiation of propranolol
- Discharge home after second dose of propranolol at 2 mg/kg with contact information if questions or problems arise
- Parents are instructed to maintain a strict feeding regimen. If the child is <6 mo of age, feedings should be every 2–4 h. Older children can be spaced to feedings every 6–8 h
- Parents instructed to hold medication if the child becomes ill and/or has decreased PO intake

Outpatient propranolol algorithm

- Diagnostic testing—same as for inpatient algorithm
- Monitor on telemetry unit for 6 h with continuous blood pressure and heart rate monitoring
- Initiate propranolol at 0.5 mg/kg
- Check blood glucose 2 h after each dose of propranolol
- Discharge instructions as for inpatient algorithm with contact information if questions or problems arise
- Continue propranolol at 0.5 mg/kg PO BID or 1 wk
- Return to hospital for 6 h admission on telemetry unit during which propranolol is increased to 1 mg/kg. An EKG is obtained prior to increasing the dose and blood glucose is checked 2 h after dose. Discharge home at this dose for a week with discharge instructions as previous
- Return to hospital for 6-h admission during which propranolol is increased to 2 mg/kg. Blood glucose is again checked 2 h after dose. Patient is discharged home with discharge instructions as previous with follow-up in 4 wk

by our vascular anomalies team. In general, we advocate inpatient protocol for infants less than 2 years of age and children with comorbidities. The parents of all other children are given the choice of inpatient or outpatient treatment. Side effects that have been reported to date include hypoglycemic seizures and sleep disturbances.

Lasers have a limited role in the treatment of hemangiomas. The PDL is often used at the end of the involution phase to reduce any residual vascular markings. PDLs are also used as mentioned above to promote wound healing, reepithelialization, and pain control for ulcerated hemangiomas that are refractory to medical management. The CO_2 and Nd:YAG (neodymium-doped yttrium aluminum garnet) lasers have been used to ablate airway hemangiomas, though overaggressive use of these lasers can cause scar deposition and subglottic stenosis.

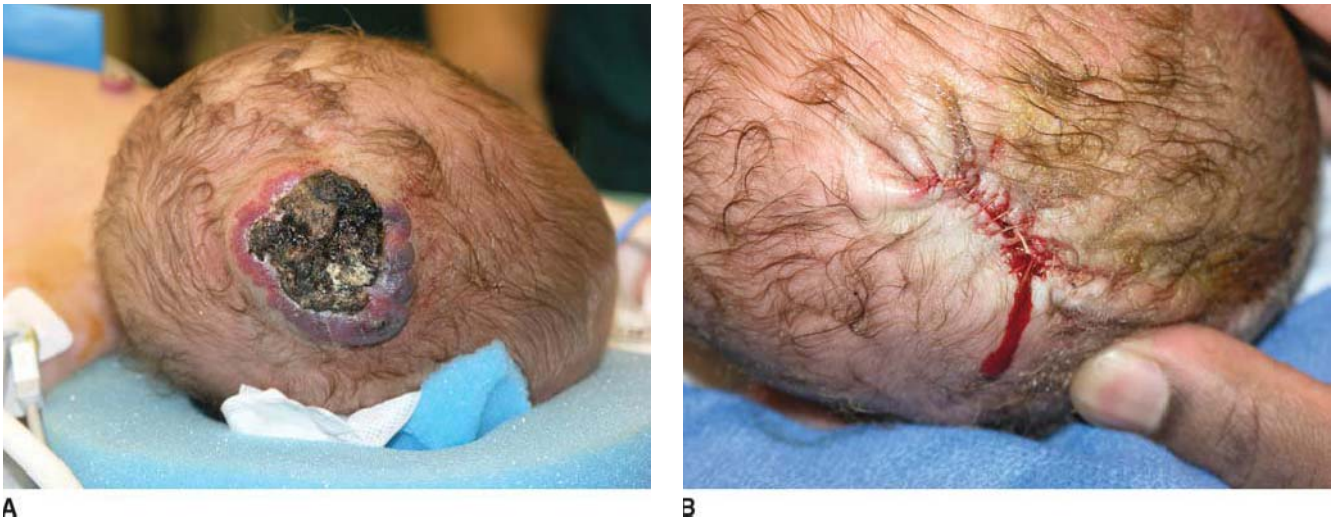
The indications for the surgical excision of hemangiomas are in evolution, especially with given the natural regression of these lesions and the efficacy of medical management. Nonetheless, there are several clinical situations in which surgical excision is an attractive treatment option (Table 104.3). Large hemangiomas that are likely to leave large amounts of fibrofatty residuum or excess skin are often good candidates for surgical excision. Ulcerative hemangiomas that fail medical management and can be excised completely are another candidate for surgical excision (Fig. 104.7). Periorbital hemangiomas and airway hemangiomas that are causing significant symptomatology and are unlikely to respond quickly or do not respond to medical management are often best treated by surgical excision. Finally, hemangiomas that are not completely resolved by school age and cause psychosocial distress can also be treated with surgical excision. The timing of surgery remains a controversial subject, particularly in regard to early surgery on hemangiomas that are disfiguring and in which the ultimate results of spontaneous involution are difficult to predict. In summary, surgical intervention should be considered when surgery is thought to provide a better overall outcome to the patient than natural regression or medical management.

TABLE 104.3 RELATIVE INDICATIONS FOR SURGICAL MANAGEMENT OF HEMANGIOMAS

- Noninvoluting congenital hemangioma
- Ulcerative hemangioma that will likely leave a large scar
- A hemangioma that is causing significant functional compromise or symptomology and is not responding expeditiously to medical management. Examples of functional compromise include obstruction of visual axis with changes in vision or airway obstruction.
- A hemangioma that has a pedunculated appearance, and therefore will likely not involute completely.
- A hemangioma that causes significant psychosocial or appearance issues to the patient as he/she enters school can be removed with a satisfactory cosmetic outcome.

VASCULAR MALFORMATIONS

Vascular malformations are the second major category of vascular anomalies (Fig. 104.1). In contrast to vascular tumors, vascular malformations are present at birth and grow commensurately with size of the child. Although the molecular mechanisms underlying the formation of these lesions remain unclear, they are known to result from abnormal development and morphogenesis. Histologic examination of vascular malformations shows no evidence of cellular proliferation but rather progressive dilation of abnormal channels. Vascular malformations are designated according to the predominant channel type present. They are classified as capillary, venous, lymphatic, arterial, or



A B

Figure 104.7 Photographs of a patient with a large ulcerative scalp hemangioma **(A)** that was surgically excised **(B)**.

combined malformations. Malformations with an arterial component are rheologically fast flow, whereas capillary, lymphatic, and venous malformations are slow flow in nature. The morbidity of vascular malformations varies greatly both within and among the clinical subgroups cited above.

Diagnostic Modalities

Accurate and expeditious diagnosis is essential to the proper treatment of vascular malformations. A diagnosis is arrived upon only after a thorough and complete history and physical exam. Key parts of the history include the age at which parents initially noticed the lesion; overall rate of growth of the lesion as well as recent changes in the size of the lesion; and acute changes in the size of the lesion concordant with upper respiratory tract infections, trauma, hormonal changes, body position, Valsalva maneuver, or high cardiac output states. In addition to the above history, a complete review of systems is essential. Fundamental aspects of the physical exam include the extent and color of the lesion, the three-dimensional morphology of the lesion, temperature, presence of vascular marking, compressibility of the lesion, and whether the lesion is pulsatile.

Radiologic imaging is frequently the next step in the diagnostic algorithm, which is used not only to validate the clinical diagnosis but also to determine the extent of the lesion. Imaging modalities used include US, MRI, and, infrequently, arteriograms. Each subclass of vascular malformation has classic radiologic findings that are helpful in diagnosis (Table 104.1). The success of using radiologic imaging as a tool in the diagnosis of vascular malformations depends on the expertise of the radiologist. In most institutions, the radiologist is a key member of the multidisciplinary team that delivers care to children with vascular anomalies.

Capillary Malformations

Capillary malformations are the most commonly occurring subgroup of vascular malformations. The two most common types of capillary malformations are salmon patches (nevus simplex) and port-wine stains (nevus flammeus) (Fig. 104.8). This malformation consists of a superficial collection of ectatic vessels that is located in the papillary and superficial reticular dermis, with a mean depth of 0.46 mm (29). Salmon patches are extremely common and manifest as macular capillary stains, colloquially referred to as "angel kisses" or "stork bites." They generally appear as pink macules on the forehead, eyelids, nose, and nuchal region and characteristically fade or disappear during childhood. Port-wine stains also present at birth as flat, light pink, macular lesions. However, in contrast to "angel kisses" or "stork bites," port-wine stains become raised, nodular, or darken to a deep red and persist throughout life. Port-wine stains occur in 0.3% of newborns and frequently appear within the distribution of the trigeminal nerve (30,31).

The majority of isolated port-wine stains occur sporadically, though an autosomal dominant inheritance pattern has been reported in some families. Port-wine stains may occur in conjunction with other vascular anomalies or congenital malformations. For example, in Wyburn-Mason syndrome, port-wine facial stains are associated with a unilateral AVM of the retina and intracranial optic pathway (30,31). When port-wine stains appear in the trigeminal nerve distribution, there may be associated structural and vascular abnormalities of the face and leptomeninges (Sturge-Weber syndrome) (32) (Fig. 104.8). Glaucoma occurs in approximately 10% of patients with facial port-wine stains and can occur without leptomeningeal involvement. For the above reasons, children with craniofacial involvement should undergo an MRI or CT scan to rule out central nervous system pathology.



A B

Figure 104.8 **A:** Photographs of a salmon patch on the posterior neck of a patient. **B:** Photograph of a port-wine stain covering the upper right half of the face.

Sturge-Weber syndrome deserves additional attention, given its unique clinical manifestations. Sturge-Weber syndrome typically presents with a facial port-wine stain in the ophthalmic distribution of the trigeminal nerve, glaucoma and vascular eye abnormalities, and an ipsilateral intracranial vascular malformation. Children with Sturge-Weber syndrome often develop progressive neurologic problems, including seizures, migraines, stroke-like episodes, learning difficulties or mental retardation, visual field impairment, or hemiparesis. Furthermore, overgrowth of the craniofacial skeleton can sometimes be noted on the side of the lesion, causing most notably a cross-bite deformity. The specific genetic and environmental factors that result in the disorder are unknown, but the localized abnormalities of blood vessel development and function affecting the facial skin, eye, and brain suggest that a developmental disruption occurs during the first trimester of pregnancy (32).

Treatment with PDL is often used to mitigate the red coloration of port-wine stains and prevent the progression to more darkly colored and raised lesions. Based on the theory of selective photothermolysis (33), PDL is able to preserve the epidermis by allowing hemoglobin to be more precisely targeted within lesions, resulting in less injury to adjacent nontargeted tissue. In capillary lesions that have thickened and become darker with age, the Nd:YAG laser has been used successfully, though patients are often left with some residual scarring. Other options, though of limited use, include surgical debulking of hypertrophied lip and eyelid tissue and skin grafting of facial aesthetic units (30,31). Medical management usually takes top priority and consists of ameliorating associated health problems such as glaucoma and seizures.

VENOUS MALFORMATIONS

Congenital venous malformations consist of either localized or diffuse ectatic veins with abnormal collections of irregular venous channels having flat, mitotically inactive endothelia and scant mural smooth muscle. These lesions may be superficial (i.e., intradermal or subcutaneous) or deep (i.e., intramuscular or intraosseous) (Fig. 104.9). For the most part, they are asymptomatic. Superficial venous malformations have a bluish compressible mass with no palpable thrill or audible bruit. These lesions often enlarge when the lesion is in a dependent position, with Valsalva maneuver, or high cardiac output states. Phleboliths can be seen on x-ray and are pathognomonic for venous malformations. Doppler echocardiography, MRI or MRA, and direct puncture phlebography may be required to confirm the diagnosis and assess the extent of the lesion. When malformations are extensive, a blood coagulation profile should be performed. Patients should also be screened for genetic polymorphisms associated with an increased risk of aberrant clotting (i.e., factor V Leiden, plasminogen activator inhibitors [PAIs], and methylenetetrahydrofolate reductase [MTHFR]). Since patients with extensive venous malformations are at risk for a pulmonary embolus following surgery, they require antithromboembolic prophylactic treatment (26).



Figure 104.9 Photograph of a young boy with an extensive venous malformation of the right check and lower lip.

Treatment depends upon the location, associated symptoms, and extent of the venous malformation. Phleboliths within the malformation often cause pain. Symptoms caused by phleboliths can be treated medically with aspirin, nonsteroidal antiinflammatory drugs, or low molecular weight heparin. When a lesion is localized and accessible, surgical excision results in excellent outcomes. More extensive lesions are often not amenable to resection or only partially resectable. To preserve function when vital structures are involved, a series of sclerotherapy procedures with one of a variety of sclerosing agents (see section below on Lymphatic Malformations) is often performed (34). Superficial lesions or the superficial component of deep lesions can be treated with the Nd:YAG laser (35). Recurrent painful intramuscular or intraarticular bleeding or thrombosis and phlebolith formation can be ongoing problems.

LYMPHATIC MALFORMATIONS

Lymphatic malformations are benign vascular lesions that arise from embryologic disturbances in the development of the lymphatic system. They encompass a wide spectrum of abnormalities, including cystic lymphatic lesions (formerly referred to as "lymphangiomas"), lymphangiectasis, and lymphedema. Given that lymphangiectasis and lymphedema usually involve sites other than the head and neck, these topics will not be further discussed in this chapter.

Cystic lymphatic malformations can be seen in any anatomic region but are more commonly seen in rich lymphatic areas, such as the head and neck (45% to 52%), axilla, mediastinum, groin, and retroperitoneum. These malformations are thought to be the result of maldevelopment of the embryonic lymphatics or lymphatic jugular sacs, with failure of these structures to connect or drain into the venous system. In some patients, a venous malformation can be seen in association with a cystic lymphatic lesion. There are

three morphologic types of cystic lymphatic lesions: microcystic, macrocystic, and combined. Microcystic malformations present as clear, tiny vesicles that permeate the subcutaneous tissue and muscles. Microcystic lesions are commonly found above the level of the mylohyoid muscle and involve the oral cavity, oropharynx, tongue, parotid gland, submandibular gland, and preepiglottic space (Fig. 104.10). These vesicles are often firm and may give the impression of a brawny edema. Macrocystic lesions are large, compressible or noncompressible, smooth, translucent masses under normal or bluish skin. Most macrocystic lesions are multilocular structures consisting of numerous cysts that vary in size. Macrocystic lesions are often located below the level of the mylohyoid muscle and involve the anterior and posterior cervical triangles (30,31).

Histologically, cystic lymphatic malformations are composed of vascular spaces filled with eosinophilic and protein-rich fluid. A single layer of flattened endothelium lines the walls of lymphatic channels. The fibrovascular vessel walls are of variable thickness, with both abnormally formed striated and smooth muscle components. Collections of lymphocytes are common throughout the contained connective tissue. Hemorrhage within the cystic spaces is common, indicating recent trauma or spontaneous intralesional bleeding.

Large cystic lymphatic lesions can be diagnosed *in utero* by US as early as the beginning of the second trimester, but lesions are more commonly noted at birth; the vast majority are evident by age 2. Although large cervical or axillary lesions identified in the perinatal period have been referred to as "cystic hygromas," this term is incorrect, as it does not encompass the morphology and distribution of most cystic malformations. The prenatal diagnosis of anterior and posterior cervical lymphatic malformations has significant clinical implications. They may be associated with airway obstruction, and prenatal diagnosis can influence the mode, timing, and place of delivery. Specifically, the prenatal diagnosis of large cervicofacial lymphatic malformations can signal the need to prepare for possible interventions to control a precarious airway in the delivery room. These patients may require the presence of a skilled surgical team capable of performing an EXIT (*ex utero*

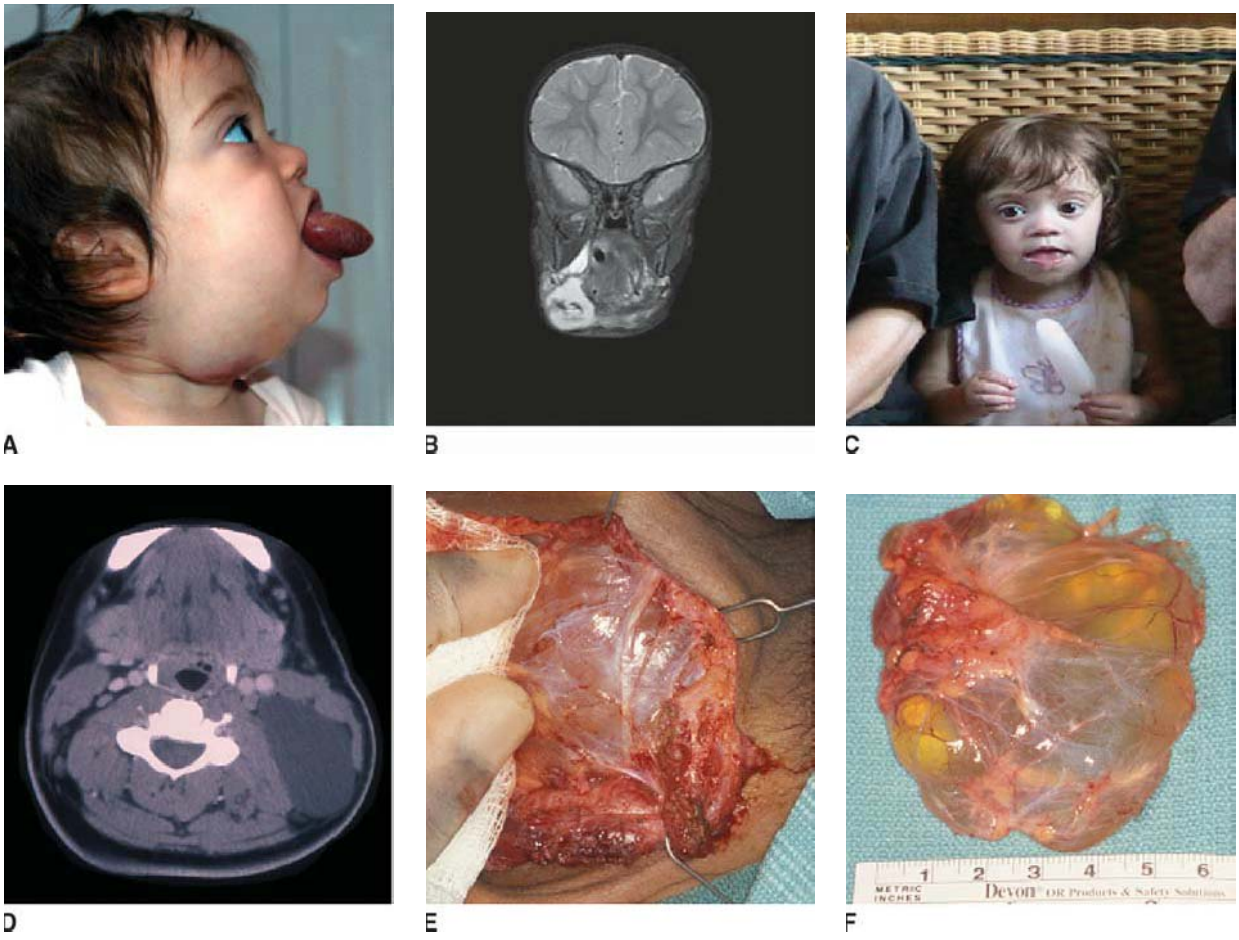


Figure 104.10 **A:** Combined microcystic and macrocystic malformation of the tongue, floor of mouth, and anterior neck. **B:** MRI with gadolinium of the same patient. **C:** Postoperative picture after excision of cervical disease and tongue reduction. **D:** CT scan of neck demonstrating macrocystic malformation of the lateral neck. **E** and **F:** intraoperative pictures demonstrating the appearance of a macrocystic lymphatic malformation.

intrapartum treatment) procedure as well as a spectrum of other techniques, including fiberoptic and rigid endoscopy and direct surgical airway access. Posterior cervical lesions that arise in the perinatal period have been associated with Turner syndrome, as well as other syndromes and congenital anomalies. In this particular situation, there is an associated high prenatal mortality rate secondary to hydrops and diffuse lymphedema. Therefore, amniocentesis with chromosomal analysis should be performed and genetic and family counseling provided (36).

Postnatally, most cases are readily diagnosed by physical examination. Transillumination can be helpful in differentiating some cystic lesions from solid masses. All patients with cervical cystic lesions should have a chest x-ray to determine the presence or absence of mediastinal involvement. Although US is helpful in confirming the diagnosis in superficial lesions, it is less valuable for showing extension into deep structures of the neck, thoracic cavity, and retroperitoneum. CT or MRI can clearly demonstrate the anatomic extent of cystic lesions and their relationship to soft tissues, muscle, and vascular structures.

Cystic lymphatic malformations are associated with numerous complications. Cutaneous involvement can be associated with spontaneous lymphatic leakage from pathologic vesicles. Bacteria can readily enter via these vesicles and quickly spread through tissues affected by the lymphatic lesion. The result is acute cellulitis and/or recurrent cellulitis, which in turn can lead to cosmetic disfigurement and life-threatening sepsis. Given the morbidity of such infections, aggressive antimicrobial therapy is mandatory (30,31).

Another very serious complication caused by large lymphatic malformations of the head and neck is respiratory obstruction of the larynx and trachea. Management is extremely difficult and requires staged operative procedures, speech and physical therapy, and long-term follow-up, preferably by a multidisciplinary team. Less commonly, dysphagia is caused by the involvement of the hypopharynx and the esophagus. Other complications include localized hemorrhage into cysts and nerve compressions that can cause paresthesias and pain. Chylothorax and chylopericardium have been reported as rare complications of cervicomediastinal lesions.

Treatment depends upon the clinical presentation, the size of the lesion, the anatomic location, and the complications. Although complete excision of the lesion is the treatment of choice, this is sometimes impossible. Whereas small lesions are generally amenable to excision with excellent results, large lesions that involve deep structures of the neck, tongue, and mediastinum entail the risk of multiple complications, including fistula formation, infection, damage to vascular structures, damage to nerves, and cosmetic deformity. Past reported mortality rates of such complex lesions vary from 2% to 6%. Persistent disease manifests in about 30% of patients who have undergone gross excisions. It is important to remember that in the absence of symptomatology, it is reasonable and appropriate to manage lymphatic lesions nonoperatively. Surgical excision cannot be done without scarring, and undesirable scars can develop after excision of large intradermal and subcutaneous microcystic and vesicular lymphatic lesions. In some patients with extensive microcystic disease, lymphatic vesicles may become apparent, in or around the scar, years after excision (37).

Sclerotherapy is frequently used as an alternative to surgery for patients with macrocystic disease, and although it is not generally curative, approximately 40% of patients will have amelioration of their symptoms (30,31). A number of sclerosing agents have been used, including ethanol, bleomycin, OK-432 (known also as Picibanil), doxycycline, and sodium tetradecyl sulfate. In the United States, medical grade (90% to 95%) ethanol is the most commonly used agent because of its efficacy and widespread availability (38). Lymphatic cysts are aspirated under US guidance and ethanol is injected into the cyst, with a dose ranging from 1 to 2 mL/kg. When lesions are large, an intralesional closed suction drain is placed for 24 hours in order to aspirate ongoing fluid drainage. Owing to concerns about pulmonary toxicity, bleomycin sulfate is not commonly used in North America (39). Injection of 0.3 to 0.6 mg/kg is given through a 21-gauge needle into the cavity of the malformation after aspiration of lymphatic fluid. Using this approach, total doses remain relatively low and do not approach doses associated with the development of pulmonary fibrosis. OK-432 is derived from a lyophilized mixture of group A *Streptococcus pyogenes* incubated with benzylpenicillin. It is not yet approved in the United States, though its use appears to show promise for macrocystic lesions. It is thought that this compound works by increasing endothelial permeability and accelerating lymph drainage from lymphatic spaces. A solution of OK-432 is prepared by dissolving 0.1 mg of OK-432 in 10 mL of normal saline. After aspirating as much cyst fluid as possible, the solution is injected to a maximal total dose of 0.2 mg of OK-432 in one treatment session. When the initial response to any sclerosant is unsatisfactory, treatment is repeated at 6-week to 3-month intervals.

Swelling of the malformation is a dangerous side effect of sclerotherapy. It can cause airway compromise, especially when the lesion is located in the cervical area and mediastinum. The procedure is thus usually performed in the hospital under general anesthesia, and patients are subsequently observed for 24 hours. Common side effects include fever for 2 to 4 days and local inflammatory reaction with tenderness, erythema, or swelling of the lesions, which lasts for 1 to 3 weeks. When treatment is unsuccessful or yields only a partial response, surgery may be required.

ARTERIOVENOUS MALFORMATIONS

AVMs are congenital vascular lesions associated with a variable degree of arteriovenous shunting (30,31). Some of these lesions are thought to originate from arteriovenous

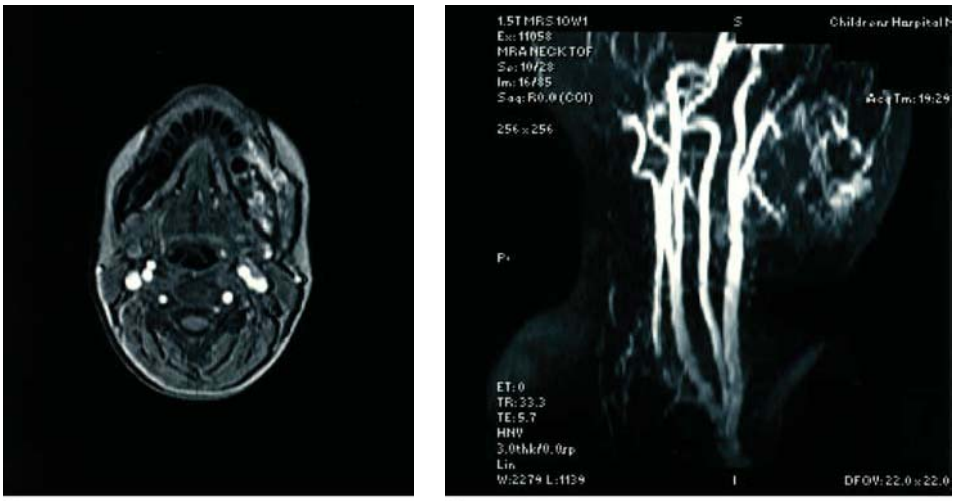


Figure 104.11 **A:** MRI and **(B)** MRA of the neck demonstrating an AVM of the left mandible.

channels that have failed to regress during development. These high-flow communications between arteries and veins are among the most dangerous vascular anomalies. They are always multiple and vary in diameter from several millimeters to the size of the normal precapillary anastomosis. The length of the channels between the arteries and the veins can vary from millimeters to centimeters, and convoluted or cavernous abnormal vascular structures may be intercalated between the arterial and venous ends of the malformation. The fast-flow character of AVMs usually becomes evident in childhood or during puberty. Rapid expansion has been reported following pregnancy, trauma, or inadequate surgical intervention. Complications associated with AVMs include cardiac hypertrophy, cardiac failure, and cardiac instability, as well as hemorrhage and stroke.

It is clinically useful to identify three major groups of AVMs, based on structural criteria: truncal, diffuse, and localized. Truncal fistulae arise from major arterial branches and commonly occur in the head and neck; however, trunk and extremity involvement is also seen. Diffuse AVMs are encountered particularly in the limbs and more frequently in lower than in upper limbs. Localized malformations are composed of a mass of abnormal intercalated tissues and can occur in any organ (30,31).

Owing to variations in position, size, length, and number, there is a wide pattern of clinical appearance. Nevertheless, these malformations are recognizable by warmth, a palpable thrill, and an audible bruit. Traditional angiography or MRA to demonstrate their vascular anatomy is essential for confirming the diagnosis and developing a treatment plan (Fig. 104.11).

When a lesion is small and asymptomatic, a period of observation is often the most prudent initial strategy. Unfortunately, however, pain, expansion, ulceration, bleeding, and cardiac decompensation can occur after a quiescent period. If so, more aggressive treatment is indicated. Intraarterial embolization combined with surgical excision currently offers the best chance for cure, but complete excision may be impossible because of location and extent of the malformation. Complex lesions require creative operations tailored to individual pathology and anatomy. When lesions cannot be excised, palliative embolization may be appropriate to control symptoms. Embolization techniques include the use of metal coils, particles, and glue (e.g., *N*-butyl cyanoacrylate). In extremity lesions, amputation may eventually be required. The long-term outcomes of early versus late treatment and the different modalities of treatment are unknown.

HIGHLIGHTS

- All congenital vascular lesions, or more appropriately called vascular anomalies, can be divided into vascular tumors and vascular malformations.
- The most common example of vascular tumors are infantile hemangiomas that present shortly after birth, grow for 6 to 9 months, and then undergo programmed cell death leading to involution.
- Vascular malformations are present at birth and are composed of dysmorphic blood vessels, which grow proportionate with the size of the child and do not involute as the child gets older.
- Kasabach-Merritt phenomenon is associated with kaposiform hemangioendotheliomas and tufted angiomas, and not infantile hemangiomas.
- Most infantile hemangiomas do not require any sort of medical or surgical intervention and require only education of the family and reassurance.
- Infantile hemangiomas that have the potential of causing long-term functional or aesthetic issues should be treated with medicine or surgery.
- Management of vascular malformations is limited mostly to laser, sclerotherapy, or surgical treatment.

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Head and Neck Masses in Children

105

Cuneyt M. Alper *Jacob G. Robison*

Primary care physicians commonly encounter children presenting with head and neck masses. Unlike adults in whom a neck mass is considered malignant unless proven otherwise, most pediatric neck masses are benign (1,2). Most generalists are comfortable in treating and following acute inflammatory masses that appear to be benign lymph nodes. However, the vast majority of cases that do not fit this description get referred to a specialist. Although most head and neck masses are benign, they commonly present a diagnostic and therapeutic dilemma to the specialist.

Congenital, developmental, and inflammatory lesions make up most of the masses in the head and neck region. Neoplastic processes comprise 10% to 15% of head and neck masses in children. A retrospective review of 445 children with neck masses revealed that 55% of the masses were congenital, 27% were inflammatory, 5% were noninflammatory benign masses, 3% were benign neoplasms, and 11% were malignancies. In another series of 239 children who underwent cervical lymph node biopsy for nodal enlargement, 49% had idiopathic lymphoid hyperplasia, 37% had infectious lymphoid hyperplasia, and 13% had neoplasms (3). Although malignant neoplasms are not common, cancer ranks second to trauma as a cause of childhood mortality. About 5% to 10% of malignancies originate in, and 25% eventually involve, the head and neck, leading to enhanced concerns of parents and the primary care physicians resulting in early, and sometimes extensive, diagnostic workup and intervention (4). The need for surgical management of the more prevalent congenital masses and benign neoplasms also requires prompt and thorough diagnostic evaluation. Moreover, a number of congenital masses presenting for the first time with an inflammatory exacerbation may enhance the diagnostic and therapeutic challenge.

A practical approach to head and neck masses in children aims to differentiate congenital, inflammatory, and neoplastic etiologies based on location of the mass (Table 105.1). This chapter addresses general approach and differential diagnosis of the head and neck masses in children and covers inflammatory and neoplastic masses. Please refer to Chapter 106 for congenital neck masses and cysts, Chapter 104 for congenital vascular lesions, Chapter 98 for salivary gland disease in children, and Chapter 96 for congenital anomalies of the nose. Coverage of neoplastic pathologies is limited to those that are relatively more prevalent in childhood. Please refer to relevant chapters for the head and neck neoplasms that are rarely seen in the pediatric population.

ASSESSMENT

History and Physical Examination

History

A thorough and systematic history and physical examination are crucial steps for the differential diagnosis. History should focus on age at onset, duration and progression (increasing, decreasing, or stable), constitutional symptoms, and symptoms specific to the mass. More specific symptoms that need to be investigated include skin changes, pain in the region of the nodal swelling, a history of recent upper respiratory tract symptoms, sore throat, otalgia, toothache, insect bites, recent travel, exposure to individuals who are ill, immunization status, and exposure to animals. Answers to these questions will help establish a better differential diagnosis.

Maternal and prenatal history may identify infectious causes of neck masses in neonatal period, such as congenital syphilis or human immunodeficiency virus (HIV). A mass presenting in early infancy may suggest a congenital lesion such as a vascular malformation, branchial cleft cyst, or thyroglossal cyst. Congenital lesions may commonly present later in childhood after becoming infected.

TABLE 105.1 HEAD AND NECK MASSES IN CHILDREN

1) Lateral neck masses
   1 Congenital neck masses (see Chapter 106)
      a) Branchial anomalies
      b) Laryngocele
      c) Thymic cyst
      d) Pseudotumor of infancy
      e) Heterotopic cervical salivary gland tissue
      f) Preauricular pit/sinus/cyst
   2 Inflammatory neck masses
      a) Infectious neck masses
         i) Lymphadenitis
            (a) Acute viral lymphadenitis
            (b) Acute bacterial lymphadenitis
            (c) Mycobacterial lymphadenitis
            (d) Cat-scratch disease
            (e) Fungal, parasitic, and opportunistic infections
         ii) Infectious presentation of congenital mass
         iii) Anatomical site of infection
            (a) Peritonsillar space
            (b) Retropharyngeal space/parapharyngeal space
            (c) Prevertebral space/danger space
            (d) Mandibular space/submandibular sialadenitis
            (e) Masticator space
            (f) Buccal space
            (g) Parotid space/parotitis
      b) Noninfectious inflammatory neck masses
         i) Sarcoidosis
         ii) Kawasaki disease
         iii) Kikuchi-Fujimoto disease
         iv) Rosai-Dorfman disease
         v) Castleman disease
   3 Neoplastic masses
      a) Benign masses
      b) Malignant masses
2) Midline neck masses
   1 Congenital masses (see Chapter 106)
      a) Thyroglossal duct cyst
      b) Dermoid cyst
      c) Plunging ranula
      d) Teratoma of the neck
      e) Thymic cyst or ectopic thymus
      f) Ectopic thyroid
   2 Inflammatory masses
      a) Lymphadenitis
         i) From infections arising from the oral cavity, nasal cavity
      b) Thyroiditis
      c) Infectious presentation of congenital mass
   3 Neoplastic masses
      a) Benign masses
      b) Malignant masses
3) Not site specific
   1 Vascular anomalies (see Chapter 104)
      a) Hemangioma
      b) Lymphatic
      c) Capillary
      d) Venous
      e) Arterial
      f) Mixed

Neck masses in toddlers and later in childhood are most commonly reactive lymphadenopathy. Periodic fever with lymph node enlargement, pharyngitis, and stomatitis should raise the suspicion of Marshall syndrome. Pediatric head and neck masses with a stable duration of months or years are likely congenital lesions or benign inflammatory processes. A history of trauma to the area with or without secondary infection may be found under this sudden presentation. The first presentation of a congenital mass such as lymphatic malformation, thyroglossal cyst, or branchial cleft cyst may also be sudden with rapid enlargement due to infection or hemorrhage.

Temporal presentation of symptoms, as well as anatomical location, is helpful in establishing a differential diagnosis (see Table 105.1). Cervical lymph node enlargement is the most common presentation of a neck mass in children. A thorough history often suggests the probable cause of the cervical lymphadenitis. In general, acute lymphadenitis, which is less than 2 weeks in duration, is due to either a viral or bacterial invasion. A recent viral infection is usually the cause of bilateral or diffuse cervical lymphadenopathy (5). Acute unilateral adenopathy, particularly in infants and young children, may be associated with pyogenic sources such as *Staphylococcus aureus* or group B streptococcal infections. Persistent adenopathy raises more concerns for malignancy but is usually still secondary to an infectious etiology (5). Subacute lymphadenitis, 2 to 6 weeks' duration, has a much broader differential and includes mycobacterial infections, fungal infections, parasitic infections, and many of the noninfectious etiologies as well. However, lymph node enlargement secondary to a variety of viral, bacterial, fungal, or protozoan infections may persist despite appropriate treatment. Enlargement of a salivary gland and pain with eating could suggest ductal obstruction, while more pain with local inflammatory symptoms could suggest sialadenitis with or without ductal obstruction. Rapid growth with fever may suggest acute inflammatory processes such as lymphadenitis, cellulitis, or abscess. Chronic lymphadenopathy, greater than 6 weeks' duration, is more likely to be due to a neoplastic process or invasion by an opportunistic organism (6).

Pediatric head and neck malignancy most commonly present as an asymptomatic neck mass (2). Neck masses that rapidly grow in a month or two should raise the suspicion of malignancy. Enlarging neck masses with systemic signs such as fever, night sweats, and malaise or weight loss suggest a malignant process. Boys have a higher incidence of neck malignancy than girls. Risk factors for malignancy include previous primary cancer, a predisposition to systemic cancer, exposure to carcinogenic drugs, and immunosuppression (7). Previous radiotherapy increases the risk for malignancy, especially thyroid malignancy (8).

Obtaining a family history may provide clues for familial processes such as branchio-oto-renal syndrome or

multiple endocrine neoplasia (MEN) syndromes. While the former often presents with branchial cleft abnormalities in addition to otologic malformations, hearing loss, and renal malformations, the latter may be associated with neuroblastoma or thyroid cancer. A family history for childhood malignancy should alert the clinician for a possible increased risk of malignancy as well.

Physical Examination

Physical examination is important for differential diagnosis. A palpable lymph node in a newborn should be considered abnormal (1). Concern for malignancy should be raised if there is a firm mass in a neonate, skin ulceration, fixation, cranial neuropathies, venous engorgement, a firm mass ≥1 cm in a child under 1 year old, or a firm mass ≥3 cm in a child over 1 year old (3). A neck mass in an infant that cannot be distinguished from sternocleidomastoid muscle with or without head tilt toward and face away from the side of the mass should prompt investigating the fibromatosis colli. Warmth or erythema of the overlying skin suggests infectious process. A draining fistula along the anterior border of sternocleidomastoid muscle suggests a branchial cleft fistula or sinus. Palpation provides information on location and consistency of the mass, whether it is cystic, fluctuant, or solid. A cystic mass in the anterior midline is consistent with a thyroglossal duct cyst; the one at the anterior border of the sternocleidomastoid muscle is likely a branchial cleft cyst. A cystic mass in the posterior triangle is usually a lymphatic malformation. A solid mass in the posterior triangle or supraclavicular region should raise the concern for malignancy. A high proportion of supraclavicular solid masses are due to lymphoma (9). Fixation of the neck mass to the surrounding or deep tissues may be seen with inflammatory or malignant processes (10). Childhood malignant neck masses may be associated with oral or pharyngeal primaries. One in six children with a malignant neck mass has a primary in the oropharyngeal or nasopharyngeal region (11). A thorough examination, including flexible fiberoptic endoscopy, should be performed in order to assess the nasopharynx, oropharynx, hypopharynx, and larynx. For those children that cannot tolerate an adequate outpatient examination, endoscopic examination should be performed under general anesthesia. This thorough exam may be performed concurrent with the neck mass biopsy, if indicated, in order to avoid multiple procedures under general anesthesia.

A number of inflammatory or malignant neck masses may also present with other systemic findings. Horner syndrome should direct attention to the cervical sympathetic chain. Examination of skin may reveal café-au-lait spots consistent with neurofibromatosis or hemangiomas associated with vascular lesions in the neck. Inguinal and axillary lymph nodes and hepatosplenomegaly should be examined. Splenomegaly may be associated with infectious mononucleosis, and a heart murmur with Kawasaki disease.

Laboratory Testing

Assessment of head and neck masses in children may include laboratory evaluation. Laboratory tests are seldom required as part of the workup for acute cervical lymphadenitis. Leukocyte count and markers of inflammation (C-reactive protein and erythrocyte sedimentation rate) are usually abnormal but nonspecific and do not assist in the diagnosis. However, for subacute, chronic, and generalized lymphadenopathy, laboratory evaluation plays a crucial role, and a complete blood count (CBC) with differential should routinely be performed in such conditions. In a more severe acute inflammatory condition such as a neck abscess, a high white blood cell count with higher lymphocytes is expected. Repeated CBC may be utilized to assess the response to the therapy. Atypical lymphocytes should raise the suspicion for infectious mononucleosis, test and heterophile antibody titers (Monospot test) may be used for confirmation.

Serologic tests for *Bartonella henselae*, syphilis, toxoplasmosis, cytomegalovirus (CMV), Epstein-Barr virus (EBV), tularemia, brucellosis, histoplasmosis, and coccidiodomycosis may suggest an infectious agent. Cervical lymphadenitis that is suspicious for either tuberculous or atypical mycobacterial infection should receive a purified protein derivative (PPD) testing. A positive intradermal tuberculin skin test is consistent with an infection due to *Mycobacterium tuberculosis*, but a negative test does not rule it out and will often manifest as a lesser reaction or negative reaction in nontuberculous mycobacterial infections (6). Any material that has been aspirated or collected due to fluctuance should be sent for culture and sensitivity. If history and physical are consistent with possible anaerobic or fungal infections, specific cultures need to be specified.

Neoplastic processes in head and neck may manifest themselves by an abnormal CBC and differential. Blood tests to help identify the cause, or the dissemination, of a malignant process are necessary, such as HIV test, chemistry panel, and a liver panel (4,12). Alkaline phosphatase levels can help determine bone metastasis. Blood urea nitrogen, creatinine, lactate dehydrogenase, and uric acid are adjunct to the workup of lymphomas and other malignancies (13). Cerebrospinal fluid analysis is useful in the workup of central nervous system involvement in malignancies such as lymphoma.

Imaging

Diagnostic radiology is useful for not only narrowing the differential diagnosis of a neck mass but in order to help define the extent of the lesion and assist in preoperative planning. Common modalities include plain radiographs, ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). Other modalities such as positron emission tomography (PET) and radionuclide scans are also available, but are not widely used, particularly

with regard to inflammatory lesions, and therefore are not be discussed in this chapter.

Plain Radiographs

Radiographic studies are usually not necessary for evaluation of recent onset of masses that appear to be inflammatory. However, persistent or progressively enlarging adenopathy warrants a chest x-ray. A plain chest x-ray may detect pulmonary or mediastinal lesions as a source for cervical or supraclavicular adenopathy (14). Plain radiographs have been supplanted by the use of other more advanced imaging techniques in many situations. Currently, the main use of plain radiographs is for evaluation of the chest for the presence of lymphadenopathy or other pulmonology pathology, as well as soft tissue lateral neck radiographs to assess the airway and prevertebral soft tissue thickening. Initial workup for children with a potential cervical neoplasm should include PA and lateral chest radiograph. This may reveal mediastinal lymph node enlargement as the underlying cause of the airway obstruction or superior vena cava syndrome.

Ultrasound

Ultrasonography has some important advantages for use in the pediatric population; it does not involve ionizing radiation and is readily available (14). Ultrasound is often considered the first-line diagnostic imaging study by many centers (6,15,16). Ultrasound can easily distinguish solid from cystic lesions. Ultrasound is helpful in evaluating the thyroid and parotid lesions and may help diagnosing confusing congenital lesions (14). High-resolution ultrasound is able to assess nodal morphology and internal architecture as well as characterize the echogenic patterns of a mass, classifying them as cystic, solid, or complex in nature. Doppler ultrasound may be used to assess the presence of perfusion and its distribution as well as obtain measures of vascular resistance. Advantages of ultrasound are that it is noninvasive, avoids ionizing radiation, is portable and inexpensive, and can be performed without sedation in most patients. Drawbacks include difficulty to interpret, subject to skill level of operator, may not be able to visualize deeper lesions, and lack of anatomic information for surgical planning (17–19). High-frequency transducers are utilized to evaluate the lymph nodes in the neck as they provide better detail. A normal node as evaluated by ultrasound is a well-defined, elliptical structure with a hypoechoic halo and central sharp linear hyperechoic fatty hilum containing a single vessel (15). Power Doppler imaging of the vascularity of nodes can be useful in differentiating benign from malignant processes. This, however, requires the patient's cooperation, which is sometimes difficult to achieve in young children. Sonographically, neurogenic tumors are elliptical or round hypoechoic solid masses posterior to the carotid sheath vessels in a paraspinal location, with or without intraspinal extension and with or without calcifications (16). Ultrasound does not have a high specificity in distinguishing benign from malignant nodes, and there is significant feature overlap. The features, when combined, that increase the suspicion of malignancy include round shape, absent or eccentric hilum, irregular borders, cystic necrosis, and chaotic capsular blood flow pattern (15). On ultrasound of lymphoma, the enlarged hypoechoic nodes show sharp borders with an absent or eccentric echogenic hilum and a tendency to form masses (20). In Hodgkin lymphoma and non-Hodgkin lymphoma, the affected lymph nodes tend to be round, hypoechoic, and without an echogenic hilum and are likely to demonstrate intranodal reticulation (16). Sonographically, most thyroid cancers are hypoechoic, and the tumor may be irregular and ill defined or smooth and well delineated. A sonolucent rim or halo may completely or partially surround the mass.

Computerized Tomography

Contrast-enhanced CT is the standard of imaging for rapid, accurate diagnosis of an acute deep neck abscesses. In a survey of pediatric otolaryngologist, CT scan was the imaging modality of choice for the evaluation of children with suspected deep neck infections (21). CT is able to differentiate between cellulitis and abscess and is also able to assess the location of the abscess in relation to important anatomical structures, helping to provide a surgical road map (17,22). However, differentiation between phlegmon and abscess is sometimes not easy, and without the addition of intravenous contrast, it is impossible (23). Workup of a neck mass with possible neoplastic characteristics should include CT with contrast of the neck (24). On CT scan, lymph nodes are noted to have homogeneous soft tissue attenuation and present as elongated structures with well-defined, sharp margins with preserved adjacent fat planes and the occasional fatty hilum. However, the internal architecture of nodes is, for the most part, beyond the limits of CT evaluation (15). The CT scan is valuable in differentiating between cystic and solid lesions, establishing the location and exact size of the lesion, identifying other nonpalpable masses, determining the relationship of the mass with the surrounding tissues, assessing bony erosion or remodeling of the bone, and assessing the vascularity within the mass when the study is done with contrast. The high spatial resolution for high-contrast structures makes CT the imaging modality of choice for osseous and fibroosseous lesions in the head and neck (25). On CT, teratomas appear heterogenous, sharply circumscribed, with solid and cystic areas with variable enhancement of the solid component (26). Staging for a number of pediatric malignancies, such as lymphoma, requires CT of the head and neck as well as mediastinum. An abdominal CT scan is used to assess the involvement of the spleen liver and retroperitoneal lymph nodes. On a CT scan, nasopharyngeal carcinoma (NPC) shows a large enhancing mass filling the nasopharyngeal airway (26). CT scan does expose the patient to low doses of radiation, but it is faster than an MRI and, therefore, usually does not require sedation.

Magnetic Resonance Imaging

MRI has the advantage of exquisite sensitivity for soft tissue imaging with excellent anatomic detail. Some studies have shown it to be more successful than CT in distinguishing cellulitis or phlegmon from a true abscess collection; however, CT still remains the standard imaging technique for the evaluation of the acute neck abscess (25,27). Advantages of MRI include the increased sensitivity of soft tissues, ability to provide multiplanar images, and the lack of radiation exposure. Lymph nodes are best seen on fluid-sensitive sequences (T2 or STIR) because they are isointense to muscle on T1 weighting (15). For assessing possible neoplastic masses, MRI provides much greater soft tissue detail and better vascular delineation. Disadvantages of MRI are the need for expensive imaging machinery and obtaining the scan often requires sedation secondary to the longer image capture times necessary. For osseous lesions, MRI can help assess the effect of an osseous lesion on the surrounding structures but should not be seen as a substitute for the CT scan (25). Neurofibromas and schwannomas are heterogenous, isointense to muscle on T1-weighted images, irregularly hyperintense on T1-weighted images, and enhance variably after gadolinium administration. T2-weighted images and fat suppression post–gadolinium-enhanced T1-weighted images are also very helpful (26). MRI has a distinct advantage over CT in evaluating for intracranial extension of tumor. Direct coronal imaging with fat suppression best demonstrates skull base involvement (26). Perfusion MRI is a noninvasive promising method that can be used for differentiation of malignant from benign cervical lymph nodes, and it helps in the characterization of malignant cervical lymphadenopathy (28).

Other

In specific clinical circumstances, radionuclide scans, PET scans, or angiographic scans may be useful. Workup of malignant disease includes searching for distant metastasis. Whole body bone scans are often used in metastatic workup such as for neuroblastoma. If alkaline phosphatase levels are elevated or there is bone pain, bone scans should be done. Gallium scanning is sensitive for identifying the sites of involvement. Recently, fluorodeoxyglucose positron emission tomography has been shown to be superior to the gallium scanning and has become the recommended procedure (29). Bone marrow core biopsies and aspirates are also part of the workup of staging in some malignant tumors such as lymphoma.

Tissue Diagnosis

Fine-Needle Aspiration Biopsy

The use of fine-needle aspiration biopsy (FNAB) in pediatric neck masses is controversial. Percutaneous FNAB is preferred when a preliminary histopathologic diagnosis better guides, modifies, or rules out a definitive surgical procedure, or if the head and neck mass is considered surgically unresectable. The FNAB is not utilized as often as in adults because of limited experience of the cytologist, lack of consensus in diagnostic value for specific malignancies, and concerns with compliance in children when performed without general anesthesia (2,7).

An experienced cytopathologist can differentiate between benign and malignant lesions and may accurately identify the tissue type (30). Similar to adults, anytime there is an indication, and a child can tolerate it, FNAB should be considered (31,32). When the mass is small, deep, or close to vital structures, performing the FNAB under ultrasound or CT guidance may be planned. Often due to noncompliance, a child may need to undergo general anesthesia to obtain the FNAB. If this is the case, the surgeon consults with the pathologist and informs the family that a potentially nondiagnostic FNAB may result that would require a second procedure or that an open incisional or excisional biopsy may need to be performed instead. However, when there is a concern for functional or cosmetic sequelae of an open biopsy, a FNAB may be preferred despite potential inaccuracy or need for a second procedure.

Otolaryngologists facing parents overly concerned with the possibility of malignancy, even when the chance of malignancy is not high, may view FNAB as a compromise between lack of definitive need for open biopsy and chance of eliminating the small risk of malignancy. This may provide comfort to the parents and possibly avoid medicolegal challenges for the delayed diagnosis of a malignancy. Often FNAB can be performed without the need for local or general anesthesia, making it ideal for patients who are unacceptable or poor surgical candidates (30). Occasionally, when there is a chance that multiple lesions may represent different pathologies, or to determine the extent of the disease, FNAB may be performed for the other masses in addition to an open biopsy of the main neck mass. It must be remembered though that FNABs are considered inadequate in establishing the diagnosis of lymphoma (14). In clinical situations when the information obtained from FNAB is not going to affect the decision to remove the neck mass, or change the extent of removal, irrespective of whether it is benign or malignant, there is no need for a FNAB.

Incisional or Excisional Biopsy

An open surgical biopsy may be necessary if there is no diagnosis after a complete evaluation. If the possibility of an inflammatory cause cannot be ruled out, a trial of 2 to 4 weeks of antibiotics is often considered before a biopsy of a neck mass. If the neck mass needs to be removed regardless of the specific pathology, an open surgical excisional biopsy is preferred. When an incisional biopsy is performed, the incision should be planned keeping in mind the need for the further possible exposure during a potential definitive surgical resection.

An open biopsy is indicated when the history, physical examination, and location of a head and neck mass

are suspicious for malignancy. Unusually large masses, those that continue to enlarge after the initial presentation, masses located in the supraclavicular area, or those associated with pain, fever, or weight loss should undergo a thorough workup and open biopsy (10). When there is a high suspicion for malignancy, an open biopsy should be performed, even if there has been a prior negative FNAB. A hematology–oncology consultation may be useful if there is a high suspicion of malignancy.

A frozen section may be planned if the mass is not suitable for total excision due to definite or potential risk for cosmetic or functional sequelae or complication. An intraoperative frozen section is useful to make sure that an adequate representative tissue sample is obtained before terminating the incisional biopsy procedure and the anesthesia. A preoperative consultation with pathology assures readiness for fresh tissue preparations, specific markers, or cell culture. Frozen section is not considered adequate for the diagnosis of lymphoma (14).

A number of pediatric malignancies, including lymphoma, may be associated with lesions in the mediastinum, requiring a focused history and physical examination for the risk of airway compromise during general anesthesia (33). Respiratory collapse under general anesthesia is a complication especially associated with anterior mediastinal masses. Preoperative workup for such risk should include measurement of the tracheal cross-sectional area by CT scans and pulmonary function tests (14). One might consider biopsy under local anesthesia to avoid the risk of airway obstruction with general anesthesia. Alternatively, a rigid bronchoscopy set should be available during induction in such a case to guard against loss of the airway.

INFLAMMATORY MASSES

Inflammatory cervical lymphadenopathy is the most common pediatric neck mass (6). The inflammatory node is usually the result of a recent viral or bacterial infection but may be due to noninfectious etiologies as well. It has been reported that palpable cervical lymphadenopathy occurs with a prevalence of 28% to 55% in otherwise normal infants and children (5). Infectious etiologies for inflammatory head and neck masses in children are listed in Table 105.2.

Infectious Etiologies

Benign cervical lymph node hypertrophy is the most common cause of pediatric neck masses. Clinically palpable cervical lymphadenopathy occurs with a reported prevalence of 28% to 55% in otherwise normal children (5). Children may normally have less than 1-cm palpable lymph nodes. It is not uncommon that children develop idiopathic self-limiting 2- to 3-cm lymph node enlargement. Infectious etiologies are the most common cause of inflammatory cervical lymphadenopathy. Acute bilateral cervical lymphadenopathy is usually caused by viral respiratory tract infections or streptococcal pharyngitis, whereas unilateral cervical lymphadenitis is caused by streptococcal or staphylococcal infection in 40% to 80% of cases (34). Subacute or chronic lymphadenitis may be caused by mycobacterial infections, cat-scratch disease, and fungal,

TABLE 105.2 INFECTIOUS ETIOLOGIES FOR INFLAMMATORY HEAD AND NECK MASSES IN CHILDREN

1. Acute viral lymphadenitis
   - a) Common viruses
     - i) Rhinovirus
     - ii) Parainfluenza virus
     - iii) Influenza virus
     - iv) Respiratory syncytial virus
     - v) Cytomegalovirus
     - vi) Epstein-Barr virus
     - vii) Coronavirus
     - viii) Adenovirus
     - ix) Reovirus
   - b) Rare viruses
     - i) Mumps
     - ii) Measles
     - iii) Rubella
     - iv) Herpes simplex
     - v) Human herpes simplex 6 (roseola)
     - vi) Coxsackie viruses
2. Acute bacterial lymphadenitis
   - a) Common bacteria
     - i) Gram-positive bacteria
       - (a) *Staphylococcus aureus*
       - (b) Group A beta-hemolytic *Streptococcus* (*S. pyogenes*)
   - b) Less common organisms
     - i) Anaerobic bacteria
       - (a) *Bacteroides* sp.
       - (b) *Peptococcus* sp.
       - (c) *Peptostreptococcus* sp.
       - (d) *Propionibacterium acnes*
       - (e) *Fusobacterium nucleatum*
       - (f) *Eikenella corrodens*
       - (g) *Prevotella* sp.
     - ii) Gram-negative bacteria
       - (a) *Francisella tularensis*
       - (b) *Pasteurella multocida*
       - (c) *Yersinia pestis*
       - (d) *Haemophilus influenzae*
       - (e) *Klebsiella* sp.
       - (f) *Serratia marcescens*
       - (g) *Moraxella catarrhalis*
3. Mycobacterial lymphadenitis
   - a) *Mycobacterium tuberculosis*
   - b) Nontuberculous mycobacteria
4. Cat-scratch disease
   - a) *Bartonella henselae*
5. Fungal, parasitic, and opportunistic infections
   - a) *Histoplasma capsulatum*
   - b) *Blastomyces dermatitidis*
   - c) *Coccidioides immitis*
   - d) *Toxoplasma gondii*
   - e) *Nocardia* sp.

parasitic, or opportunistic infections. Additionally, congenital neck masses may also present with an acute infection of the congenital mass.

Acute Viral Lymphadenitis

Many cases of bilateral cervical adenitis are caused by upper respiratory tract infections of viral etiology, including rhinovirus, parainfluenza virus, respiratory syncytial virus, CMV, EBV, coronavirus, adenovirus, and reovirus. Less common viral agents include mumps, measles, rubella, herpes simplex, human herpes simplex 6 (roseola), and coxsackie viruses (6,35). Involved nodes are usually multiple, relatively small, and without warmth or erythema of the overlying skin. Acute bilateral or diffuse cervical lymphadenopathy is often the result of a recent viral infection and is usually a self-limited process (14). Viral-induced adenopathy rarely suppurates and generally resolves spontaneously over a short period of time (6). Acute viral lymphadenitis is variably associated with fever, conjunctivitis, pharyngitis, and other upper respiratory tract symptoms. Rashes and hepatosplenomegaly may also be present, particularly when CMV is the causative organism. These infections rarely require additional diagnostic testing or specific therapy. Treatment is directed at symptom relief and specific antiviral therapy is seldom indicated except in the rare patient with severe respiratory tract or hepatic involvement, or in the immunocompromised patient (6).

Acute Bacterial Lymphadenitis

Bacterial etiologies of cervical lymphadenopathy tend to be unilateral in nature. While the source of the initial infection may raise the suspicion for specific bacterial organisms, *S. aureus* and group A beta-hemolytic *Streptococcus* (*Streptococcus pyogenes*) are the most frequently isolated bacterial organisms from all cervical sites as a whole (36–39). Bacterial-induced adenopathy tends to produce larger (greater than 2 to 3 cm), solitary, tender, unilateral lymph nodes that rapidly enlarge. Suppurative adenitis indicates an infected lymph node that has undergone liquefaction necrosis. Fluctuance develops in about 25% of patients with acute bacterial adenitis (6,14). Common symptoms include fever, malaise, poor feeding, irritability, and swelling over the infected area with overlying skin erythema.

Over the past 10 to 15 years, there has been a sharp increase in the number of methicillin-resistant *Staphylococcus aureus* (MRSA) cases that have been reported. Reports from different hospitals/geographical areas indicate a 6% to 65% (22,39–43) increase in incidence with time, and reports of resistance to other antibiotics have varied. With this trend noted, selection of an appropriate antibiotic for treatment needs to address the local incidence and antibiotic susceptibility of the common offending organisms. Usually antibiotics that are beta-lactamase stable or those that inhibit beta-lactamase are most desirable. The combination ampicillin–sulbactam has been used with good success in multiple studies and has activity against gram-positive, gram-negative, and anaerobic bacteria (44–46). When the patient has improved sufficiently to change from intravenous to oral therapy, the oral form of ampicillin–sulbactam, the prodrug sultamicillin, as well as amoxicillin–clavulanate are appropriate agents. Other good choices include cefuroxime axetil, cefprozil, and clindamycin. If there is suspicion for MRSA, recent studies have shown the majority of the community-acquired MRSA is still sensitive to clindamycin and Bactrim (22,43).

Anaerobic bacteria may be found in older children with dental caries or periodontal disease. The most commonly isolated anaerobic bacteria are *Bacteroides* sp., *Peptococcus* sp., *Peptostreptococcus* sp., *Propionibacterium acnes, Fusobacterium nucleatum, Eikenella corrodens*, and *Prevotella* sp. (6,47). Other more rare bacterial isolates include gram-negative bacilli such as *Francisella tularensis, Pasteurella multocida, Yersinia pestis, Haemophilus influenzae, Klebsiella* sp., *Serratia marcescens*, and *Moraxella catarrhalis* (6,36,39). Treatment of these bacteria is dependent on their individual susceptibility to antibiotics, though clindamycin usually has good coverage against the anaerobic bacteria, but poor coverage against gram-negative organisms. Ampicillin–sulbactam, or its oral form sultamicillin, is another good choice for these organisms with its broad range of coverage that includes anaerobic and gram-negative bacteria (45,46).

Mycobacterial Lymphadenitis

Chronic cervical lymphadenitis may be caused by *M. tuberculosis* or by nontuberculous strains of mycobacteria (*M. avium–intracellulare, M. scrofulaceum, M. kansasii, M. fortuitum*, and *M. hemophilum*). In the United States, 70% to 95% of cases of mycobacterial lymphadenitis are due to nontuberculous strains (6). Characteristic presentation includes rapid onset of nodal enlargement followed by a gradual increase in nodal size over 2 to 3 weeks. Constitutional signs are unusual, but a characteristic change of the overlying skin to a pink to lilac-red hue is common. Approximately 50% will develop fluctuance and spontaneous drainage occurs in about 10% (6). The definitive treatment for nontuberculous strains is surgical excision (6,48), but there is increasing evidence that macrolide antibiotics may be beneficial (49). With *M. tuberculosis*, multiagent antituberculous antibiotic therapy for 12 to 18 months is standard treatment.

Cat-Scratch Disease

Cat-scratch disease is a lymphocutaneous syndrome characterized by regional lymphadenitis associated with a characteristic skin lesion at the site of inoculation. It is caused by inoculation of the bacteria *B. henselae* through broken skin or mucous membranes. The most common sites of lymphadenopathy are the axilla (52%) and the neck (28%) (6). Clinically, patients typically present with a single large (greater than 4 cm) tender node with suppuration in 30% to 50% of cases (50). Constitutional symptoms are usually mild and include low-grade fever, body aches, malaise,

or anorexia. Standard for diagnosis is serologic testing for antibodies to *Bartonella*. In the immunocompetent patient, cat-scratch disease is usually self-limited with spontaneous resolution after 1 to 3 months. However, a study has shown azithromycin to be associated with more rapid resolution of nodal enlargement (51,52).

Fungal, Parasitic, and Opportunistic Infections

The soil saprophytes *Histoplasma capsulatum, Blastomyces dermatitidis*, and *Coccidioides immitis* are endemic to certain geographic regions of the United States and can cause fungal infections in humans. Most patients will have pulmonary infections with secondary cervical lymphadenopathy. Diagnosis is through serologic or skin testing. Most infections do not require treatment and resolve spontaneously. Patients with severe respiratory or systemic symptoms may require prolonged courses of antifungal therapy (6,14).

Infection with the intracellular protozoan *Toxoplasma gondii* can present with cervical, suboccipital, supraclavicular, axillary, or inguinal adenopathy. Involved nodes may be tender but do not suppurate. Diagnosis is by culture or serologic testing. Most patients do not require antimicrobial therapy, but if symptoms are severe or persist, treatment is with a combination of pyrimethamine, sulfadiazine, and leucovorin for at least 4 to 6 weeks (6).

Infections caused by *Nocardia* sp. are infrequent and usually present as lung disease in immunocompromised hosts. Infection usually occurs through inhalation or direct skin inoculation. Diagnosis is through culture of the skin pustules or involved nodes. Sulfonamides are the treatment of choice (6).

Infected Congenital Masses

Congenital masses also may become acutely infected. Infected congenital masses should be included in the differential diagnosis, particularly in the absence of a dental or pharyngotonsillar cause, or in recurrent neck infections (53). Thyroglossal duct cysts, the most common congenital neck anomaly, will become infected 40% to 60% of the time (54). It has also been reported that any unilocular, nontranslucent cystic swelling in relation to the deep anterior portion of the sternocleidomastoid muscle is very suggestive of an infected brachial cyst (53). A history of recurrent neck infections with multiple incision and drainage procedures may represent a congenital sinus tract that has never been completely excised. Diagnosis usually is made by utilization of CT scans (17,53). The use of a barium swallow for diagnosis of a pharyngeal fistula/sinus tract also has been reported (55). Treatment consists of IV antibiotics and surgical excision of the congenital lesion. Some controversy exists with regard to timing of surgical treatment. Some authors promote treatment with antibiotics for at least 6 weeks for resolution of the infection/inflammation prior to surgical excision (56), and others advocate for immediate surgical excision with concomitant treatment with antibiotics (53).

Characterization of Infection By Anatomical Location

The location of the enlarged lymph node(s) is a good indication of the likely site of entry of the offending organism. Involvement of superficial nodes usually indicates an epithelial surface (i.e., buccal mucosa, skin, scalp, etc.) as the site of entry, whereas deep nodal enlargement results from an infectious process arising from more central structures such as the posterior pharynx or middle ear (6). Each of the following anatomical subsites has specific sites of origination of infection as well as common presenting signs and symptoms.

Peritonsillar

The peritonsillar space lies between the capsule of the palatine tonsil and the pharyngeal muscles. It is the most common site of head and neck space infections (36). Peritonsillar infections originate from the oropharynx and may spread by direct communication to the lateral pharyngeal space. Clinical findings usually include pain, fever, dysphagia, trismus, and cervical adenopathy. Physical examination shows swelling of the tissues lateral and superior to the tonsil with subsequent medial and anterior displacement of the tonsil and medial displacement of the uvula. Medical treatment includes antibiotics with some evidence that steroids help with subjective symptoms (57). Differentiating between peritonsillar cellulitis versus abscess may not be straightforward. Otolaryngologists rarely order a CT scan for this condition. However, if performed, rim enhancement at the wall of hypodense center would indicate an abscess. When there is no imaging available, clinical judgment should suspect an abscess with the severity of inferomedial displacement of the tonsils, with an obvious bulge at the superolateral aspect of the tonsil, and most importantly with the presence of significant trismus. Surgical treatment options include incision and drainage, needle aspiration, and immediate tonsillectomy (quinsy tonsillectomy). All three options have been shown to be efficacious and safe, but definitive proof of superiority for any one of them has not been established, and each continues to play an important role in managing these abscesses (57–60).

Retropharyngeal/Parapharyngeal Space

The retropharyngeal space lies posterior to the buccopharyngeal (visceral) fascia covering the pharynx and anterior to the alar fascia. The buccopharyngeal fascia is adherent to the alar fascia in the midline so infections are usually unilateral in nature. The lymph nodes in this area receive drainage from the nose, paranasal sinuses, pharynx, and eustachian tube. The parapharyngeal space is bounded by layers of deep cervical fascia. The space resembles an inverted pyramid with the base at the skull base and the apex at the level of the hyoid bone. Anterior and posterior compartments are separated by the tensor veli palatini

tendon and fascia. Parapharyngeal space contains many important neurovascular structures, including cranial nerve V3, internal maxillary artery, deep lobe of the parotid gland, great vessels, cervical sympathetic chain, and cranial nerves IX to XII. Due to the close proximity of the parapharyngeal and retropharyngeal spaces, with frequent extension of infection from one space to another, these spaces will be considered together.

Clinical presentation of an inflammatory process in these spaces usually includes irritability, fever, dysphagia, muffled speech or cry, noisy breathing, torticollis, and stiff neck. Stridor and drooling may develop later if left untreated. Physical exam findings include unilateral posterior pharyngeal swelling for retropharyngeal abscesses; however, significant swelling of the contralateral side of the pharynx can give the impression of symmetric swelling. A CT scan for assessment of extent of disease is usually necessary and is helpful in presurgical planning (61). Surgical approaches include both transoral and lateral external routes for incision and drainage, with transoral approaches more commonly employed (58,61,62). Recent advances in antimicrobials have led to multiple studies advocating for initial medical management with intravenous antibiotics, reserving surgical intervention for those patients who fail medical treatment (60,61,63–65).

Prevertebral Space/Danger Space

Prevertebral space is located between the prevertebral layer of the deep cervical fascia and the alar layers of the deep cervical fascia. There is some controversy as to whether or not there is a space between the vertebral bodies and the prevertebral fascia and whether there are two distinct spaces separated by the prevertebral layer of the prevertebral fascia. Here, space between the vertebra and the alar fascia is discussed as a common space named as prevertebral space. Prevertebral space extends from the cranial base to the level of the diaphragm, which facilitates the spread of neck infection into the mediastinum making it the "danger space." Infection may spread to this space from the vertebral bodies. Clinically, these infections are seen as a bulging mass in the midline of the pharynx with extension to both sides of the pharynx due to the absence of a midline raphe (different from the retropharyngeal space). Surgical approaches are through open external approaches in order to help prevent a persistent draining fistula into the pharynx, better access to the frequent lateral extension of the infection/abscess, and the possible need to debride osteomyelitic lesions of the vertebral column (66). If the infection arises from a tuberculous infection of the vertebral bodies, prolonged antimicrobial therapy also may be needed (67,68).

Mandibular Space

The mandibular space is formed by splitting of the two leaflets of the superficial layer of the deep cervical fascia. These leaflets attach to the inferior border of the mandible on its lateral surface and the medial surface of the mandible at the level of the mylohyoid muscle. The space is limited anteriorly by the attachment of the anterior belly of the digastric muscle and posteriorly by the attachment of the medial pterygoid muscle to the mandible. Infections in this area usually follow dental infection, trauma, or surgery. Pain and intraoral swelling are present but no external facial swelling is noted unless the infection involves the dependent lymphatics in the submandibular space. Drainage of the abscess may be done via an intraoral incision along the medial surface of the body of the mandible (68).

Submandibular Space/Submandibular Sialadenitis

The submandibular space is a continuation of the lateral pharyngeal space at its most anterior extent. The limits of the space are the mucosa of the floor of the mouth and the tongue superiorly and the superficial layer of the deep cervical fascia inferiorly. This space is sometimes subdivided into submaxillary space and the sublingual space by location superior (sublingual) or inferior (submaxillary) to the level of the mylohyoid muscle. The submaxillary space may be further subdivided into the submental space and the subsidiary submaxillary space by the anterior bellies of the digastric muscles. Infections in this space arise primarily from mandibular dental disease but may also result from sialoadenitis, suppurative adenitis, or tonsillar disease. Infections in these spaces may progress to abscess formation or persist as cellulitis. Bilateral involvement of the submandibular spaces can lead to massive edema of the tongue and floor of the mouth with posterior displacement of the tongue. This may lead to respiratory compromise. Patients frequently have halitosis and difficulty handling their secretions. This constellation of signs and symptoms is called Ludwig angina. Surgical treatment is based on the principle of releasing tension. It is important to perform adequate exploration for abscesses and to drain them, since they may be loculated. Even if imaging studies do not show an abscess, open surgical intervention is recommended in all but an exceptionally mild, early case. Surgical control of the airway via tracheotomy is considered strongly in all but exceptional mild cases as well. The surgical approach includes a generous horizontal incision approximately 1 cm above the hyoid bone (68).

Masticator Space

The masticator space is created by the splitting of the superficial layer of the deep cervical fascia around the masseter and internal pterygoid muscles. The space ends posteriorly at the posterior border of the mandible, superiorly at the origin of the temporalis muscle, laterally at the temporalis fascia, and medially it extends into the pterygopalatine fossa. Infections most commonly arise from the mandibular teeth and usually are related to dental infection, trauma, or surgery. Symptoms include deep pain along the ascending ramus of the mandible, trismus, sore throat, dysphagia, and pain with tongue movement. Swelling may

be present either in the area of the retromolar trigone or, externally, overlying the masseter muscle and mandible. If medial swelling/infection is present, an intraoral incision medial to the ascending ramus of the mandible is used to drain the abscess. If lateral/external swelling is present, an open approach with an incision just below the mandible is often utilized (68).

Buccal Space

The buccal space is lateral to the buccopharyngeal fascia and medial to the skin of the cheek. The inferior limit is the lower border of the mandible, and the posterior limit is the pterygomandibular raphe. Infections here arise from dental infections of both the maxillary and mandibular teeth. Clinically, infections are characterized by marked swelling of the cheek, which is typically warm, tender, and red. Trismus may be present if the inflammation extends to the masseter muscle. Usually abscesses occur subcutaneously. These are treated with surgical incision and drainage through an external approach and appropriate antimicrobials (68).

Parotid Space/Parotitis

The parotid space is formed by splitting of the superficial layer of the deep cervical fascia to cover the medial and lateral surfaces of the parotid gland. The medial fascia is thin and allows parotid space infections to extend into the adjacent lateral pharyngeal space. The lateral fascia is much thicker and tougher and usually prevents the palpation of fluctuation in the parotid space. Infections in this space arise from dental infection of the mandibular teeth, parotid gland infections, or suppurative adenitis of lymph nodes contained within the space (68). Infections that arise from within the parotid gland (parotitis) are usually due to blockage/obstruction of salivary outflow by thick secretions, sialoliths, or compression of the duct by external mechanisms. Inflammation of the gland from other etiologies such as viral infection (measles, mumps), Sjögren syndrome, or sarcoidosis also may lead to blockage of salivary flow (69,70). Treatment of early parotitis with warm compresses, hydration, massage, antibiotics, and release of the salivary obstruction (also includes treatment of intraparotid inflammation from viral infection or other inflammatory disorders) is necessary to prevent progression to abscess formation (71,72). Once an abscess is formed, the surgical approach for drainage is through a standard parotidectomy-type incision (71). If extension into the parapharyngeal space is present, this same approach may be utilized (68).

Noninfectious Etiologies

Cervical lymph node involvement may be a manifestation of a systemic disease with an inflammatory component. Most of these diseases are very rare but a brief description of several of the more common diseases follows. This list is not meant to be all-inclusive.

Sarcoidosis

Sarcoidosis is a chronic noncaseating granulomatous disease of unknown etiology. The lung is the most common organ involved but any organ can become involved. The most common finding on physical exam is peripheral lymphadenopathy. Cervical nodes tend to be bilateral, discrete, firm, and rubbery. Supraclavicular nodes are involved in more than 80% of patients (6). Diagnosis is via biopsy with histologic examination. Treatment is usually supportive in nature but corticosteroids may suppress acute manifestations (6,73).

Kawasaki Disease

Kawasaki disease is an acute febrile vasculitis of childhood of unknown etiology. One of the earliest manifestations is lymphadenitis. Involved nodes are usually unilateral, confined to the anterior triangle, and only moderately tender and are nonfluctuant (6). Diagnosis is made clinically based on the presence of a fever for at least 5 days in the presence of several other characteristic clinical features (polymorphous rash, conjunctival injection, red lips, red tongue, oropharyngeal erythema, erythema or cracking of the lips, indurative edema of the hands and feet, and diffuse erythema of the palms and soles (74)). Twenty-five percent of patients will present with cervical lymphadenopathy (75). Treatment is with salicylates and intravenous immunoglobulin (74), but infectious diseases and cardiology consults are also necessary since this is a clinical diagnosis with significant morbidity if not diagnosed and treated accordingly. One of the more devastating effects of this disease is coronary artery lesions. Kawasaki disease has now become the most common cause of acquired heart disease in children in the United States (74). However, there does not appear to be any association between cervical lymphadenopathy presence/severity and risk for development of coronary lesions (76). Resolution of the cervical lymphadenopathy usually occurs early in the course of the disease.

Kikuchi-Fujimoto Disease

Kikuchi-Fujimoto disease is a necrotizing lymphadenitis of unknown etiology. It usually presents with bilateral, enlarged, firm, painful lymph nodes in the posterior cervical triangle (77,78). Associated findings include skin lesions, fever, nausea, weight loss, night sweats, and splenomegaly. Diagnosis is made by biopsy with histologic examination. Treatment is symptomatic in nature with corticosteroids reserved for more severe cases. Most cases will resolve spontaneously in 1 to 4 months (6,78).

Rosai-Dorfman Disease

Rosai-Dorfman disease is also known as sinus histiocytosis with massive lymphadenopathy. It is a rare disorder of unknown etiology, which usually presents with mobile, discrete nontender nodes, which then progress to massive bilateral cervical nodal enlargement. Ninety-seven percent of patients have cervical lymphadenopathy and 30% will

have lymphadenopathy elsewhere. Thirty to forty percent will have extranodal manifestations, with 75% of those occurring in the head and neck regions. Extranodal manifestations include involvement of the skin, orbits, eyelids, salivary glands, upper respiratory tract, thyroid, peritoneum, bone, kidney, testes, and the central nervous system (79,80). Laboratory evaluation will show hypergammaglobulinemia. Diagnosis is based on biopsy or fine-needle aspiration (81), with histologic evaluation demonstrating florid hyperplasia, marked histiocytosis, plasmacytosis, and phagocytosed lymphocytes (emperipolesis) (79). Resolution usually occurs after 6 to 9 months but an indolent course with periodic remissions and exacerbations is also possible (80). However, extensive or progressive disease may require treatment with combination chemotherapy or corticosteroids. Surgery is reserved for diagnostic biopsy or relief of obstructive symptoms (79,80).

Castleman Disease

Castleman disease is a rare lymphoproliferative disorder of unknown etiology. There are two distinct histologic types, hyaline–vascular and plasma–cell (82). The disease may present as either localized or multicentric. The chest is the most common location affected with the neck as the second most common site (82,83). The localized form is 90% hyaline–vascular type and usually has a solitary mass that follows a benign course (83). The multicentric form usually is the plasma–cell type and is accompanied by systemic illness, disseminated lymph nodes, constitutional symptoms, autoimmune abnormalities, recurrent infections, and laboratory abnormalities (83,84). The multicentric form is aggressive and often culminates in death secondary to infectious complications or malignancy (33% of Castleman disease patients will develop malignancies (84)). Diagnosis is made through surgical biopsy with histologic examination. Of note, fine-needle aspiration usually leads to misdiagnosis, frequently being confused with lymphoma (82). Treatment is dependent on the extent of disease. For localized disease, complete surgical resection is the treatment of choice, with radiotherapy as an alternative (85). Incomplete resection can lead to recurrence (83). For multicentric disease, combination chemotherapy, with or without steroids, is the best option for treatment. Treatment with monoclonal antibodies against IL-6 has been shown to alleviate symptoms, but symptoms return upon stopping the therapy (86).

NEOPLASTIC MASSES

Evaluation of neoplastic pediatric head and neck masses requires broad knowledge of head and neck embryology and anatomy, a clear understanding of the varied differential diagnosis of these lesions, and an orderly and thorough history and physical examination to help direct evaluation and management. Neoplastic head and neck masses in children are listed in Table 105.3. Although masses of this

TABLE 105.3 NEOPLASTIC HEAD AND NECK MASSES IN CHILDREN

1. Benign lesions
   - a) Vascular neoplasms/malformations (see Chapter 104)
     - i) Hemangiomas
     - ii) Venous malformations
     - iii) Lymphatic malformations
     - iv) Arteriovenous malformations
     - v) Venular malformations (port-wine stains)
   - b) Soft tissue neoplasms
     - i) Neural tumors
       - (a) Neurofibromatosis type 1 (NF-1, von Recklinghausen disease)
       - (b) Neurofibromatosis type 2 (NF-2)
       - (c) Schwannomas
     - ii) Muscular tumors
       - (a) Rhabdomyoma
       - (b) Leiomyoma
     - iii) Fibrous neoplasms
       - (a) Fibrous histiocytoma
       - (b) Dermatofibroma
     - iv) Lipoma
     - v) Bone/cartilage
     - vi) Teratoma
     - vii) Skin (pilomatrixoma)
     - viii) Torticollis of infancy
2. Malignant lesions
   - a) Hematopoietic
     - i) Lymphoma
       - a) Hodgkin disease
       - b) Non-Hodgkin lymphoma
     - ii) Leukemia
     - iii) Posttransplant lymphoproliferative disease
   - b) Sarcomas
     - i) Rhabdomyosarcoma
     - ii) Other
       - (a) Fibrosarcoma
       - (b) Synovial sarcoma
       - (c) Neurofibrosarcoma
       - (d) Hemangiopericytoma
       - (e) Kaposi sarcoma
       - (f) Extraskeletal Ewing sarcoma
   - c) Neuroblastoma
   - d) Thyroid carcinoma
     - i) Papillary
     - ii) Follicular
     - iii) Medullary
     - iv) Mixed
     - v) Anaplastic
   - e) Salivary gland malignancies (see Chapter 98)
     - i) Mucoepidermoid carcinoma
     - ii) Adenocarcinoma
   - f) Epithelial malignancy
     - i) Nasopharyngeal carcinoma
   - g) Malignant teratoma
   - h) Skin malignancy
     - i) Basal cell
     - ii) Melanoma
     - iii) Squamous cell
   - i) Metastatic neoplasms

region are common, very few are malignant. Appropriate radiographic and laboratory evaluation for suspected or diagnosed malignancies are essential. When malignancy is confirmed, a multidisciplinary team including the surgeon, pediatric medical oncologist, radiologist, and pathologist should be assembled to facilitate staging and an appropriate treatment strategy (13).

Benign Head and Neck Neoplasms

Teratomas

Teratomas are the most common congenital tumors with elements derived from all three germ cell lineages in various degrees of differentiation. Teratomas arise in a variety of locations throughout the body. Most are sacrococcygeal, with cervical teratomas representing less than 10% (87). Most teratomas are benign. The head and neck region is the second most common site for teratomas in infants, usually presenting at birth or even prenatally. Teratomas of the head and neck occur in the nasopharynx, oral cavity, orbit, neck, and thyroid (88). The unusual size of teratomas, along with their intracranial location during intrauterine development provides a combination that often is not compatible with life (89). After birth, teratomas may present as large neck masses that cause airway obstruction. Imaging studies demonstrate a large, heterogenous mass that has both cystic and solid components (26). The diagnosis is usually obvious at birth, but due to the widespread use of prenatal ultrasound, there has been an increase in the diagnosis of fetal neck masses, particularly airway-threatening lesions. Prenatal diagnosis may be made with ultrasound or MRI. With the prenatal diagnosis of a large mass that is expected to cause life-threatening airway obstruction, an *ex utero* intrapartum therapy procedure is planned in order to secure the airway via a C-section during ongoing placental perfusion (14,90).

Neural Tumors

Neurofibromas and schwannomas are benign tumors of the peripheral nervous system. Neurofibromas may originate from any of the cranial, peripheral, or autonomic nerves. They may present as solitary masses; however, they more commonly present as multiple masses associated with a systemic genetic condition such as neurofibromatosis type I (NF-1, von Recklinghausen disease), neurofibromatosis type II, or other less common forms. Nearly all children with head and neck neurofibromas are diagnosed with NF-1 (26). Neurofibromatosis type I (85% of the NF patients) has an incidence of 1:4,000 live births and has autosomal dominant inheritance with variable penetrance. About 50% of cases are new mutations (91). Approximately 33% of the NF-1 patients have otolaryngologic manifestations, including neck masses that impinge upon the airway. Superficial neurofibromas may present as nodular or pedunculated lesions, while plexiform neurofibromas occur deep in the neck, sometimes expanding toward the oropharynx or hypopharynx. Plexiform neurofibromas traditionally have posed a surgical challenge in pediatric patients. Expert preoperative planning, advanced surgical techniques, and vigilant postoperative care result in minimal morbidity and resolution of tumor symptomatology (92). Neurofibromatosis type II occurs at a frequency of 1 in 50,000 live births, usually presenting as bilateral tumors of the eighth cranial nerve.

Schwannomas originate from the peripheral nerve sheath. They usually present as solitary encapsulated masses. Approximately 40% to 50% of all schwannomas manifest in the head and neck, with the lateral neck being the most prevalent site (93). Although benign, these lesions can cause secondary symptoms relevant to the location of the lesion, including nasal obstruction, dysphagia, and hoarseness (94). In the lateral neck, the vagus nerve and cervical sympathetic chain are the most commonly affected nerves. Treatment is complete surgical excision with preservation of the underlying nerve if possible. Treatment of schwannomas by enucleation may be the most reliable function-sparing technique of these slowly growing benign neoplasms (95).

Lipomas

Lipomas present as a slowly enlarging, relatively soft, asymptomatic, subcutaneous mass in the cervical region. Rarely, a deeply located lipoma may compress the aerodigestive tract. Treatment is complete surgical excision.

Pilomatrixoma

Pilomatrixomas are firm, nontender, intradermal, or subcutaneous masses. Also known as a calcifying epithelioma of Malherbe, histopathologically they are hamartomas of hair follicle origin. High-density calcium deposition, or calcification, is responsible for the firmness of the masses. About 60% of pilomatrixomas occur in the head and neck region and 40% occur in children under 10 years of age (96). They are considered benign masses without malignant potential. Surgical excision is diagnostic and curative. However, pilomatrixomas are variable in size and location, occasionally making surgical excision cosmetically challenging.

Fibromatosis Colli

Fibromatosis colli or congenital muscular torticollis presents in the neonatal period with a firm mass within the sternocleidomastoid muscle. Affected babies aged 2 to 4 weeks present with a unilateral, often rock-hard, anterior neck mass, which is right sided in 75% of cases (16). Often it is noticed several weeks after birth with turning of the infant's face in the opposite direction and tilting of the head toward the mass. Birth trauma such as breech delivery or use of forceps may have taken place although it can be seen in births with atraumatic vaginal delivery or C-section (97). Hemorrhage within the muscle followed by fibrosis is thought to be responsible for the shortening

of the sternocleidomastoid muscle and the resulting torticollis. Ultrasound or CT scan is usually necessary to rule out malignancy or a congenital lesion and confirm the diagnosis. Rarely, if imaging is not typical or diagnostic, a FNAB may be necessary. The mass usually resolves within 4 to 8 months (16). When torticollis is present, physical therapy is recommended. About 10% to 20% of children may progress to persistent muscular torticollis with risk of craniofacial deformity (98). If fibromatosis colli persists beyond 12 months of age despite adequate physical therapy, or there are early signs of developing craniofacial asymmetry, surgical intervention with release of the muscle is indicated (99).

Malignant Head and Neck Masses

By far, the most common head and neck malignancy in children is lymphoma. Rhabdomyosarcoma (RMS), neuroblastoma, and teratoma account for the majority of the other malignant pediatric neck lesions (14).

Lymphoma

Over half of pediatric neck malignancies are lymphomas (3,9). Lymphomas represent 13% of newly diagnosed childhood cancers (12,100). Lymphomas account for only 3% of the cancers in children younger than age 5 years and 24% of the cancers in children 15 to 19 years of age. It is unlikely that lymphoma will occur before 3 years of age. Lymphoma manifests itself in two distinct histopathologic and clinical types, Hodgkin disease and non-Hodgkin lymphoma.

Hodgkin disease is a malignancy of the lymphoreticular system, commonly presenting in the cervical region in adolescents and young adults with less than 10% occurring in children younger than 15 years old. Boys are affected twice as frequently as girls. More than 80% of the patients present with asymptomatic, firm, rubbery cervical lymphadenopathy, especially in the supraclavicular fossa. Involvement of mediastinal lymph nodes is common and may be noted by symptoms associated with compression of the airway or superior vena cava. Hodgkin disease may be associated with nonspecific symptoms such as fever, night sweats, weight loss, weakness, anorexia, and pruritus. The Ann Arbor staging classification system is utilized to determine the stage of disease and the treatment protocol (see Chapter 128). Immunohistochemical techniques performed on biopsy samples are capable of distinguishing lymphoid from epithelial, mesenchymal, or neural proliferations (101). After diagnosis, treatment, including chemotherapy, radiotherapy, or both, generally achieves over 90% initial complete remission. Long-term outcome is dependent on the stage of the disease at the time of diagnosis (102).

Non-Hodgkin lymphoma is a primary lymphoreticular system neoplasm consisting of a heterogeneous group of solid tumors presenting primarily in the pediatric population between 2 and 12 years old. Non-Hodgkin lymphomas comprise about 60% of the newly diagnosed lymphomas (12). Parents with congenital or acquired immunodeficiency and EBV are associated with non-Hodgkin lymphoma (12). Unlike Hodgkin disease, non-Hodgkin lymphoma often presents with advanced disease already involving multiple systemic sites including the head and neck region (12). In general, the majority of patients present with painless lymphadenopathy. However, in children, the usual presentation is rapidly growing extranodal disease that involves the head, neck, and mediastinum. Lymphoid tissue of Waldeyer ring commonly is involved (103). The early detection of non-Hodgkin lymphoma may be difficult due to prevalent symmetric or asymmetric enlargement of the tonsils and adenoids in otherwise healthy patients. Although nonspecific, attention to the associated symptoms is essential to avoid delay in diagnosis. Respiratory distress or superior vena cava syndrome requires prompt evaluation. Dissemination is hematogenous and nearly two-thirds of children have locally advanced or metastatic disease at the time of diagnosis (12). Systemic symptoms of malaise, weight loss, and fever are associated with more advanced disease. Central nervous system spread manifests itself with cranial nerve palsies, mental status changes, and pleocytosis. Pancytopenia is associated with bone marrow involvement and greater than 25% of the bone marrow replacement is associated with leukemic transformation (12). Incisional or excisional biopsy for special staining leads to classification of the non-Hodgkin lymphoma into B-cell, T-cell, and histiocytic categories and into further subtypes based on morphologic appearance and the degree lymphocytic transformation (see Chapter 128). The resulting classification and grading system helps predict the response to therapy and the outcome. Histologic type, leukemic transformation, hematogenous dissemination, and central nervous system involvement all indicate poor prognosis. Since systemic dissemination results in frequent advanced stage at presentation, systemic chemotherapy is the primary treatment modality in children. Multidrug chemotherapeutic protocols have resulted in improved survival rates (12). Surgery is reserved for patients with aerodigestive compromise that may benefit from debulking. The prognosis is excellent for children with limited disease regardless of subtype. Despite significant improvements in outcome of advanced stage non-Hodgkin lymphoma, nearly 30% of patients relapse or never achieve a first remission, which is indicative of a poor prognosis. Patients that have a second remission are considered candidates for bone marrow transplantation (12).

Posttransplant Lymphoproliferative Disease

Diffuse enlargement of lymphoid tissues or, less commonly, a solid tumor may be seen in immunosuppressed pediatric transplant patients (104). While this may be indistinguishable from normal adenotonsillar hypertrophy, it

may also present with tan-brown adenotonsillar discoloration (105). Significant adenotonsillar hypertrophy or paratracheal compression may lead to airway compromise. Treatment consists of reducing immunosuppressive therapy and usually results in disease resolution.

Rhabdomyosarcoma

The most common pediatric soft tissue malignancy of the head and neck is RMS, accounting for 50% to 70% of all childhood sarcomas (106,107). Seventy percent of those children have disease before the age of 12, and 50% are younger than 5 years of age (108). The disease has a peak presentation at 2 to 5 years and again at 15 to 19 years with a slight male predominance (26). RMS manifests itself in the head and neck in 35% to 40% of the cases, including the orbit, nasopharynx, middle-ear, mastoid, and sinonasal cavities (4). Presenting symptoms include nasal airway obstruction, bloody rhinorrhea, otorrhea, and proptosis. Delay in diagnosis is not unusual due to the varied sites and nonspecific symptoms. Direct intracranial extension or lymphatic and hematogenous metastasis may be present. Metastasis from nonorbital RMS to cervical lymph nodes is seen in 8% of children and distant metastasis is seen in 13% (109).

The diagnosis of RMS generally requires either a core needle biopsy or open biopsy to obtain adequate tissue for pathologic and molecular analysis (13). The clinical staging system is based on the extent of the disease and whether excision of the local or regional disease is performed (110). Surgical excision is recommended for localized disease as it improves survival and, if complete, avoids the need for radiotherapy, which is associated with a high risk of morbidity in children (such as facial growth retardation and second neoplasm). In large or extensive RMSs of the head and neck in which the morbidity of surgical resection is excessive or complete resection is unobtainable (e.g., nasopharynx, paranasal sinuses, and temporal bone), or both, treatment with combination chemotherapy and radiotherapy is indicated (111). Multimodal therapy including surgery and radiotherapy is used to control the local and regional disease while chemotherapy is used to control the distant metastases. Surgical resection is performed if this does not lead to major functional compromise. For orbital or other nonresectable RMS, biopsy is the only indicated surgery. If there are no neck metastases, the patient is followed after receiving chemotherapy. If there are enlarged lymph nodes, a neck dissection is indicated, and if the nodes are positive, additional radiotherapy is performed. The main prognostic factor is presence or absence of metastatic disease (110). RMSs may directly erode through bone or extend through skull base foramina via perineural spread to develop epidural masses and, sometimes, meningeal involvement (26).

Those individuals without metastatic disease may have greater than 90% survival rates. Patients with locally invasive, unresectable, but nonmetastatic, disease also can expect a 60% to 70% long-term survival rate. The survival rates for advanced disease also have improved in the recent years (112). More than 80% of patients with RMS of the head and neck are cured of their disease using surgery and vincristine, dactinomycin, and, in some cases, cyclophosphamide with or without radiotherapy. Early, limited exposure to cyclophosphamide might reduce recurrence in low-risk embryonal patients, and that reduced dosage might achieve comparable results with improved toxicity profiles (113). Orbital location of disease has the best prognosis and parameningeal disease has the worst (26). Multimodality therapy for head and neck RMS can result in dentofacial abnormalities that affect the patient's quality of life (114).

Other Soft Tissue Sarcomas

Sarcomas other than RMS are rare in childhood. Sarcomas account for less than 1% of all malignancies in the United States with only 5% to 15% of these sarcomas occurring in the head and neck region. However, about one in three pediatric sarcomas will occur in the head and neck region. Occasionally, these tumors are associated with genetic syndromes or previous radiation exposures, but more commonly, no clear etiology exists (115). Pathologic classification is critical to the ultimate treatment and prognosis of sarcoma of the head and neck. Osteosarcoma, rhabdomyosarcoma, malignant fibrous histiocytoma, and angiosarcoma are the most common types of sarcoma to occur in the head and neck region; however, up to 20% of head and neck sarcomas will remain unclassified. Other sarcomas are also tumors of mesenchymal cell origin, including leiomyosarcoma (smooth muscle), liposarcoma (fat), and fibrosarcoma (connective tissue). Diagnostic approaches to non-RMS soft tissue sarcomas are essentially the same as for RMS. Because of their extreme rarity, there is no meaningful staging system to guide therapy

Neuroblastoma

Neuroblastoma is the second most common solid tumor of childhood. Neuroblastoma accounts for the most common neck malignancy under 6 years of age (107). Neuroblastoma commonly presents as a solitary painless mass or lymphadenopathy (116). Cervical neuroblastoma may occur as a primary tumor but is more commonly a site of metastatic disease from an abdominal or thoracic primary tumor (14). Pain from bone metastases, Horner syndrome, or proptosis also may be present. Prognosis is related to age at presentation, stage, and lymph node metastasis. Treatment is based on the degree of regional extension and systemic dissemination and includes surgical excision, with or without chemotherapy and radiotherapy. In cases with delayed diagnosis and advanced disease, nonsurgical options with or without autologous bone marrow transplant are also considered. Localized lesions or low-stage disease has an excellent prognosis with complete surgical resection. Radiation therapy or chemotherapy, or both, and secondary surgeries are strategies to eradicate residual disease. Primary cervical neuroblastoma

has a favorable outcome (13,14). Children younger than 1 year of age and older children with localized disease have an excellent prognosis (117).

Thyroid Malignancies

Thyroid malignancies used to account for 50% of the pediatric neck malignancies (107). However, with more cautious use of irradiation, the incidence recently has been reduced. Pediatric thyroid carcinoma accounts for 0.5% to 3% of all pediatric malignancies (118,119). Most thyroid carcinoma patients are between 15 and 19 years of age (8). It is rare for thyroid cancer to present before age 10 years; however, it can be seen in all pediatric ages. Female to male ratio of thyroid carcinoma is 2:1 (8). Thyroid cancer usually presents with an asymptomatic, firm, and mobile midline neck mass. Over 70% have clinical, and almost 90% histologic, lymph node metastases (8). Risk of malignancy includes a history of rapid growth, new-onset hoarseness, odynophagia, hemoptysis, vocal cord paralysis, or fixation to surrounding tissues. At presentation, 8% to 22% have pulmonary metastases (120). Surprisingly, despite this advanced initial presentation, 15- to 20-year survival rates are over 90% (118,121).

As opposed to adult thyroid carcinoma, over 90% of childhood tumors are well differentiated (120). Prior radiation exposure increases the risk for thyroid malignancy with the risk peaking 10 to 20 years after exposure (8). Other risk factors include iodine deficiency, Hashimoto thyroiditis, Grave disease, Pendred or Gardner syndrome, MEN IIA and IIB, and specific oncogenes. A solitary thyroid nodule is not common in children but 10% to 24% of such are malignant (122,123). Ultrasonography differentiates cystic and solid masses. However, cystic nodules in children do not exclude malignancy (8). Recently, FNAB, with ultrasound guidance when indicated, with or without sedation, is more frequently performed in children.

The surgical approach for children remains controversial due to the desire to achieve improved disease eradication with the possibility of increased risk from total thyroidectomy versus the increased chance of residual or recurrent disease with hemithyroidectomy. Newer techniques for thyroidectomy, including microbipolar dissection, minimize potential risks of nerve injury and hypocalcemia (111). Children with thyroid nodules suspicious for malignancy are recommended to undergo ipsilateral lobectomy with frozen section. A frozen section diagnosis of well-differentiated thyroid carcinoma leads to near-total or total thyroidectomy (8). Palpable lymph nodes are addressed with a modified neck dissection. Gross extracapsular spread requires radical neck dissection (8). If the postoperative I 131 scan is positive, an ablative dose of I 131 is administered. Please refer to Chapter 133 for additional information on thyroid carcinomas.

Nasopharyngeal Carcinoma

In contrast to adults, epidermoid malignancies in the pediatric population are uncommon (4). NPC is a rare neoplasm in children, but is the most common pediatric epithelial neoplasm, occurring primarily in the adolescent age group (26). It is classified according to the WHO system into WHO I (keratinizing squamous), WHO II (nonkeratinizing squamous), and WHO III (undifferentiated). Most NPCs in children are undifferentiated (WHO III). It is associated with elevated EBV titers, suggesting an infectious etiology (26). Most children present with asymptomatic cervical lymph node metastasis. Commonly, unilateral otitis media, progressive nasal obstruction, and rhinorrhea are present. Headaches and cranial nerve palsies suggest skull base involvement. The tumor may mimic the common cold or rhinitis by presenting with nasal obstruction. Other symptoms may include epistaxis, otalgia, and conductive hearing loss. NPC may invade the skull base directly and involve cranial nerve VI, causing weakness of lateral gaze and diplopia. Other cranial nerves that can become involved include III, IV, and V, and, eventually, cranial nerves IX to XII (111). Distant metastases are common at the time of presentation. Undifferentiated NPC is radiosensitive. Adjuvant chemotherapy may improve the prognosis in some patients who have disseminated disease. Extensive surgical resection is not applicable to children due to skeletal immaturity, surgical morbidity, and concern about incomplete resection (111). Overall 5-year survival in children with NPC approaches 40%.

CONCLUSIONS

Head and neck masses in children are a common clinical concern. The differential diagnosis for a head and neck mass is broad, including congenital, inflammatory, and neoplastic lesions. A thorough examination of the head and neck and other systems with appropriate workup will narrow the differential diagnosis. The common pathologies can be differentiated with a clear understanding of embryology and anatomy of the region and knowing the natural history of the common diseases. While benign masses are much more common, care must be taken to rule out malignancy, particularly when early diagnosis and treatment leads to very high survival rates in general.

HIGHLIGHTS

- The majority of pediatric head and neck masses are congenital and inflammatory, with 80% to 90% representing benign conditions.
- Congenital masses may not be identified at birth or during infancy and may become apparent secondary to an infection later in childhood.
- The most common etiology for cervical adenopathy in children is reactive lymphadenopathy following a viral or bacterial illness.

- Adenopathy of viral etiology is usually bilateral, rarely suppurates, and generally resolves spontaneously, while bacterial adenitis is usually unilateral and develop fluctuance in 25% of cases.
- Any palpable solid mass at birth is abnormal and requires an evaluation to develop a definitive diagnosis.
- A lymph node greater than 1 cm in size in an infant younger than 1 year old is considered abnormal and a lymph node 3 cm or larger in a child older than 1 year old should be investigated.
- A rapidly enlarging, nontender, or long-standing neck mass with overlying skin changes raises the suspicion of malignancy. This suspicion is heightened when associated with fever, night sweats, and weight loss or located in the posterior triangle or supraclavicular space.
- A malignant lymph node may have metastasized from an oro-naso-hypopharyngeal primary; therefore, a thorough endoscopic examination of those sites should be performed in such cases.
- RMS is the most common soft tissue malignancy in childhood; however, diagnosis often gets delayed due to nonspecific symptoms at presentation as well as variable site presentation.
- Over 50% of pediatric neck malignancies are lymphomas (Hodgkin disease and non-Hodgkin lymphoma), which are treated with chemotherapy, and, sometimes, radiation therapy.

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Congenital Cysts and Sinuses of the Head and Neck

106

Robert F. Yellon

INTRODUCTION

Embryologic developmental anomalies are fairly common in the pediatric population. Failure of involution embryologic structures and duplication of structures can lead to fistulas, sinuses, and cysts. These include first, second, third, and fourth branchial cleft anomalies (BCAs), as well as preauricular cysts and sinuses and thyroglossal duct cysts (TGDCs). A fistula has an opening from the pharynx to the skin. A sinus is an incomplete fistula and has an opening to either the pharynx or skin. A cyst is an enclosed structure with no opening to the pharynx or skin. Failure of migration or incomplete or excessive migration of embryologic structures results in ectopic structures such as lingual thyroid and ectopic thyroid. Failure of involution of the embryologic thyroglossal duct leads to formation of TGDCs anywhere along the pathway from the base of tongue, submental region, and the anterior neck. Dermoid and epidermoid cysts arise from ectodermal tissues. They represent early embryonic displacements of epithelial nests.

These congenital anomalies may remain asymptomatic, not be obvious on clinical exam, and never require any treatment. Alternatively, enlargement of the lesion may lead to concern for possible malignancy or cosmetic deformity. Mild infections, drainage, or abscess formation may also occur. Enlarging and infected lesions and lesions that interfere with normal functions are possible indications for surgical excision.

Infected cysts and sinuses may be treated with oral or intravenous antimicrobial agents. More severe infections may require needle aspiration possibly guided by ultrasound or computed tomography (CT). Failure of these lesions to respond to these interventions and severe infections and abscesses may require incision and drainage. However, incision and drainage should be used as the last resort when other lesser measures have failed. The reason for avoiding incision and drainage if possible is to avoid violation of tissue planes and violation of the walls of the congenital anomaly, which may possibly make complete excision at a later date more difficult due to scarring and unclear extent of the lesion. The definitive surgical excision may usually be delayed until 3 to 4 years of age unless the severity warrants earlier excision, which may be necessary at any age.

TGDCs are the most common congenital neck anomaly in children. For BCAs, the second BCA is most common. In a series of 97 BCAs, 18% were first BCAs, 69% were second BCAs, and 7% were third BCAs (1). Thirty-two percent of these lesions had infections previous to surgery and 71% of those had more than one infection. Fistulas and sinuses were infected more frequently (67%) than cysts (21%).

Diagnostic studies include CT with contrast, magnetic resonance imaging (MRI) with gadolinium contrast, ultrasound, and fine-needle aspiration. Of course the most definitive diagnostic test is surgical excision with pathologic examination.

There have been recent reports showing efficacy of fine-needle aspiration and sclerotherapy for selected second BCAs and TGDCs in adults with OK-432. In one series, 7/12 (58%) BCAs treated with OK-432 had complete resolution of the lesion (2). In another series, 14/23 (61%) BCAs had complete resolution of the lesion (3). Unilocular lesions had a higher success rate than multilocular lesions, which had only partial or no response to OK-432. In a third series, OK-432 was successful for resolution for 9/18 (50%) second BCAs and 5/11 (46%) TGDCs (4). Fever, pain, and odynophagia may occur following OK-432 sclerotherapy.

First Branchial Cleft Anomalies

First BCAs are not very common and are often confused with other less complex lesions. Any mass that is located near the lobule of the ear may be a first BCA. The differential diagnosis includes lymph nodes, sebaceous cysts,

dermoid cysts, lymphatic vascular malformations, and parotid and other tumors. CT and MRI are critical prior to any surgical intervention other than fine-needle aspiration. Solid lesions are likely to be lymph nodes and tumors. Multilocular lesions are likely to be lymphangiomas. Cystic lesions filled with solid rather than fluid material are likely to be dermoids. Fluid-filled cystic lesions may be simple cysts; however, it is possible that the fluid-filled cystic lesion may represent a first BCA (Fig. 106.1).

If a first BCA is suspected, and a surgery for removal is planned, the critical point to keep in mind is that there may be a deep portion of the lesion that may run medial or lateral to the main trunk of the facial nerve or between branches (5,6). If the deep portion of first BCA lesion is not removed along with the cystic portion, recurrence is likely. Since the deep tract of the first BCA runs in proximity to the facial nerve, injury of the facial nerve is possible unless the facial nerve is first identified and preserved. Then the entire first BCA lesion can be safely removed. Facial nerve monitoring and intraoperative testing are helpful for the dissection (Fig. 106.2) (Table 106.1).

Thus, it is wise to suspect that any cystic lesion in proximity to the lobule is possibly a first BCA with a deep tract extending to the facial nerve. The lesion should be approached carefully, and if a deep tract is noted, then the facial nerve is identified and preserved prior to removal of the deep tract.

First BCAs occur in two varieties as described by Work (7). A Work type 1 first BCA contains only ectoderm, often has a pit in the external auditory canal, and is considered a duplication of the external auditory canal. A Work type 2 lesion will contain derivatives of two germ cell layers, ectoderm and mesoderm.

Since the relationship of the first BCAs and the facial nerve may not be recognized, it is not uncommon for a surgeon to encounter a lesion that recurs following an inadequate resection by another surgeon. In one series of 18 first BCAs, 65% had undergone incomplete surgery prior to referral (5). The scarring resulting from the first surgery makes the dissection and preservation of the facial nerve more difficult, which may result in a very challenging surgery. Occasionally, a first BCA may present along the anterior border of the sternocleidomastoid muscle slightly lower in the neck than the inferior aspect of the lobule. It is therefore also possible to confuse a first BCA with a second BCA that usually occurs along the anterior border of the sternocleidomastoid muscle in the midneck area.



Figure 106.1 Surgical exposure of first BCA.

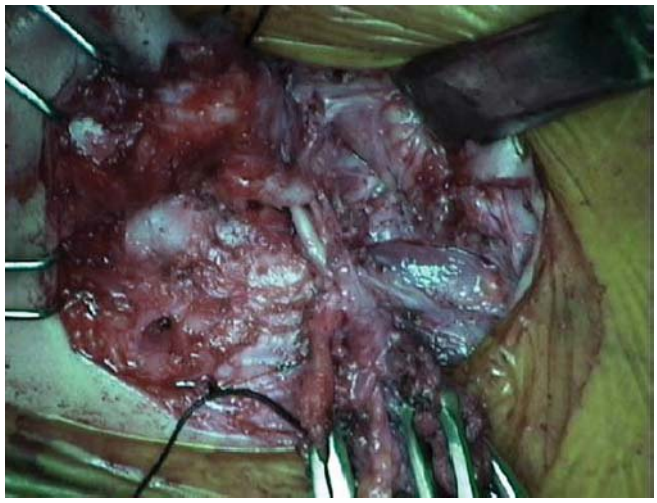


Figure 106.2 Seventh nerve dissection is required to fully and safely excise deep portion of first BCA. Note trunk of seventh nerve (*white*) with tract of first BCA adjacent to right side.

Second Branchial Cleft Anomalies

Second BCAs are the most common of the three types of branchial cleft lesions. As noted above, these lesions commonly occur along the anterior border of the

TABLE 106.1 ANATOMIC PATHWAYS FOR DEEP TRACT OF FIRST, SECOND, THIRD, AND FOURTH BCAS

- First BCA
  - The tract may run medial or lateral to the main trunk of the facial nerve or between branches.
- Second BCA
  - The deep tact runs between the internal and external carotid arteries and superior to the glossopharyngeal and hypoglossal nerves and finally ends at the tonsillar fossa.
- Third BCA
  - The deep tract passes posterior to the internal and external carotid arteries, between the 9th and 12th cranial nerves, and ends in the apex of the pyriform sinus.
- Fourth BCA
  - The deep tract begins with a sinus at the apex of the pyriform sinus and travels inferiorly in the tracheoesophageal groove, posterior to the thyroid gland, and into the thorax. Next, it loops below the aorta on the left or below the subclavian artery on the right and then ascends posterior to the common carotid artery to loop over the hypoglossal nerve and ends at the anterior border of the sternocleidomastoid muscle.

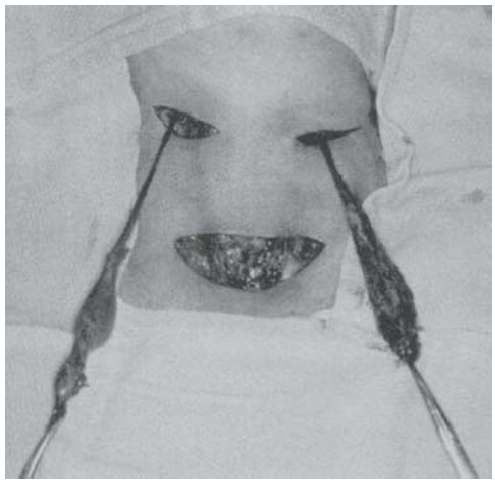


Figure 106.3 Surgical excision of bilateral second branchial cleft cysts in a child with BOR syndrome.

sternocleidomastoid muscle in the midneck region. Like the first BCAs, the second BCAs may also have a deep tract (Fig. 106.3). It is critical to understand the anatomic path of the second BCAs for safe and complete excision. The deep tact runs between the internal and external carotid arteries and superior to the glossopharyngeal and hypoglossal nerves and finally ends at the tonsillar fossa (Table 106.1).

A particular cyst or sinus may or may not have a deep extension. The surgeon must be prepared to dissect out a possible deep tract that ends at the tonsillar fossa and then tie off the tract. If the deep portion is not dissected out and excised, recurrence of the lesion is more likely. Gently placing a lacrimal probe into the skin opening of a sinus or fistula can help determine the direction and depth of the tract, which may aid dissection, but care must be taken to avoid rupturing the tract. Other surgeons prefer to inject methylene blue into the tract to aid dissection, but again rupturing the tract can lead to staining of uninvolved tissues and a more difficult dissection. If a branchial remnant is infected, intravenous antimicrobial agents should be administered. If an uninfected lesion is breached, a culture should be taken and intravenous antimicrobials should be administered. Antimicrobials are not required for clean cases with no breach of the lesion.

Although some surgeons advocate excision of the tonsil on the side of the lesion, most surgeons do not excise the tonsil and tie off the tract close to the tonsillar fossa.

Third Branchial Cleft Anomalies

The third and fourth BCAs are rare, often misdiagnosed, and thus often recurrent. The most common presentation is a cystic mass or abscess along the anterior border of the sternocleidomastoid muscle in the mid- to lower neck. Over 90% occur on the left side (8,9). These lesions are often misdiagnosed as recurrent neck abscesses or thyroid abscesses or cysts. The key to diagnosis is to understand the potential for these lesions to have a deep tract that extends

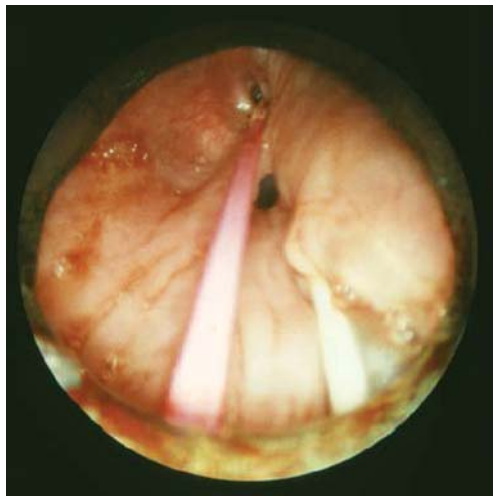


Figure 106.4 Third BCA with sinus opening into the pyriform sinus. Fogarty catheter has been placed into sinus to facilitate dissection of deep tract to pyriform sinus.

near the thyroid gland to end as a sinus in the pyriform sinus. Simple incision and drainage often leads to recurrence of the abscesses. The diagnosis is made by several means. One is a thorough pharyngoscopy at the time of incision and drainage that shows a sinus tract in the apex of the pyriform sinus (Fig. 106.4). CT scan may show an air-filled structure in the apex of the pyriform sinus or a cystic structure with a deep extension approaching the pyriform sinus (Fig. 106.5). Modified barium swallow may show a barium-filled sinus in the apex of the piriform sinus.

To properly excise the third BCAs, the anatomic course of the tract must be known. The tract of this anomaly passes posterior to the internal and external carotid arteries and between the ninth and twelfth cranial nerves and ends in the apex of the pyriform sinus (Table 106.1). A small catheter placed in the sinus opening in the apex of the pyriform sinus is helpful prior to excision since palpation of the catheter makes the tract easier to identify during excision (Figs. 106.4 and 106.6). Hemithyroidectomy may



Figure 106.5 CT of third BCA.

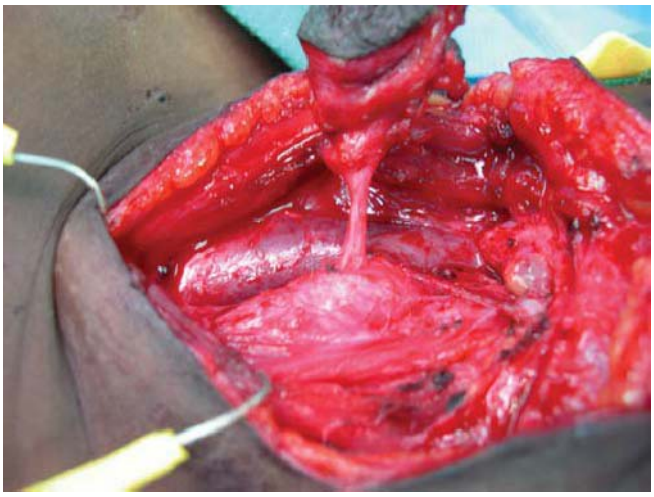


Figure 106.6 Dissection of third BCA to pyriform sinus.

be required for some third branchial cleft lesions that are intimately associated with the thyroid gland.

Some recent reports have described success in treating third and fourth BCAs by electrocautery or laser of the sinus opening in the pyriform apex (8,9). This approach may be helpful in very young or very ill children. This approach also makes the differentiation between the third and fourth BCAs irrelevant since the clinical presentation and endoscopic treatment are the same for both lesions (8).

Fourth Branchial Cleft Anomalies

The uncommon fourth BCA also has a sinus opening into the pyriform sinus; however, the anatomic pathway differs from that of the third BCA. Indeed, it is often impossible to discern whether a particular anomaly is a third or fourth BCA without surgical dissection. Over 90% occur on the left side (8,9). The diagnosis of a fourth BCA may be made by the following methods. These are the same methods used to identify the third BCAs. Thorough pharyngoscopy at the time of incision and drainage will show a sinus tract in the apex of the pyriform sinus. CT scan may show an air-filled structure in the apex of the pyriform sinus. Modified barium swallow may show a barium-filled sinus in the apex of the pyriform sinus. Similar to the third BCAs, the fourth BCAs are often misdiagnosed as neck abscesses or recurrent thyroiditis.

The anatomic pathway of the tract of a fourth BCA begins with a sinus at the apex of the pyriform sinus and travels inferiorly in the tracheoesophageal groove, posterior to the thyroid gland, and into the thorax. Next, it loops below the aorta on the left and below the subclavian artery on the right and then ascends posterior to the common carotid artery to loop over the hypoglossal nerve and ends at the anterior border of the sternocleidomastoid muscle (9) (Table 106.1).

In one series, 19/20 third and fourth BCAs in children were treated with endoscopic electrocautery or laser for ablation of the sinus opening in the pyriform sinus (8). Thirteen of nineteen (68%) were successful with a single procedure, 78% were successful with 2 procedures, and 89% were successful with 3 procedures. In two of five neonatal cases, open surgical excision was required to relieve severe airway obstruction, one after failed endoscopic treatment.

PREAURICULAR CYSTS AND SINUSES

Embryologically, the six hillocks of His, derived from the first and second branchial arches, fuse to form the auricle. A preauricular cyst or sinus arises from partial failure of involution of the epithelium between the first and second hillocks. These common congenital lesions usually have a punctum anterior to the root of the helix (Fig. 106.7), a short tract, and a sinus, which ends with an attachment to the perichondrium of the root of the helix.

These lesions often remain asymptomatic. However, it is not uncommon for these lesions to leak a small amount of mucoid discharge, or to get infected. Treatment of infected preauricular sinuses includes oral antimicrobials, but needle aspiration or incision and drainage may be required for some infections/abscesses. Avoidance of incision and drainage is preferable if possible since violation of the sinus may make definitive surgical excision more difficult due to scarring and less clear tissue planes.

A period of approximately 6 weeks is allowed following infection of preauricular sinuses to allow for resolution of inflammation. Surgical excision then can begin with gentle



Figure 106.7 Preauricular sinus.

insertion of a small lacrimal probe into the punctum to identify the direction of the sinus cavity, which almost always goes to the perichondrium of the root of the helix. The punctum should be excised using an elliptical incision. The tract and then sinus are then traced to the perichondrium of the root of the helix. The perichondrium is scored sharply and peeled off the cartilage of the root of the helix (Fig. 106.8). Any associated scar tissue or granulation tissue is excised along with the lesion. There is no concern for injury to the facial nerve during dissection in the preauricular area. The facial nerve is deeper and inferior to the area of dissection.

It is not uncommon to see patients with recurrence of preauricular cysts or sinuses following surgery. A portion of the sinus may have been left in situ following surgery complicated by scar, inflammation, or granulation tissue. It is very common that the attachment of the sinus to the root of the helix was left behind, and this is the focus of the recurrent infection. For revision cases with abscess or inflammation adjacent to the root of the helix, it is difficult to peel the perichondrium in this area off the helical cartilage. It is therefore recommended that the full thickness of cartilage is excised to assure complete removal.

Occasionally, a surgeon encounters a case of infected preauricular sinus that has undergone multiple prior attempts at excision. For such cases, a block dissection is performed in the preauricular area with excision of all the inflamed and scarred tissue down to the preauricular/parotid fascia (Fig. 106.9). As described above, the area of the cartilage of the root of the helix must be addressed. Again, the facial nerve is not at risk since the nerve is deep to the fascia and inferior to the area of dissection. Local cheek advancement flaps are usually sufficient to allow closure of the wound. Rarely a superiorly pedicled postauricular skin flap is rotated to fill the defect in the preauricular area.



Figure 106.8 Dissection of preauricular sinus down to perichondrium of root of helix. It is important to excise this perichondrium to assure complete excision.



Figure 106.9 Recurrence of infected preauricular sinus requiring block dissection down to fascia.

BRANCHIOOTORENAL (MELNICK-FRASER) SYNDROME

Patients with a combination of bilateral preauricular sinuses, bilateral second or third BCAs in the neck, and renal disease most likely have branchiootorenal (BOR) syndrome (Fig. 106.3) (10). This is an autosomal dominant genetic syndrome with variable penetrance. It can be detected prenatally with genetic testing. Hearing loss may be conductive or sensorineural. The auricle may be normal, slightly anomalous, or microtia may be present. The kidneys may be normal, anomalous but functioning, or absent (Table 106.2).

If a child is found to have only bilateral preauricular sinuses, the chance of hearing loss is 1 in 200. If a child is found to have bilateral preauricular sinuses and bilateral

TABLE 106.2 CLINICAL FINDINGS IN BOR (MELNICK FRASER) SYNDROME (10)

- Hearing loss
- Preauricular pits
- Branchial fistulas or cysts
- Anomalous pinna
- Renal dysplasia

From Melnick M, Hodes ME, Nance WE, et al. Branchio-oto-renal dysplasia and branchio-oto dysplasia: two distinct autosomal dominant disorders. *Clin Genet* 1978;13:425–442.

BCAs in the neck, the chances of hearing loss are much higher and renal studies are indicated. Family members should also be examined and tested, when appropriate.

THYROGLOSSAL DUCT CYSTS

The embryonic thyroid gland arises at the foramen cecum at the junction of the anterior two-thirds and posterior one-third of the tongue. The gland then usually passes inferiorly through the base of tongue. Next, it passes anterior or posterior to the center of the hyoid bone. It then continues to migrate inferiorly into the lower neck to its final location. This embryologic path of the thyroid gland is known as the thyroglossal duct. Failure of involution of a portion of the thyroglossal duct results in a TGDC.

A TGDC may be small and remain occult. Alternatively, it may be discovered on routine physical exam. Other presentations include slow enlargement of a midline neck mass, or infection of the mass with rapid enlargement (Fig. 106.10). Children with TGDCs are usually euthyroid. However, if hypothyroidism is suspected, thyroid function tests should be obtained with endocrinology consultation when indicated.

The differential diagnosis of a midline neck mass includes TGDC, dermoid cyst, and lymph node. Ultrasound or CT is useful to determine whether the mass is solid or cystic. Obviously solid lesions are more likely to be lymph nodes and cystic lesions are more likely to be TGDCs or dermoids. Fluid-filled TGDCs often have a lower density center compared to dermoid cysts, which are usually filled with thick cheesy material. The presence of the normal thyroid gland in the normal location is also important to evaluate on the ultrasound or CT exam to know that the mass in question is not in fact ectopic thyroid gland. Ultrasound has the advantage of no radiation exposure compared to CT scan.

Excision of TGDCs is usually recommended. This is recommended to confirm the diagnosis, prevent recurrent infections, and to be certain that the lesion does not contain thyroid cancer. The standard surgery for TGDCs was described by Walter Sistrunk in 1920 (11). Sistrunk understood the embryologic pathway of the thyroid gland and TGDC and incorporated it into the definitive surgery he described. The "Sistrunk procedure" includes resection of the cystic mass, the associated deep tract, the middle third of the hyoid bone, and a portion of the base of tongue deep to the foramen cecum. When this method of excision is used, the chance of recurrence of the lesion is reduced compared to simple excision of the cyst (Figs. 106.11 and 106.12). At the Toronto Hospital for Sick Children, they reviewed 143 patients with TGDCs that underwent 214 surgical procedures. One hundred five patients needed only one operation. Thirty-eight had recurrent disease and needed 109 procedures for cure. Inadequate surgery was the direct cause of recurrence. The authors had a 6.5% recurrence rate using the Sistrunk procedure versus general surgeons who did less and had a 23% recurrence rate (12).

Postsurgical recurrence of the TGDCs may still occur especially when there has been inaccurate initial diagnosis, previous infection, incision and drainage with scarring and distortion of tissue planes, unusual presentations (lateral neck, base of tongue), or lack of base of tongue muscle removal (13). Since the tract of a TGDC may pass posterior to the hyoid bone, dissection of the hyoid bone



Figure 106.10 Typical TGDC in midline of neck.

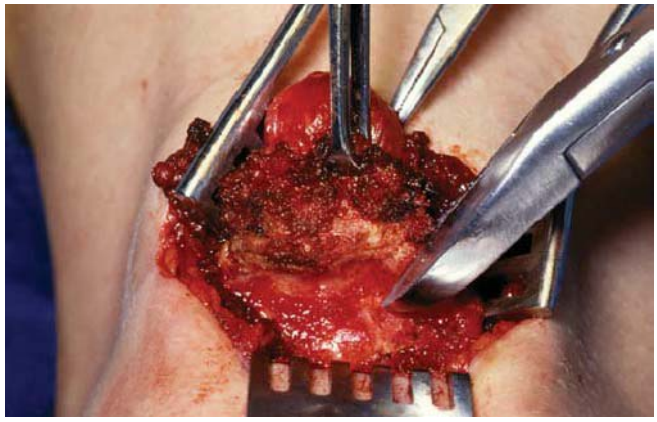


Figure 106.11 Sistrunk procedure. The TGDC has been mobilized, and the central portion of the hyoid bone is being transected with a rongeur.

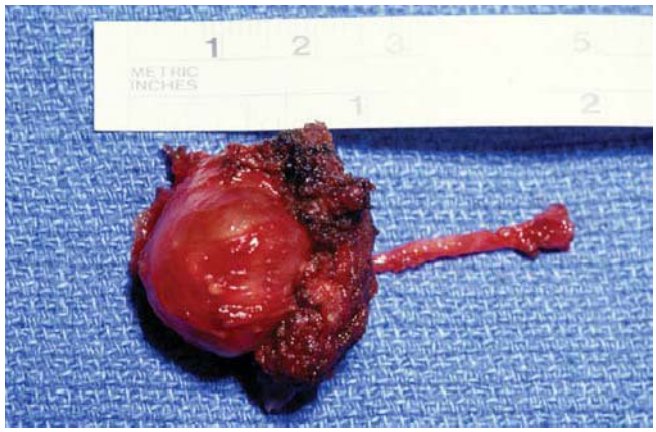


Figure 106.12 Specimen following Sistrunk procedure with TGDC, central portion of hyoid bone, and tract from base of tongue.

and "posterior hyoid space" has been recommended with removal of all tissue posterior to the middle portion of the hyoid bone and anterior to the thyrohyoid membrane to decrease recurrence (14).

For recurrent cases of TGDC, the so-called central compartment neck dissection is performed (Fig. 106.13). This procedure would include all aspects of the standard Sistrunk procedure plus excision of all tissue between the skin and fascia over the strap muscles and mylohyoid muscles that occurs medial to the sternocleidomastoid muscles and the digastric muscles. Any skin that is adherent to the mass is excised as well.

Suture-guided transhyoid pharyngotomy was described as a helpful procedure to address recurrent TGDCs (13). In this procedure, a 20-gauge spinal needle is passed through the area of recurrent TGDC in the neck to the foramen cecum of the tongue. A heavy permanent suture is passed through the spinal needle and retrieved via the oral cavity. The spinal needle is removed. A portion of a red rubber catheter is tied to the oral side of the suture. The central compartment neck dissection and the revision Sistrunk procedure are then performed. After the central portion of the hyoid bone is excised, the suture and red rubber catheter are pulled for traction to allow excision of the base of tongue musculature and foramen cecum to remove thyroglossal duct remnants. The foramen cecum is then closed with eversion of the mucosal edges. The success rate was 8/8 (100%) for this revision procedure.



Figure 106.13 Recurrent infected TGDC that will require central compartment neck dissection and revision Sistrunk procedure.

Lingual TGDCs may be discovered incidentally or may be associated with life-threatening airway obstruction. Microsuspension laryngoscopy with endotracheal intubation has been reported to be successful for management of these cases using electrocautery, cold dissection, and microdebrider (15).

Antimicrobials are not usually administered unless the lesion is obviously infected. Cultures should be obtained prior to antimicrobial administration in such cases. If a lesion is ruptured intraoperatively, or the pharynx is entered, the wound is closed, cultures are taken, and antimicrobials are administered. If the pharynx is inadvertently entered, the mucosa is closed and a feeding tube is placed. Inadvertent entry into the pharynx is more likely to occur during revision cases or cases associated with multiple infections when excessive scarring and anatomic distortion are present. A radiographic contrast swallowing study is obtained after 3 to 5 days to assure closure prior resumption of oral feeding. In contrast to adult cancer patients with such injuries, children heal rapidly as there is no cancer or radiation to impair healing.

The chance of a TGDC containing cancer is only about one in one hundred. These are usually discovered inadvertently at surgery. The distribution of thyroid malignancies found mirrors the distribution of malignancies seen in the main thyroid gland with papillary (16) and follicular types as the most common. The criteria for diagnosis of thyroid carcinoma arising in TGDC include a thyroglossal remnant that can be distinguished from a cystic lymph node metastasis and a normal thyroid gland (17). When thyroid cancer is found in association with a TGDC, thyroid nuclear medicine scan is advised. Further surgery is contraindicated if the thyroid scan is normal. The patient should be referred to a surgeon specializing in head and neck oncology. I^{131} scan is indicated to prove the thyroid gland is present and to rule out other tumors in the gland. Total thyroidectomy is performed if additional tumor is found. I^{131} scan is performed after surgery if differentiated cancer is diagnosed. Synthroid is administered for replacement and suppression of thyroid-stimulating hormone.

ECTOPIC THYROID AND LINGUAL THYROID

As discussed above in the section on TGDCs, the thyroid gland anlaga begins at the foramen cecum at the junction of the anterior one-third and posterior two-thirds of

the tongue. It then passes inferiorly through the base of tongue and then passes anterior or posterior to the central portion of the hyoid bone. Next, the descent continues to the lower central neck. Ectopic thyroid may occur at any location along the embryologic pathway of descent when migration is arrested. The ectopic tissue may be at the base of tongue (90%), within the tongue, submental area, and anterior aspect of neck. Additional rare sites for ectopic thyroid include trachea and mediastinum. Cases of dual ectopic thyroid have been reported with more than one focus of ectopic thyroid (18). Hypothyroidism associated with ectopic thyroid is not uncommon and thyroid function tests are indicated.

Ectopic thyroid that remains at the base of tongue is referred to as "lingual thyroid." Lingual thyroid occurs in 1:100,000 people. Female to male ratio is 4:1. Seventy to one hundred percent of those affected have no other thyroid tissue, and 14% to 33% of patients with lingual thyroid are clinically hypothyroid.

The majority of excised lingual thyroids reveal histologically normal thyroid tissue. Lingual thyroid may cause dysphagia, dysphonia, airway obstruction, or bleeding. Lingual and ectopic thyroid when symptomatic may require treatment. Endocrinology consultation for thyroid suppression may be helpful for milder cases. Severe cases with airway obstruction or bleeding may require surgical excision via a transoral approach, transhyoid pharyngotomy, lateral pharyngotomy, or rarely midline labiomandibulotomy. It is helpful to place sutures around the lingual thyroid tissue prior to excision that are left long and then tied after the mass is excised to decrease blood loss. Autotransplantation of excised ectopic thyroid is not advised due to the small chance of the presence of thyroid carcinoma (19).

DERMOID CYSTS

Epidermoids contain only epidermal tissue, while dermoids may also contain hair follicles and sebaceous glands. Epidermoid and dermoid cysts of the head and neck usually occur in the so-called T distribution involving the midline of the face and anterior neck and the orbits and periauricular area. When a round mass occurs in the anterior neck of a child, the differential diagnosis includes TGDC, dermoid, and lymph node (Fig. 106.14). On CT or ultrasound examination, a TGDC will usually have a cystic appearance and low-density, fluid-filled contents, while the dermoid will have cystic appearance but a more dense center. The lymph node will have a solid tissue density center.

Dermoids may occur in the region of the nasal dorsum. The primitive frontonasal region or anterior neuropore develops medial to the optic recesses in the third week of fetal life. Through the 8 weeks, a transient fontanelle called the foramen cecum is present between the inferior frontal bone and nasal bone. A dural projection extends inferiorly through the opening anterior to the crista galli of the ethmoid bone. The apex of the dural projection approximates the subcutaneous region posterior to the frontal and nasal bones and anterior to the nasal cartilage. Failure of involution of these structures results in dermoid, glioma, and encephalocele (20).



Figure 106.14 Specimen of midline neck mass. The mass was originally approached as a TGDC with a Sistrunk procedure, but when hair was seen coming from the mass, it was clearly a dermoid cyst and simple excision was performed.

Thus, when a cystic-appearing mass occurs in the dorsum of the nose or in the intranasal region in a child, the differential diagnosis includes dermoid (Fig. 106.15), glioma, and encephalocele. Since the mass may have an intracranial extension, biopsy or excision of the mass without CT and possibly MRI is to be condemned as it may cause cerebrospinal fluid leak and meningitis. Gliomas are heterotopic brain tissue. For nasal dermoids or gliomas without intracranial extension, open rhinoplasty approach or direct incision over the mass (Fig. 106.16) is adequate. Endoscopic-assisted, closed rhinoplasty approaches have been recently described (21). Nasal bone osteotomy may be necessary for adequate exposure, and permanent nasal deformity is not uncommon. It is wise to advise the parents of the possibility of significant nasal deformity and



Figure 106.15 Dermoid sinus with pit splaying apart the nasal bones.

that secondary rhinoplasty may be required when the child is older.

If intracranial extension of the mass is detected on CT or MRI, consultation from neurosurgery (22) or surgeons specializing in the extended endonasal endoscopic approach is required (23).



Figure 106.16 Incision over nasal dermoid for excision.

ACKNOWLEDGMENT

The author would like to acknowledge Dr. Eugene Myers for providing several excellent photographs.

HIGHLIGHTS

- Infected congenital cysts and sinuses and BCAs may be treated with antimicrobial agents and possibly needle aspiration. Incision and drainage should be avoided if possible since scarring may make excision more difficult.
- Recent reports have shown some efficacy of fine-needle aspiration and sclerotherapy for selected second BCAs and TGDCs with OK-432.
- It is wise to suspect that any cystic lesion in proximity to the lobule is possibly a first BCA with a deep tract extending to the facial nerve. The lesion should be approached carefully, and if a deep tract is noted, the facial nerve is identified and preserved.
- Second BCAs, the most common of the BCAs, occur along the anterior border of the sternocleidomastoid muscle in the midneck. Second BCAs may have a deep tract that runs between the internal and external carotid arteries and superior to the glossopharyngeal and hypoglossal nerves and ends at the tonsillar fossa.
- Third BCAs are rare, often misdiagnosed, and often recurrent. Over 90% occur on the left. These lesions often present as recurrent neck or thyroid abscesses or cysts. The tract passes posterior to the internal and external carotid arteries, between the ninth and twelfth cranial nerves, and ends in the pyriform sinus. Hemithyroidectomy may be required.
- The rare fourth BCA also has a sinus opening into the pyriform sinus. Over 90% occur on the left. The tract begins with a sinus opening in the pyriform sinus, takes an intrathoracic path, and then ends at the anterior border of the sternocleidomastoid muscle.
- Third and fourth BCAs may be selectively treated with electrocautery or laser ablation of the sinus in the pyriform sinus. Surgical excision is required for airway obstruction.
- When excision is necessary for preauricular sinuses, the tract and sinus are traced to the perichondrium of the root of the helix, which is scored sharply and peeled off the cartilage. It is common to see patients with recurrence when perichondrium was not excised. Full thickness of cartilage is then excised to assure removal.
- Patients with a combination of bilateral preauricular sinuses, bilateral second or third BCAs in the neck, and renal disease most likely have BOR syndrome. This is an autosomal dominant genetic syndrome.

- TGDCs are the most common congenital neck anomaly. Definitive surgery is called the "Sistrunk procedure," which includes resection of the mass, the deep tract, the middle third of the hyoid bone, and a portion of tongue base.
- Ectopic thyroid may occur at the base of tongue (90%), within the tongue, submental area, anterior neck, intratracheal, or mediastinum, and is often the only thyroid tissue. Hypothyroidism is common and endocrinology consultation is helpful. Severe cases with airway obstruction or bleeding require surgical excision.
- The differential diagnosis of a mass in the dorsum of the nose or intranasal region includes dermoid, glioma, and encephalocele. There may be intracranial extension, and biopsy without CT or MRI may cause cerebrospinal fluid leak and meningitis.

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The Syndromal Child

107

Ted L. Tewfik

Congenital anomalies are involved in about half of all pediatric hospital admissions and next to accidents constitute the leading cause of death in children. They involve all medical branches, cross all human medical disciplines, and present worldwide challenges. The significance of these birth defects and the accurate diagnosis of each condition or of complex syndromes are often difficult to determine.

The goal of any dysmorphic assessment is to interpret the pattern of structural anomalies correctly and arrive at the diagnosis. The practicing specialist dealing with the ear, nose, and buccopharyngeal region is confronted frequently with problems related to congenital anomalies. The spectacular advances in basic and clinical genetics during the past three decades have brought congenital malformations and inherited disorders to the forefront of medical attention and care. Congenital anomalies affect 3% of neonates; by age 5 years, as more subtle anomalies manifest, the percentage climbs from 7% to 10%. The shared spectra of dysmorphic phenotypes and their inherent variability can be overwhelming. Several thousand distinct syndromic entities have been described, and because of their rarity, the typical specialist will not encounter the vast majority of them. The purpose of this chapter is to provide the otolaryngologist with a systematic approach to the dysmorphic neonate, infant, or child and to demonstrate that dysmorphology is a learned discipline that can be practiced by any physician who is inquisitive, thorough, and willing to cultivate his or her powers of observation.

Inheritance of traits and disorders may be monogenic or multigenic or the result of the transmission of an abnormal chromosome (e.g., a deletion or a duplication). The expression of specific genes is influenced by other genes or environmental conditions. Besides the classical mendelian patterns of inheritance, several nonclassical patterns of inheritance have been discovered and studied in recent years.

Single genes are usually inherited according to one of the following mendelian patterns: autosomal dominant (AD), autosomal recessive, X-linked dominant, and X-linked recessive. These patterns may be apparent in pedigrees, the proper drawing of which is the first step in the study of inherited diseases in families. They should be included in all case histories in which a familial disease is suspected. They are also essential for linkage studies, gene mapping, genetic counseling, and prenatal diagnosis. The symbols commonly used are standard and generally accepted (Figs. 107.1 to 107.3).

A person is homozygous for a certain gene when both alleles at the same locus are identical. Heterozygosity implies the presence of two different alleles. Usually the term is used for situations when one of the alleles bears a pathogenic mutation.

There is no absolute distinction between "dominant" and "recessive" genes. By definition, a "recessive" gene has no detectable expression in a heterozygote under the conditions of study and analysis. Diseases resulting from deficiency of enzymatic activity behave as recessives because, in the heterozygous situation, the amount of enzymatic activity produced by the unaffected allele allows a normal metabolic function. When the gene codes for an abnormal structural protein, the mutant allele usually acts as a dominant. In that case, the cells of the heterozygote carry the mutant gene and synthesize a mixture of the structurally normal and abnormal proteins. As a result of changes in the physical properties of the protein, heterozygotes may show phenotypic abnormalities (1,2).

The following are the characteristics of AD inheritance:

1. At least one of the parents of an affected person is also affected, except when the penetrance is reduced or the trait arises by a new mutation or when there is germline mosaicism. The trait appears in every generation. There is no "skipping" except when the "penetrance" is reduced.

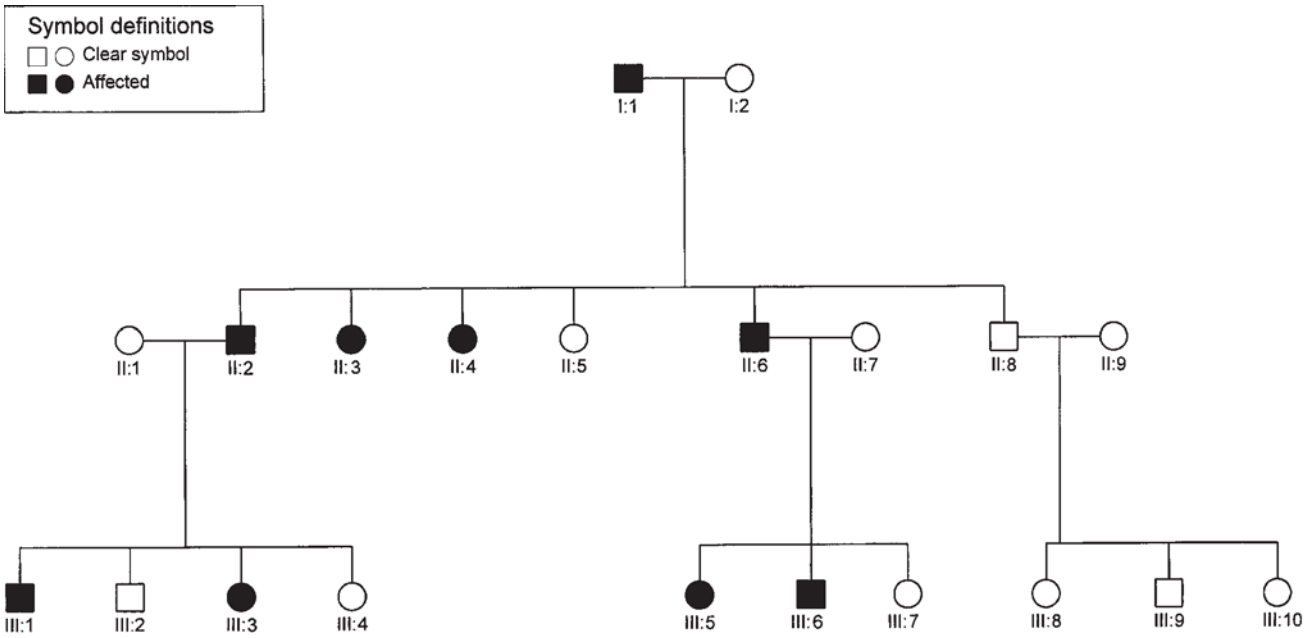


Figure 107.1 Autosomal dominant inheritance. Vertical pattern of trait expression; males and females are equally affected.

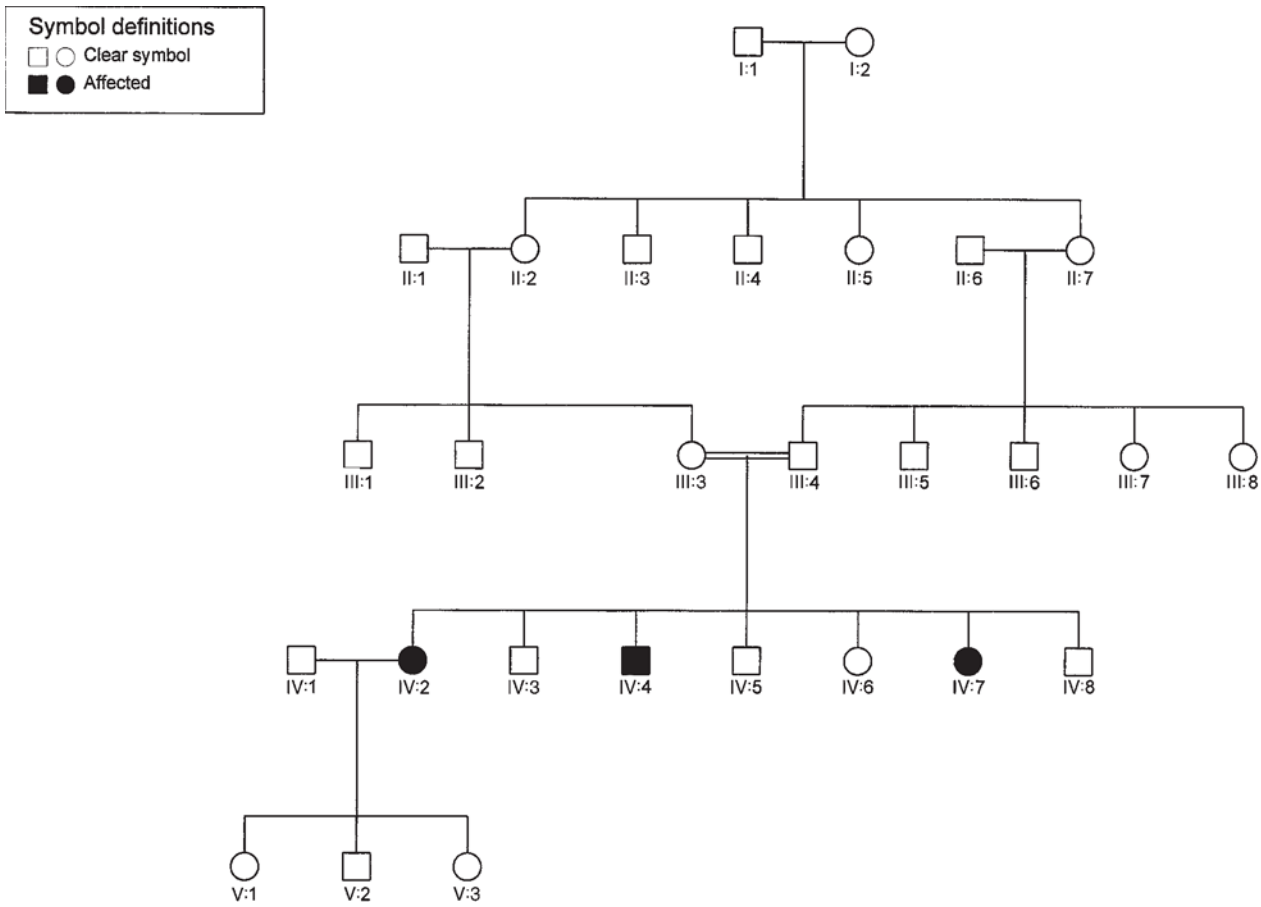


Figure 107.2 Autosomal recessive inheritance. Horizontal pattern of trait expression. Parental consanguinity is often present in families with autosomal recessive disorders.

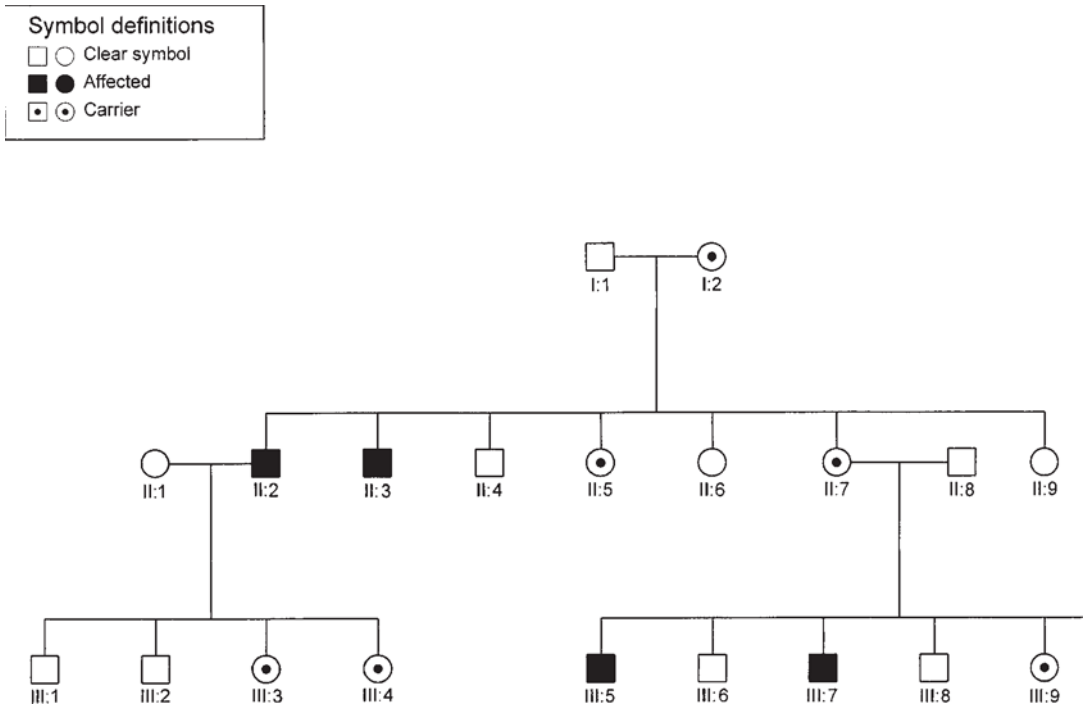


Figure 107.3 X-linked recessive inheritance. Males only are affected. There is no male-to-male transmission, and daughters of affected males are carriers.

2. An affected person heterozygous for the trait has an equal chance of transmitting the mutant or the normal allele to each child.
3. Males and females can have and transmit the trait equally.

Two traits are said to be codominant when their genes are allelic and are both expressed in a heterozygote individual. For example, in a person with blood group AB, genes for both groups A and B are expressed.

The following are the characteristics of autosomal recessive inheritance:

1. The parents are heterozygous and phenotypically normal; the trait appears only in the children who are homozygous for the mutant gene.
2. Statistically, one-fourth of the children of heterozygous parents are affected and thus there is a chance of 25% at each pregnancy.
3. Males and females have equal chance of being affected.

When an individual carries two different mutated alleles at the same locus, the condition is called a genetic compound. In consanguineous marriages, both partners have a higher risk of being carriers of the same rare recessive gene. Thus, the children who are products of consanguineous marriages run an increased risk of being affected with autosomal recessively inherited conditions. This risk may be increased by 100-fold. However, in absolute terms, it is of the order of 1%.

X-linked recessive inheritance occurs when the mutant gene is on the X chromosome. It has the following characteristics:

1. The trait is much more common in males than in females. Females have two X chromosomes, and males have only one. All males carrying the X-linked gene express the trait. Females are affected when they are homozygous and in certain rare heterozygous cases, as an effect of the Lyon hypothesis, when a high percentage of cells have random inactivation of the X chromosome carrying the normal allele.
2. An affected man passes his X-linked gene to all of his daughters who thus become carriers but are not affected. He does not transmit it to any of his sons.
3. A carrier woman passes her X-linked gene to half of her sons who manifest the trait and to half of her daughters who become carriers.

X-linked dominant inheritance has the following characteristics:

1. Affected men transmit the trait to all their daughters who then display the clinical manifestations of that particular condition. They transmit the gene to none of their sons.
2. Heterozygous women are affected. They transmit the trait to half of their sons and half of their daughters.

Y-linked genes occur only in males. They are transmitted to all the sons and none of the daughters. There are very few genes known to be definitely on the Y chromosome.

PENETRANCE

Certain traits may be modified by other genes and by environmental factors to such an extent that they may not be recognizable either clinically or by laboratory tests, although the gene causing the trait is present. In such cases, the gene or trait is said to have incomplete or reduced penetrance. Thus, certain AD traits with reduced penetrance may "skip" a generation.

EXPRESSIVITY

Expressivity indicates the variation in expression of a phenotype that a gene may have. In clinical medicine, a certain gene with variable expressivity may produce mild, moderate, or severe disease. A *forme fruste* is an extremely mild and clinically insignificant expression of a condition. Variable expressivity and *formes frustes* are noted especially in AD inheritance. For example, certain patients with cleidocranial dysostosis may not be identified clinically and are diagnosed in retrospect by special radiographic testing when other more affected members of their families are detected.

PLEIOTROPY

Pleiotropy is the occurrence of multiple phenotypic effects of a mutant gene or gene pair. For example, the primary defect in Hurler syndrome is the specific deficiency of α-L-iduronidase, with accumulation of the substrate in the lysosome. Secondary effects are mental retardation, craniofacial anomalies, dysostosis multiplex, corneal opacification, and hepatosplenomegaly.

HETEROGENEITY

A condition is causally heterogeneous when multiple causes result in the same effect. Genetic heterogeneity of a disease may result in confusing pedigrees. Thus, inherited congenital neurosensory deafness in different families may be the result of two autosomal recessive genes at two different loci. The children of two deaf individuals, each homozygous for a recessive trait at a different locus, may all have normal hearing because they will be heterozygous for two separate loci.

The craniosynostoses are also genetically heterogeneous. Thus, Pfeiffer syndrome may be the result of mutations of FGFR1 (fibroblast growth factor receptor 1) on chromosome 8 (8p11.2-p12) or FGFR2 on chromosome 10 (10q25.3-q26).

Moreover, many malformations are pathogenetically heterogeneous, separate mechanisms being responsible for the same effect. Robin sequence is an example. It is commonly present in Stickler syndrome, which is a single-gene, AD condition. Alternatively, it may be the result of predominantly environmental conditions *in utero*, such as oligohydramnios, in which case the chin is compressed against the sternum, thus restricting mandibular growth and impacting the tongue between the palatal shelves (3).

MALFORMATION

A malformation by definition is a structural morphologic defect of an organ, part of an organ, or a larger region of the body resulting from a developmental process that is intrinsically abnormal.

A major malformation is one that requires intervention, represents a significant medical or psychologic challenge, and may seriously impair or prevent normal functioning. Examples are ambiguous genitalia and anencephaly. A minor malformation is one that does not represent a lifelong medical or psychologic challenge. Such anomalies can be corrected (unilateral cleft lip, postaxial polydactyly). Minor malformations and variants are important flags for the dysmorphologist. One or two may be found in otherwise normal individuals, but the simultaneous finding of three or more minor anomalies has special significance. In such a patient, the clinician should be prompted to search for occult major malformations and consider a syndromic diagnosis.

Some hereditary traits are transmitted in a nonmendelian pattern, and they cannot be classified as AD, recessive, or X-linked. Mosaicism, uniparental disomy, genomic imprinting, and mitochondrial inheritance are examples that are not discussed here.

SYNDROME

The term *syndrome* is used to describe a broader error of morphogenesis in which the simultaneous presence of more than one malformation is known or assumed to be the result of a single etiology.

DEFORMATION

Abnormalities in form, shape, or position resulting from normal responses of the affected tissues to the presence of nondisruptive mechanical forces are known as deformations. Potter sequence is an example of deformation.

DISRUPTION

Disruption is when an originally normal developmental sequence is the victim of a process causing ischemia, tissue breakdown, or both.

The most commonly observed disruption is the result of early amnion rupture when entanglement of the fetus in free-floating amniotic bands produces partial or complete amputation of normally formed structures such as digits, limbs, or bizarre facial clefts (3).

SEQUENCE

The term *sequence* is used to designate a series of anomalies resulting from a cascade of events initiated by a single malformation, deformation, or disruption.

ASSOCIATION

An association is the nonrandom occurrence in two or more individuals of multiple anomalies not known to represent a polytopic field defect, sequence, or syndrome.

A PRACTICAL APPROACH TO THE INFANT OR CHILD WHO IS SYNDROMIC

Given the fact that several thousand distinct syndromic entities have been described, one cannot possibly successfully use a vague memorization strategy in dysmorphology. Instead, what is necessary is a systematic approach that concentrates on meticulous attention to the details of history and physical examination, combined with a method that allows the physician to sift through these details and come up with the best "clues."

History

The elements of the dysmorphologic history are identical to those of a general pediatric history, but the physician must be particularly tenacious in obtaining specific details. Keep in mind that the parents of a newborn with congenital anomalies may be unable to provide a complete and coherent account of events during the pregnancy and labor and may not have been fully aware of the nature or extent of abnormal ultrasound findings.

If you are assessing an older child, the parents may not recall many obstetric details or they may inadvertently overemphasize the importance of particular prenatal or peripartum events in an effort to explain their child's difficulties. When possible, it is always best to obtain the relevant medical records.

Physical Examination

The dysmorphology examination differs significantly from a general pediatric examination in its emphasis and attention to detail. The sequence of the examination varies with the examiner, but it should be systematic to prevent omissions.

Precise measurements with comparisons made to standardized curves are helpful in defining the problem. The most useful clues are often the most subtle. A single minor anomaly can be found in up to 30% of newborns. However, less than 10% of neonates have two or more minor anomalies, and only 4% have three or more. The presence of three unrelated minor anomalies is associated with a 20% risk of major structural defects, and most of these infants will, in fact, have a dysmorphic syndrome.

It may be necessary to examine family members, particularly for the presence of minor variants detected in the proband. Examination of the family members may also help you decide whether a mildly dysmorphic facial feature is really only a familial trait. Most parents will be happy to provide you with access to the family photo album, from which age-appropriate comparisons with your patient can be made.

Interpreting the Findings

Having identified the pertinent elements of your patient's history and physical examination, the next step is to interpret your findings from a developmental and morphologic viewpoint.

Genetic counseling is based on averaged data pooled from the general population. Information should be presented to the parents ensuring that they understand the different issues related to recurrent risks, inheritance, and prognosis.

In summary, the spectrum of dysmorphic phenotypes is broad and includes malformations, deformations, disruptions, sequences, associations, and syndromes. An effective assessment involves a meticulous history and physical examination combined with a developmental and morphologic interpretation of the findings. Additional clues are provided by ancillary investigations and the use of computer databases and literature searches. In attempting to serve the patient and family, our efforts to identify, categorize, and rationalize the abnormal will continue to provide exciting revelations into normal processes of human development. Ultimately our understanding of these processes will be greatly enhanced by rapidly advancing deoxyribonucleic acid technology. A valuable tool accessible on the World Wide Web is Online Mendelian Inheritance in Man (www3.ncbi.nlm.nih.gov/omim/). Other databases include the London Dysmorphology Database and POSSUM.

Many classifications for the congenital syndromes have been attempted; we found that the following are more inclusive. We present two classifications: one based on system involvement and the other based on etiology. A few examples are included under the different headings.

I. Classification of Otolaryngologic Syndromes and Conditions (based on system involvement)

1. Syndromes associated with ocular disease
   Usher, Norrie, Fraser, Alstrom, Bardet-Biedl
2. Syndromes associated with craniofacial anomalies
   a. Craniosynostosis
   Apert, Crouzon, Pfeiffer, Saethre-Chotzen, Jackson-Weiss, Carpenter, Antley-Bixler
   b. Abnormal contour
   Encephalocele (with absent corpus callosum, clefting, Dandy-Walker and Arnold-Chiari malformations, ectrodactyly, hypothalamic pituitary dysfunction)
   c. Orofacial clefting

Facial clefts and associated anomalies, Tessier clefting system, lateral facial clefts, oblique facial clefts, median mandibular defects
d. Branchial arches
Goldenhar, Treacher Collins, Nager, Miller, Wildervanck, Möbius, oro-facial-digital syndromes (I–VIII)
e. Unusual facies
Opitz BBB/G, Noonan, Robinow, Binder, Coffin-Siris syndromes
3. Syndromes associated with nervous system disease
Neurofibromatoses (1–8), Melkersson-Rosenthal, Cockayne, Friedreich ataxia, Hallgren, Prader-Willi
4. Syndromes associated with integumentary system disease Waardenburg, Leopard
5. Syndromes associated with musculoskeletal anomalies ichthyosis syndromes (Desmons, KID), oculocutaneous albinism syndromes, Ehler-Danlos syndromes
a. With contractures
Multiple pterygium, Whistling face, Schwartz-Jampel, Marden-Walker
b. Abnormal stature
i. Short
Aarskog, Cornelia de Lange, Hallerman-Streif, Rubinstein-Taybi, Silver-Russell, Bloom, Seckel
ii. Moderate
Smith-Lemli-Opitz
iii. Overgrowth
Sotos, Marshall-Smith, Weaver, Beckwith-Wiedeman
iv. Senile appearance
Progeria
c. Osteochondrodysplasia
Achondrogenesis (types I–IV), achondroplasia, campomelic dysplasia, chondrodysplasia punctata, Kniest, Nance-Sweeney, osteogenesis imperfecta (OI) (types I–IV)
d. Other skeletal disorders
Craniometaphyseal dysplasia, Van Buchem disease, sclerosteosis, Camurati-Engelmann disease, cleidocranial dysplasia, Marfan syndrome, McCune-Albright, Stickler
6. Syndromes with urogenital anomalies
Branchio-oto-renal (BOR), Alport, Renal tubular acidosis
7. Syndromes with metabolic (and endocrine) anomalies
Mucopolysaccharidoses (I–VII), mannosidosis, gangliosidoses, lipodoses, diabetes and associated syndromes, Pendred, Kallmann, Perrault
8. Hamartoneoplastic syndromes
Sturge-Webber, Von Hippel–Landau, Goltz, Peutz-Jegher, Maffuci
9. Gingivodental syndromes
Gingival fibromatosis and its syndromes, Rieger, tricho-dento-osseous, LADD
10. Syndromes associated with environmental and teratogenic agents*
Fetal alcohol, rubella, thalidomide, vitamin A
11. Chromosomal syndromes*
Trisomy 21, trisomy 13, trisomy 18, cri-du-chat, Wolf-Hirshhorn, Turner, FragileX
12. Associations*
CHARGE, MURCS, VATER, or VACTERL
13. Sequences*
DiGeorge, Klippel-Feil, Robin, Potter
14. Spectra*
Facio-auriculo-vertebral, oromandibular limb hypogenesis
15. Miscellaneous syndromes*
Jervell and Lange-Nielsen, Kartagener, Shprintzen, Coffin-Lowry, Kabuki make-up, Keutel, Pallister-Hall, Floating-Harbor

II. Classification of Otolaryngologic Syndromes and Conditions (Based on Eetiology)

1. Chromosomal abnormalities
Turner, Down (trisomy 21), trisomy 13, trisomy 18, cri-du-chat, 4p-, 9p-
2. Microdeletion chromosomes
Velocardiofacial (Shprintzen), Williams, Rubinstein-Taybi, Langer-Gideon
3. Single gene disorder
a. AD: achondroplasia, Marfan, neurofibromatosis (NF), Noonan, Apert, Crouzon
b. Autosomal recessive: phenylketonuria (PKU), Bardet-Biedl, Smith Lemli Opitz
c. X linked: Aaskog, ichthyosis, aqueductal stenosis
d. Mitochondrial
4. Environmental and teratogenic
Rubella, thalidomide, dilantin, PKU embryopathy
5. Multifactorial
Anencephaly, cleft lip/palate, congenital heart disease
6. Syndromes with uncertain etiology
Klippel-Feil, Cornelia-de Lange, associations

APERT SYNDROME

Acrocephalosyndactyly Type I

The major diagnostic criteria are the craniosynostosis and syndactyly of the hands and feet.

The skull is acrocephalic with a shortened anteroposterior diameter and a flat occiput. The craniosynostosis involves the coronal suture. However, the acrocephalic feature of Apert syndrome is not only due to synostosis of the coronal suture, but is a result of the primary disturbance in growth of the cranial base with precocious endochondral ossification (4). The forehead is prominent. The fontanelles are large and close at a later age. The palpebral fissures are downslanting. The corners of the mouth are downturned, and it is sometimes described as "trapezoid mouth." Dental anomalies include delayed and ectopic

*These entries do not represent other systems; their inclusion in the classification is meant to help the reader memorize the different conditions.

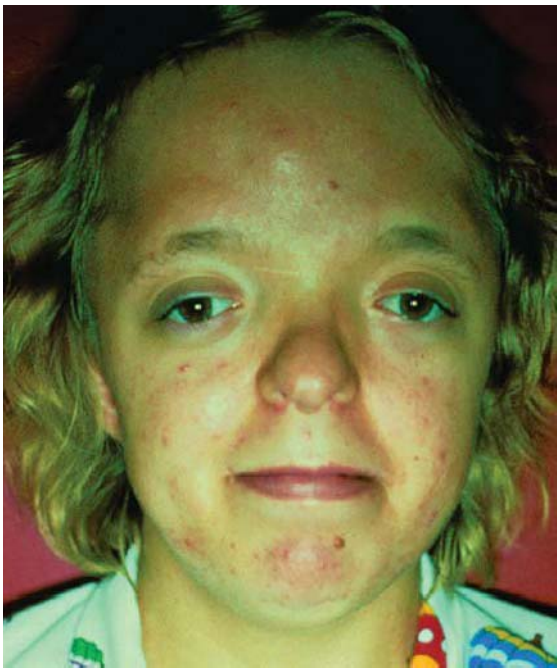


Figure 107.4 Apert syndrome: Typical facies of Apert's syndrome. Note antimongoloid slanting of the palpebral fissures, exophthalmos, hypertelorism, oxycephaly, and midfacial hypoplasia. Photo Courtesy of Meinhard Robinow, MD from Gold DH, Weingeist TA. *Color atlas of the eye in systemic disease.* Baltimore, MD: Lippincott Williams & Wilkins, 2001, with permission.

eruptions and shovel-shaped incisors. Malocclusion with mesial molar occlusion and severe crowding of the teeth are also frequently noted. A significant number of patients with Apert syndrome are mentally retarded. Malformations of the corpus callosum, the limbic structures, or both do occur. Other findings include gyral abnormalities, megalencephaly, hypoplasia of the white matter, and heterotropic gray matter. Of patients, 70% have normal intelligence (4,5).

The pituitary fossa and the basiocciput are significantly larger than normal in patients with Apert syndrome. Anomalies of the hands include syndactyly of the second, third, and fourth fingers that form a mid-digital mass (Fig. 107.4). The first and fifth fingers may join the hand mass or be separate from it. The distal phalanx of the thumb is often broad. Syndactyly is also noted in the feet and involves the second, third, and fourth toes. Fusion of the tarsal bones and an extra metatarsal have been noted. Other anomalies include abnormalities of the cervical vertebrae (single fusion 37%, multiple fusion 31%). C5 and C6 are often involved. Moderate to severe acne at adolescence occurs in 70% of patients. Synostosis of the radioulnar complex, pyloric stenosis, ventricular septal defects, and polycystic kidneys are rare occurrences.

The nasal bridge is depressed, and the midface usually is hypoplastic. The palate is narrow and is described as "byzantine-arch shaped." Cleft palate may also occur (30%). Anomalies of the ears include otitis media, conductive hearing loss, fixation of the stapedial foot plate, and wide cochlear aqueduct. Temporal bone studies revealed absence of the internal auditory canals (IACs) in one patient and enlarged subarcuate fossa in another report. Anomalies of the airway as well as tracheal stenosis, obstructive sleep apnea (OSA), and *cor pulmonale* with resultant early death were also reported (3,4). In general, OSA is related with a lower quality of life in children with syndromic craniosynostosis. Behavioral problems are more common in boys with Apert syndrome. OSA-18 scores are correlated with OSA severity (4).

The syndrome is AD inherited. An increased paternal age is a factor in sporadic cases, which accounts for the majority. The incidence of Apert syndrome is estimated to be 15.5 per 1 million, and it represents 4.5% of all cases of craniosynostosis. Mutations have been found in FGFR2 (3). The primary site of the acrocephalic feature in Apert syndrome is a dwarf cranial base with accelerated chondrocytic differentiation due to aberrant activation of the FGFR2 signaling (5).

BRANCHIOOTORENAL SYNDROME

Melnick-Fraser Syndrome

The association of auricular malformations, branchial fistulae, deafness, and renal anomalies was first described in 1975. The prevalence is estimated to be 1:40,000 in the general population.

Renal dysplasia is reported in more than two-thirds of patients and varies from tapered superior poles (duplication of the collection system) to marked agenesis of the kidney. The syndrome may include Potter sequence. Mitral valve prolapse is a new finding in BOR syndrome. It was reported in five individuals from the same family (1,7).

The preauricular pits are blind, pin head-sized depressions in the superior part of the pinna of the ear. They are seen in 75% to 85% of the patients. Other external ear malformations (40% to 60%) may include preauricular tags, lop or bat ears, and microtia (Fig. 107.5A and B). The external auditory canals (EACs) may be atretic. Anomalies of the middle ear include anomalies of the ossicles, facial nerve, and fallopian canals. Computed tomography (CT) of the temporal bones may demonstrate hypoplastic cochlea and absent or hypoplastic semicircular canals. Mondini dysplasia, widened vestibular aqueduct, and vestibular sac were also reported. The hearing loss is usually stable and may be conductive, sensorineural, or mixed. It is estimated that 2% of profoundly deaf children have BOR syndrome. The branchial fistulae (63%) are usually bilateral in the lower part of the neck, and the external openings are on the medial border of the sternomastoid muscle. Other associated manifestations include aplasia or stenosis of the lacrimal ducts (8% to 9%), high-arched or cleft palate, deep overbite, and facial nerve anomalies.

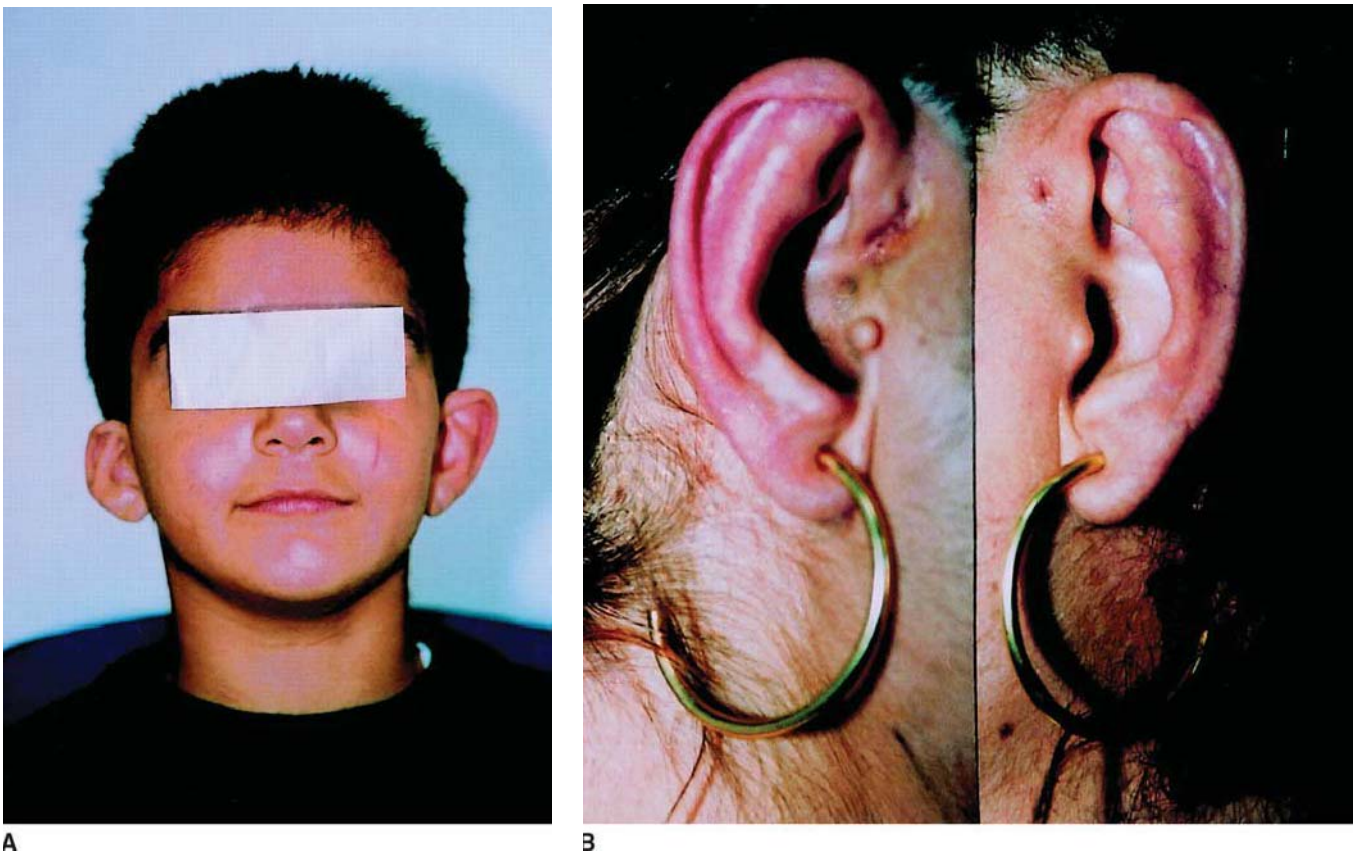


Figure 107.5 **A,B:** Branchiootorenal syndrome (BOR) syndrome. Note the ear deformity in **(A)** and the preauricular pit in **(B)**. From Pierides AM, Athanasiou Y, Demetriou K, Koptides M, Deltas CC. A family with the branchio-oto-renal syndrome: clinical and genetic correlations. *Nephrol Dial Transplant* 2002;17:1014–1018.

BOR syndrome is AD with high penetrance and variable expression. Pathogenesis is presumed to be the result of deficiency in the differentiation of the first and second branchial arches. The anomalies of the renal system are the result of abnormal interaction between the ureteric bud and the metanephric blastema. It is interesting to note that the inner ear (stria vascularis) and the renal glomeruli share a common antigen and more than one group has described histopathologic changes on temporal bone examinations (1). Mutations in EYA1 are the most common cause of branchiootic syndrome. Large chromosomal aberrations of 8q13, including complex rearrangements, occur in about 20% of these individuals. However, submicroscopic deletions and the molecular characterization of genomic rearrangements involving the EYA1 gene have been rarely reported (1,2,6,7).

CHARGE ASSOCIATION

The components of the CHARGE condition are as follows: C (*c*oloboma of the eye), H (*h*eart disease), A (*a*tresia of the choanae), R (*r*etarded development and growth), G (*g*enital anomalies), and E (*e*ar anomalies, deafness, or both).

Choanal atresia is associated with more than 65% of cases. It is bilateral in more than two-thirds of the patients. In unilateral cases, it is more common on the left side. The colobomatous malformations are seen in 80% of the cases. They range from iris coloboma with intact vision to anophthalmia and retinal colobomas. Microphthalmia and nystagmus may also occur. Cardiac anomalies may include tetralogy of Fallot, patent ductus arteriosus, ventral septic defects, atrial septic defects, coarctation of the aorta, or right-sided aortic arch. Mental deficiency is reported in the majority of cases, ranging from mild to severe. Central nervous system (CNS) malformations have also been described, such as arrhinencephaly or holoprosencephaly. Agenesis of the internal carotid artery was recently reported (1,8).

Minor kidney anomalies, cryptorchidism, microphallus, congenital hypothyroidism, imperforate anus, and pectus carinatum have also been reported.

Anomalies of the external ear include low-set ear or posteriorly angulated, asymmetric, or cup-shaped pinnae (Fig. 107.6). Anomalies of the inner ear have been coined as "charge dysplasia of the temporal bone"—which includes Mondini dysplasia of the pars inferior and complete absence of the pars superior. The hearing loss is conductive or sensorineural and often asymmetric (1).

Other anomalies include Robin or DiGeorge sequence, facial asymmetry, micrognathia, feeding difficulties,



Figure 107.6 A CHARGE association. Note the low-set posteriorly angulated pinna. Description = CHARGE syndrome: unusually shaped ears showing cochlear transplant. From Blake KD, Prasad C. CHARGE syndrome. *Orphanet J Rare Dis* 2006;1:34.

tracheoesophageal (TE) fistula, esophageal atresia, cleft lip or palate, and upper airway abnormalities.

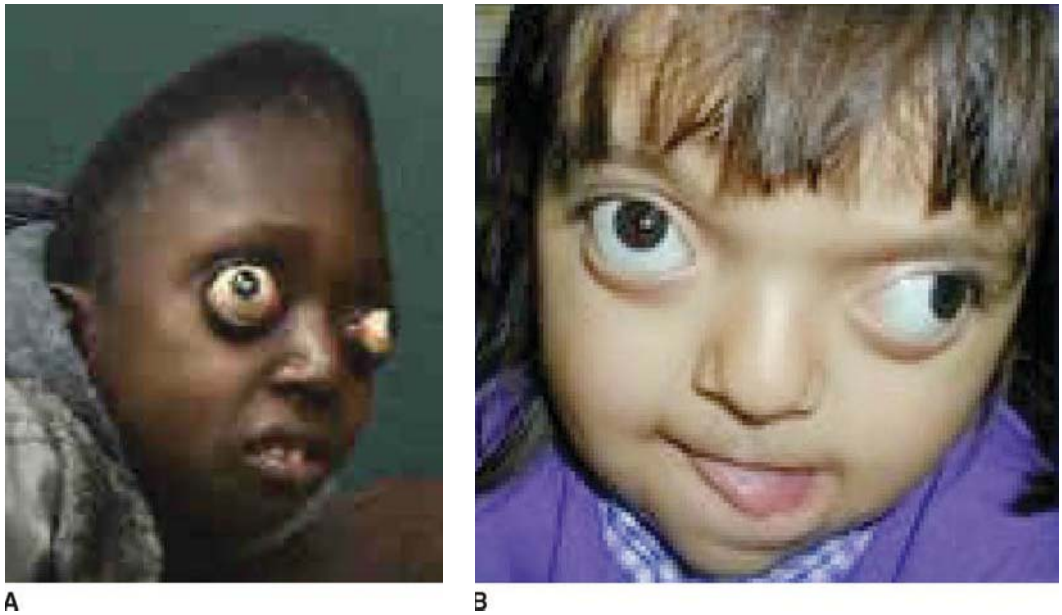
In most cases, the syndrome is sporadic. The CHARGE association is most probably the result of an abnormality in the migration or development of the cephalic neural crest cells (1,2). AD or recessive inheritance has been suggested. Translocations involving chromosome 6 and 8 have been reported. Other chromosomal abnormalities have also been suggested. The CHD7 gene on chromosome 8q12.1 was recently shown to be a major gene involved in the etiology of CHARGE syndrome (2,8).

CROUZON SYNDROME

Craniofacial Dysostosis

Craniofacial dysostosis is characterized by cranial deformity resulting from premature craniosynostosis, hypoplastic midface, exophthalmos, hypertelorism, and mandibular prognathism. The syndrome is estimated to occur in 16.5 people per 1 million.

Craniosynostosis of the coronal, sagittal, and lambdoid sutures may occur, giving the skull a brachycephalic shape. Occasionally, scaphocephaly or clover leaf deformity may occur. Crouzon syndrome constitutes approximately 4.8% of cases with craniosynostosis in general. Proptosis occurs in most cases secondary to the shallow orbits (Fig. 107.7A and B). It may result in exposure keratitis. Optic nerve involvement is usually evident in half of the cases. Other ocular findings include megalocornea, nystagmus, keratoconus,



A B

Figure 107.7 **A,B:** Patients with Crouzon syndrome. Note the proptosis in both patients due to the shallow orbits. **A:** From http://www.mymultiplesclerosis.co.uk/misc/petero-byakatonda.html, with permission, **B:** Courtesy of Dr. Stephen R. Cohen, with permission.

ectopia lentis, or colobomas of the iris. Frequent headaches, seizures, and mental deficiency may also occur. Acanthosis nigricans has been described in association with Crouzon syndrome. The surgical treatment is usually directed toward correcting craniosynostosis. The facial abnormalities may be corrected using the Tessier procedure.

It is estimated that 30% to 55% of patients with Crouzon syndrome have hearing loss. The hearing loss is usually conductive. The EACs may be atretic. Ossicular fixation and deformities have been described as well. Anomalies of the palate include lateral palatal swellings in 50% of cases, but cleft lip or palate is not common. The maxillary teeth are often crowded, and there is usually an anterior open bite. The nose is often parrotlike. Calcification of the stylohyoid ligament occurs most of the time. Anomalies of the cervical vertebrae involve mostly C2 and C3.

Surgical intervention involves fronto-orbital and midfacial advancement, usually done in stages in childhood. The occlusion is corrected adequately with orthodontics and final maxillary advancement after skeletal growth is completed (1).

The syndrome is inherited as an AD trait with complete penetrance. The expressivity is variable. Increased paternal age is a factor in the sporadic cases. Mutations have been described in the genes of FGFR 2. Crouzon syndrome with acanthosis nigricans results from a mutation in FGFR 3 (1,2,4,).

DOWN SYNDROME

Trisomy 21 or Down syndrome is the most common of the chromosomal abnormality syndromes. The diagnosis of Down syndrome can be made in the early newborn period. Four out of 10 signs are needed to make a clinical diagnosis (Table 107.1). However, a final diagnosis may be made only after having the results of the chromosomal pattern. Adaptive behavior in Down syndrome is described to increase until middle childhood and to begin to decline in adolescence, whereas significant deterioration in middle adulthood has been attributed to early onset of dementia. Nevertheless, opinions diverge about when the slowing down of adaptive and cognitive abilities starts. In a recent prospective cross-sectional study, Dressler et al. concluded that individuals with Down syndrome continue to increase competence in adaptive behavior until age 30, even when cognitive abilities reach a plateau. There was no major decline in middle adulthood. This may be due to exposure to daily life, but needs to be supported by further studies.

TABLE 107.1 TEN CARDINAL FEATURES OF DOWN SYNDROME IN THE NEWBORN

Features	Percentage
Flat facial profile	90
Poor moro reflex	85
Hypotonia	80
Hyperflexibility of joints	80
Excess skin on back of neck	80
Slanted palpebral fissures	80
Dysplastic pelvis	70
Anomalous auricles	60
Dysplasia of midphalanx of 5th finger	60
Simian crease	45

The eyes have speckled irises (Brushfield spots), and fine opacities are seen in the lens on slit lamp examination. Mental deficiency is a hallmark of the syndrome. The intelligence quotient (IQ) varies between 30 and 50. Various brain lesions have been described including abnormalities of the cerebellar peduncles and fibrous gliosis of the white matter. The frequency of epilepsy is estimated to be 5%. Older patients develop changes characteristic of Alzheimer disease. Cardiac anomalies are seen in approximately 40% of patients; atrioventricular communis or ventricular septal defects, Fallot tetralogy and patent ductus arteriosus occur in decreasing order of frequency. Atlantoaxial instability is seen in 10% to 20%. The hands have short metacarpals and phalanges with clinodactyly and hypoplastic midphalanx of the fifth finger. Single palmar creases and ulnar loop dermal ridge patterns are seen in a high percentage of cases. There is a wide gap between the first and second toes. Male patients have a small penis and low testosterone production and are almost all infertile. The hair is often sparse; cutis marmorata and dry hyperkeratotic skin are not uncommon (1).

Other uncommon anomalies include TE fistula, incomplete fusion of the vertebrae, cryptorchidism, syndactyly, and keratoconus. The main cause of death is the cardiovascular malformation and is highest in the first 2 years of life. Leukemia occurs in 1% of patients. Lymphomas, testicular carcinoma, and CNS tumors have also been reported. Flat facial features, small or absent paranasal sinuses, hypertelorism, small nasal bridge, and oblique palpebral (upward-slanting) fissures occur in more than 80% of patients. The tongue is relatively large and protrudes from the mouth. It may be furrowed or fissured. Occasionally true macroglossia exists. The ears are small with overfolding of the superior part of the helix. The EACs are stenotic, especially at the isthmus (bony-cartilaginous junction). Conductive hearing loss occurs in 60% of patients, with a high incidence of serous otitis. Sensorineural hearing loss (SNHL) occurs in 10% of patients. The cochlea is sometimes shorter than usual. Ossicular chain anomalies, especially the stapes, may be seen. The lips are broad and dry, and rhagade furrows around the mouth are seen (Fig. 107.8). The tonsils are often hypertrophied and not recessed in the fossae. The palate is narrow. Cleft lip or palate is occasionally seen. Gingivitis, periodontal disease, and dental caries exist. Microdontia, hypoplasia of the enamel, posterior cross-bite, and widely spaced teeth are frequent occurrences. Articulation defects and dysrhythmic or explosive speech are associated with a low-pitched hoarse voice.

Of all cases, 95% are the result of trisomy 21 with 47 chromosomes. Mosaicism is observed in 2.4% of patients.



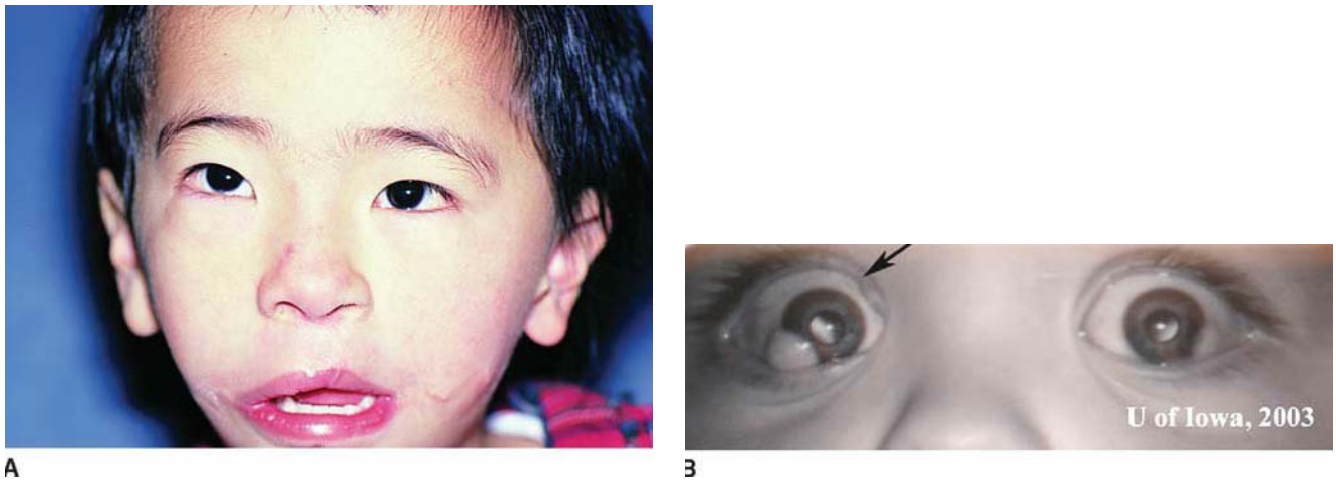
Figure 107.8 Down Syndrome. Reprinted from Pillitteri A. *Maternal and child health nursing*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2003, with permission.

Translocations account for 3% to 5% of cases involving chromosome 14, 21, or 22 (i.e., 14/21, 21/21, or 22/21). The incidence of the syndrome increases with advanced maternal age, being 1:1,500 for mothers aged 15 to 29 and 1:50 for those older than age 40. The general incidence is 1:600 of all live births (1,2,9).

GOLDENHAR SYNDROME

Oculoauriculovertebral Dysplasia Spectrum or Facioauriculovertebral Sequence

Gorlin proposed the term *oculo-auriculo-vertebral dysplasia* for the spectrum of anomalies ranging from hemifacial microsomia (HFM) that denotes unilateral microtia, mandibular hypoplasia, and microstomia to Goldenhar syndrome, which also includes epibulbar dermoids (Fig.107.9B) and vertebral anomalies. Blepharoptosis, microphthalmia, epibulbar tumors, and retinal abnormalities have been documented. The visual acuity is usually reduced. Mental retardation varies in the reported series between 5% and 15%. Children with anophthalmia or microphthalmia and cleft lip or palate seem at increased risk for cerebral malformation and mental retardation. Various cardiac anomalies are described ranging from ventricular septal defect, patent ductus arteriosus, and Fallot tetralogy to coarctation of the aorta. Renal ectopia and hydronephrosis are less common. Talipes equinovarus deformities and other limb anomalies are rare occurrences. The mandibular ramus and condyles are hypoplastic. The maxilla, malar, and temporal bone are smaller on one side (Fig. 107.9A). The mastoid is also poorly pneumatized. Approximately one-third of the cases show bilateral involvement. The right side is involved in 60% of the cases. Macrostomia or pseudomacrostomia (lateral cleftlike extension of the corner of the mouth) is a usual occurrence. The parotid gland is also affected (agenesis or displaced salivary tissue). Cleft palate or lip occurs approximately 10% of the time. Delayed dental development, as well as lingual and palatal malformations, occurs



A B

Figure 107.9 **A:** Patient with Goldenhar syndrome: Note the unilateral microtia, mandibular hypoplasia, and microstomia B subconjunctival dermoids of the right eye in patient with Goldenhar syndrome. **A:** From Tasman W, Jaeger E. *The Wills eye hospital atlas of clinical ophthalmology*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2001. **B:** From Graff JM, Bhola R, Olson RJ. Goldenhar Syndrome (Oculo-Auriculo-Vertebral Spectrum): 6-day-old male with limbal dermoids on http://webeye.ophth.uiowa.edu, with permission.

on the hypoplastic side. Microtia or occasional anotia and preauricular tags occur between the tragus and the corner of the mouth. The middle ear demonstrates ossicular anomalies and abnormal course of the facial nerve. The hearing loss is more commonly conductive than sensorineural. Cervical vertebral anomalies occur in 30% of cases. Hemivertebrae and fused vertebrae have been described. Tracheal and pulmonary anomalies and TE fistula are less common (1,10,11). Esophageal atresia has been reported to occur in about 5% of Goldenhar syndrome patients. Anesthetic problems and surgical complications may be associated with gastroesophageal reflux.

Several classifications for HFM have been proposed. The most inclusive and flexible is OMENS. The acronym represents each one of the five major manifestations of HFM: O for orbital distortion, M for mandibular hypoplasia, E for ear anomaly, N for nerve involvement, and S for soft tissue deficiency. The term *OMENS-plus* is used to include the expanded spectrum: cardiac, skeletal, pulmonary, renal, gastrointestinal, and limb anomalies. Of patients with HFM classified using OMENS and analyzed statistically, 154 showed a positive association between the severity of the mandibular hypoplasia and the severity of orbital, auricular, neural, and soft tissue involvement. This study documented that HFM was associated with macrostomia (62%), facial nerve involvement (45%), ear tags (40%), palatal deviation to the normal side (39%), epibulbar dermoids (20%), horizontal discrepancy of the orbits (15%), and deformational frontal plagiocephaly (5%). The management of HFM exemplifies the need for an interdisciplinary approach to craniofacial anomalies. In the past, there has been a tendency for each specialist to concentrate on his or her own particular area of interest or expertise. The infant or child with HFM presents not only with congenital anomalies but also with the result of abnormal growth and the potential interference of prior treatment. A systematic approach focuses on the hypoplastic mandible as the key to the management of the deformity. In infancy, treatment includes excision of preauricular tags, closure of macrostomia, and transposition of the microtic ear lobule, if it is located low and anteriorly on the cheek. The mandibular deformity is graded according to the size of the mandible. Type I is a miniature mandible with identifiable anatomy; type II is a functioning temporomandibular joint (TMJ) but with an abnormal shape and glenoid fossa; type II is subcategorized as either type IIA, if the glenoid fossa is in an acceptable functional position (in reference to the opposite TMJ), or type IIB, if the TMJ is abnormally placed and cannot be incorporated in the surgical construction. Type III deformity indicates an absent ramus and nonexistent glenoid fossa.

The concept for treatment of the child with HFM is elongation of the affected ramus (types I, II) or construction of a ramus and condyle if it is missing (type III). Elongation or construction of the ramus creates an open bite on the affected side. This space is slowly closed over a period of 2 years with gradual reduction of an orthodontic splint. This appliance regulates eruption of maxillary teeth and thereby stimulates maxillary (midfacial) growth. The goal is to achieve a horizontal occlusal plane (10,11).

Type I, a mini-mandible skeletal deformity, often can be managed with a "functional" orthodontic appliance called an "activator." This device can be placed by age 3 years. If the appliance fails to prevent obliquity of the occlusal plane, then elongation of the ramus or mandibular distraction is indicated between ages 6 and 12 years during mixed dentition. If a type I deformity presents late in adulthood, then bilateral mandibular osteotomies are required to prevent abnormal forces from acting on the normal TMJ. A Le Fort I maxillary osteotomy can also be necessary. Type II mandible can also be treated for a time with a "functional" appliance; however, all children with type II mandible require mandibular elongation. Children with type IIA mandible have a well-placed but short ramus. They are candidates for a vertical osteotomy and elongation or a simple oblique or transverse corticotomy and gradual mandibular distraction. In type IIB or type III mandible, construction of the ascending ramus is needed, usually when the child has a full complement of deciduous teeth. TMJ reconstruction has been done by some as early as age 2 years and by others between age 6 and 12 years. Patients with type III mandible rarely present in adulthood. These patients require full construction of the mandible, TMJ, zygomatic arch, and in some cases a leveling orbital osteotomy. Le Fort I or maxillary osteotomy is required to give a level occlusal plane and symmetry. The condyle is constructed with costal cartilage, and bone graft is used to construct the glenoid fossa. Sliding genioplasty is often necessary in combination, with or without a mandibular procedure as the final surgical step for the young adult with HFM.

Ear construction must be conceptualized prior to mandibular correction to avoid improper placement of incisions and scarring. In high-grade mandibular deformity (i.e., type IIB or type III), it is usually best to defer ear construction until skeletal symmetry is achieved, usually after 10 years of age. In low-grade mandibular hypoplasia, the ear construction can be done any time after age 6 years, when the costochondral elements are large enough to build an autogenous auricular framework.

Soft tissues can be hypoplastic in HFM. In rare cases, after restoration of the skeletal framework, soft tissue must be added. Onlay bone grafts to the ramus usually give symmetric lateral facial contour. Free tissue transfer by microsurgical techniques is another option. In minor cases, a dermal graft can be sufficient.

"Mandibular distraction" is a new method for ramus elongation for type I, type IIA, and some type IIB mandibles. This technique was originally described for long bones by Ilizarov in Russia. It involves an osteotomy (corticotomy) and placing metallic pins through the hypoplastic ramus on each side of the osteotomy. The distraction device is attached and secured to the pins, and then the device is turned 1 mm/day. The mean amount of

lengthening or distraction is 24.5 mm at a rate of 1 mm/day. It can be done as early as 2 years of age. Distraction osteogenesis gives more mandibular bone than with elongation by sliding vertical osteotomy or rib graft construction. Careful follow-up documentation of the ramus height and occlusal plane is necessary. Nevertheless, the concept and possibilities for skeletal distraction are very promising for the ramus and for correction of other craniofacial skeletal abnormalities.

The syndrome occurs sporadically in the majority of cases. Of reported cases, 1% to 2% occur in families, suggesting AD transmission. Animal models showed that vascular disruption and hematoma formation affect the developing structures of the jaw and ear regions *in utero*. Other hypotheses suggest that disturbance of the population of the neural crest cells occurs during the 30th to 45th days of gestation. The frequency of the condition ranges between 1:3,500 and 1:25,000 births (1,2,11,12).

KARTAGENER SYNDROME

Dextrocardia, Bronchiectasis, and Sinusitis

Pansinusitis in childhood, absence of the frontal sinuses, and thick nasal rhinorrhea are characteristic presenting symptoms of Kartagener syndrome. The mastoid air cells are poorly developed. Otitis media as a result of eustachian tube dysfunction results in deafness, usually of the conductive type. Anosmia and nasal polyps are frequent complications. Recurrent pneumonia and chronic cough are common. It is estimated that one-tenth of the cases of bronchiectasis are the result of Kartagener syndrome.

Situs inversus with gross defects in cardiac septation may occur. One-sixth of situs inversus cases have the syndrome. Myringotomy and insertion of bilateral tympanostomy tubes are required for treating the serous middle ear effusion. However, a recent retrospective study demonstrated that despite continuous antibiotic therapy, the middle ear condition in primary ciliary dyskinesia remained severe throughout childhood, with improvement only after age 18. Tympanostomy tube placement did not improve the middle ear condition (1,13).

Early treatment of respiratory infection may help in preventing bronchiectasis. Removal of affected lobes of the lung may be needed later to treat the bronchiectasis. *In vitro* fertilization may be used in the management of sterility. Associated anomalies include polysplenia or asplenia syndrome, rheumatoid arthritis, thyrotoxicosis, biliary atresia, abnormal subclavian artery, and glomerulonephritis (13).

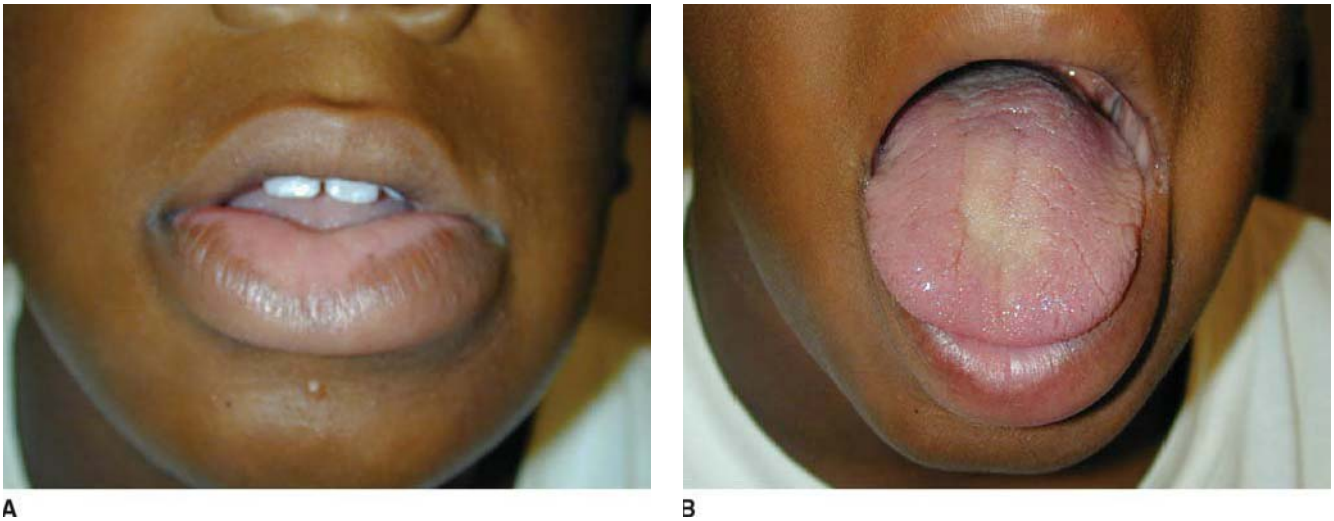
The mode of inheritance is autosomal recessive. AD or X-linked inheritance has also been suggested. The primary defect is abnormality of the cilia of the respiratory tract. This leads to blockage of the paranasal sinuses, Eustachian tubes, and the lungs. Immobility of the sperm produces sterility in the males; affected females may have decreased fertility. The lack of dynein arms is the most common structural abnormality in the respiratory and fallopian cilia and the sperm tails (1,2,13).

MELKERSSON-ROSENTHAL SYNDROME

Cheilitis Granulomatosa

Melkersson-Rosenthal syndrome is characterized by recurrent or persistent lip swelling, facial swelling, facial palsy and furrowed tongue, auditory and visual disturbances, swelling in the hands and chest, blepharospasm, epiphora, and megacolon. Other eponyms of the syndrome include (Fig. 107.10A and B):

Miescher cheilitis, Melkersson-Rosenthal-Schuermann syndrome, Melkersson syndrome, Rossolimo-Melkersson-Rosenthal syndrome, and Rosenthal syndrome II (14,15). Surgical excision and reconstruction are recommended for the swollen orofacial tissues. Total facial nerve decompression for recurrent facial palsy is also advocated.



A B

Figure 107.10 **A,B:** Furrowed tongue and lip swelling in Melkerson-Rosenthal syndrome. From http://dermatlas.med.jhmi.edu/ Copyright Dr. Bruce Cohen with permission.

The swelling of the lips is usually of sudden onset, unilateral or bilateral. The upper lip is affected in most cases and may remain swollen permanently. This occurs in 75% of patients. The facial palsy occurs after the lip swelling and sometimes precedes it. The facial swelling usually involves the eyelid, chin, and forehead in 50% of cases. The oral mucosa and the gingiva may show swelling. Histologically, the swollen tissues exhibit chronic granulomatous changes similar to sarcoidosis or tuberculosis (1). Orofacial granulomatosis is a generic term applied to manifestations of several diseases including sarcoidosis, Crohn's disease, Melkersson-Rosenthal syndrome, tuberculosis, and foreign body reaction. What bonds these conditions together is the presence of noncaseating granulomas (1,15).

The lingual fissures occur in 40% of the cases. Defects of taste along the anterior two-thirds of the tongue, lip fissuring, and exposure keratitis are seen in long-standing cases.

Most cases of Melkersson-Rosenthal syndrome are sporadic. Familial occurrences suggest an AD transmission. The syndrome is remarkably variable in its expression. The disease begins in childhood or early adulthood. It is considered a local immune response and vasomotor disturbance affecting the vasa vasorum of the vessels supplying the facial nerve and neighboring structures (2,15).

NEUROFIBROMATOSIS 1

Von Recklinghausen Disease or NF1

The criteria for diagnosis of NF1 include two or more of the following: more than five café-au-lait spots with or without axillary or inguinal freckling; multiple cutaneous neurofibromas; or at least one plexiform neurofibroma, optic glioma, Lisch iris nodule, a distinct bony lesion such as tibial bowing or pseudoarthrosis, sphenoid wing dysplasia, and affected first-degree relative.

The café-au-lait spots and axillary freckling may be present at birth and become more evident with age.

The presence of multiple café-au-lait, large segmental café-au-lait, associated facial dysmorphism, other cutaneous anomalies, or unusual findings on physical examination should suggest the possibility of an associated syndrome. While NF type 1 is the most common syndrome seen in children with multiple café-au-lait, other syndromes associated with one or more café-au-lait include McCune-Albright syndrome, Legius syndrome, Noonan syndrome and other neuro-cardio-facio-cutaneous syndromes, ring chromosome syndromes, and constitutional mismatch repair deficiency syndrome (16). Cutaneous neurofibromas may be sessile or pedunculated. They develop around the second decade and increase with age as well. Plexiform neurofibroma occurs in one-third of the patients (Fig. 107.11). Malignant degeneration is estimated to be 5% to 15%.

Mental retardation, learning disabilities, and speech defects are not uncommon. Macrocephaly, hydrocephalus, aqueductal stenosis, and seizures may occur (2,16).

Lisch iris nodules are present in 90% of patients. They cause no visual impairment. Other ocular findings include optic glioma (15%), optic nerve meningioma, and congenital glaucoma (1%).

Multiple organ involvement may cause serious complications. Paraspinal, retroperitoneal, mediastinal, renal, laryngeal, and cardiac tumors are reported. Acoustic neuromas do not occur in NF1. Scoliosis, kyphosis, and cervical spine anomalies may develop.

Precocious puberty, hypopituitarism, gigantism, hypogonadism, intracranial calcifications, and diabetes insipidus have been described.

Velopharyngeal insufficiency, macroglossia, jaw lesions, hypoplasia of the facial bones, enamel, and dentin defects may be seen.

NF1 syndrome is AD. NF1 gene location is in the 17q11.2 region. Fresh mutations represent about 50% of cases. The prevalence is 1:3,000. NF1 is caused by deletions, insertions, translocations, and point mutations in the NF1 gene, which spans 350 kb (1,2,16).

NEUROFIBROMATOSIS 2

Café-au-lait spots and cutaneous neurofibromas are not consistent findings of NF2. Axillary freckling is uncommon. Other neurogenic tumors are common. They include schwannomas, intracranial or spinal meningiomas, or astrocytomas. Increased symptoms may be noted during late pregnancy. Posterior capsular cataracts are common (80%). Lisch nodules are absent in NF2. The symptoms usually develop unilaterally, and involvement of the other side occurs within 2 years.

Diagnostic criteria include the following:

1. Bilateral acoustic neuroma seen with appropriate imaging technique (CT or magnetic resonance imaging [MRI]), or
2. A first-degree relative with NF2 and either unilateral 8th nerve mass, or two of the following: neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacity. The incidence is estimated to be 1:50,000.

Symptoms are usually the result of pressure on the vestibulocochlear (VIII nerve) and facial nerve complex. Hearing loss is often the first symptom, which occurs in the teens or early 20s with an average age of 20. Tinnitus, imbalance, and vertigo accompany the deafness. Small acoustic neuromas of less than 8 mm were detected in asymptomatic children (aged 7 and 11) by the use of gadolinium-enhanced MRI. One patient had normal audiometry and brainstem-evoked responses.

Other symptoms of facial pain, numbness or weakness and paralysis, headache, diplopia, nausea, and vomiting may develop. Cervical kyphoscoliosis may be related to a paraspinal neurofibroma.

NF2 is AD, with 95% penetrance and linkage to 22q11-q13. The NF2 gene has been isolated. It encodes a protein named merlin. Mutational analysis of patients has been done (1,17).

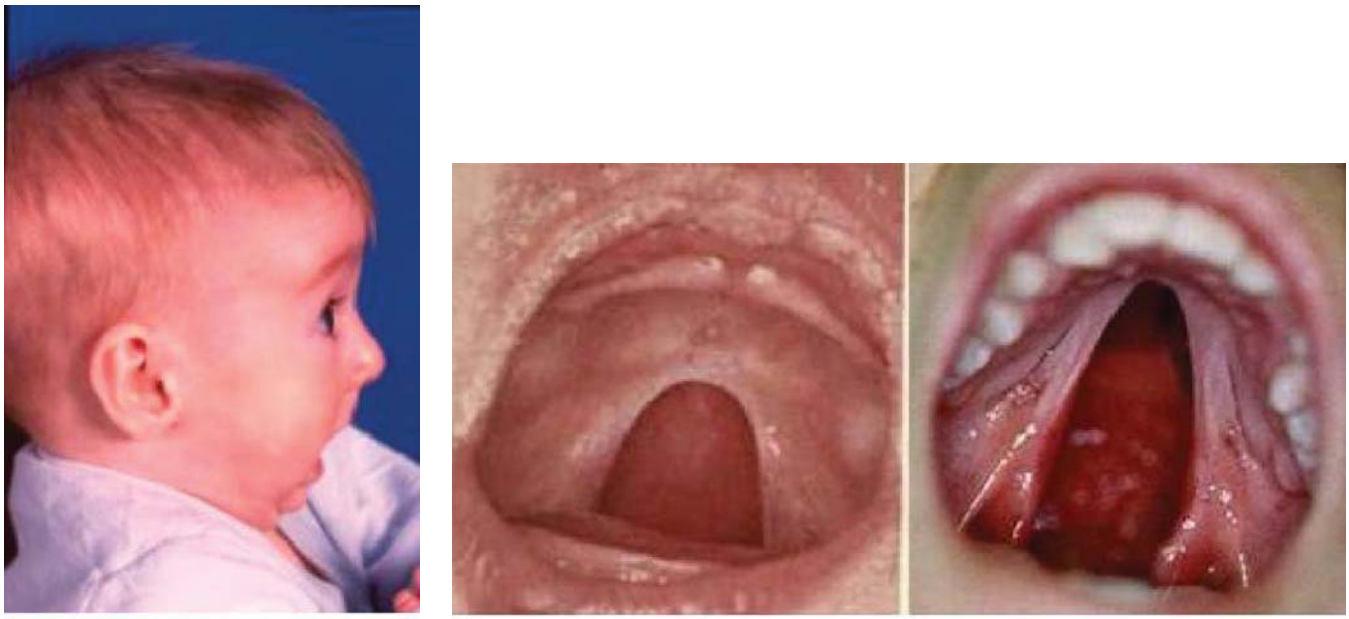


Figure 107.11 **A:** Patient with PRS with micrognathia and recessed chin. **B:** Inverted U and inverted V types of cleft palate in PRS.

ROBIN SEQUENCE

The major diagnostic criteria of Robin sequence are micrognathia, glossoptosis, and inverted U-shaped cleft palate. Congenital heart defects are associated with Robin sequence in 14% of cases. Limb anomalies, ocular malformations, rib and sternal abnormalities are described. The infant is kept in the prone position, and respiration is monitored. Repair of the cleft palate is done at a later age.

In a recent study comparing the jaw size, jaw relationship, and facial proportions of children with Pierre Robin Sequence (PRS) to children with nonsyndromic or isolated cleft palate (iCP). The authors found that during early childhood (1 to 4 years) mandibular and maxillary lengths were similar in both PRS and iCP groups. In older children (10 to 13 years), mandibular length was significantly shorter in the PRS group compared to the iCP group. Maxillary length in PRS and iCP groups was similar, but significantly shorter in comparison to age-matched norms with a difference 14.5 mm ($P = 0.037$) for PRS and 12.4 mm ($P = 0.045$) for iCP (1,18). Radiologically, the mandibular ramus and body are smaller than normal and the mandibular angle is obtuse (19).

Respiratory difficulty with periodic cyanotic attacks are associated with sternal retraction and are more apparent when the baby is in the supine position (2,18,20).

A few patients may require tracheotomy for airway management in the first 3 years of life (Fig. 107.11A and B). Distraction osteogenesis has been described as an alternative surgical treatment.

Robin sequence is very heterogeneous with birth prevalence of 1:8,500. The initial defect is thought to be hypoplasia of the mandible, before 8 weeks of gestation. This would result in the posterior location of the tongue, which prevents the closure of the posterior palatal shelves. The cleft is different from the usual inverted V-shaped cleft that is not the result of mandibular involvement. Oligohydramnios is thought to play a role in the pathogenesis. The reduced amniotic fluid will result in compression of the chin and impaction of the tongue between the palatal shelves. Other hypotheses include neurogenic hypotonia and connective tissue disorder (2,18).

Differential Diagnosis

Robin sequence may occur as an isolated anomaly, but it may also be a feature of a malformation syndrome. Examples are diastrophic dysplasia, Nager acrofacial dysostosis, otopalatodigital syndrome II, popliteal pterygium, Stickler, Shprintzen, del 6q, Möbius, and other syndromes, as well as CHARGE association (1,2).

SHPRINTZEN SYNDROME

Shprintzen described the syndrome in 1978. Previous reports are found in the literature describing patients with similar features. The ocular findings include retinal vascular tortuosity, posterior embryotoxon, narrow palpebral fissures, suborbital discoloration, small optic nerves, iris nodules, and cataracts. The cardiothoracic anomalies include pulmonary atresia, ventricular septal defects, and hypoplastic pulmonary arteries. Severe abnormalities of the arborization of the pulmonary arterial tree were reported.



Figure 107.12 **A,B:** Patient with velocardiofacial syndrome. Note that the nose is tubular, mandible is retrognathic, and the philtrum is elongated.

Fallot tetralogy, aberrant subclavian arteries, and right-sided aortic arch are also described. The fingers appear tapered and slender in most cases. Most children experience learning disability and difficulty with abstraction and reading comprehension. Verbal IQ score ranged between 69 and 87 in one study (21). Other less common traits include herniae (inguinal or umbilical), hypocalcemia, and absent thymus. The nose is prominent and tubular, and the alae nasi and nasal cavities are hypoplastic. The mandible is retrognathic, and the vertical diameter of the maxilla is increased (Fig. 107.12A and B). The upper lip and the philtrum are elongated. More than 80% of cases have adenoid hypoplasia, which contributes to the nasal speech. Velopharyngeal insufficiency and hypernasal speech are the main presenting symptoms. Approximately 15% of the patients have Robin sequence, and 35% have cleft palate. OSA is common. Some authors classify the facial features into humorous or nervous depending on the pursed lips versus the upslanting palpebral fissures. Hearing loss of the conductive type is more frequent than the sensorineural variety. The pinnae are usually small (1,12,22). Roizen et al. studied the motor function in children with 22q11.2 deletion syndrome (22q11.2) and a Full Scale IQ comparable control group. They concluded that school-aged children with 22q11.2 have specific motor deficits in axial stability and graphomotor skills (23).

Velocardiofacial syndrome is AD. Velocardiofacial and DiGeorge syndromes may represent part of a spectrum seen with monosomy for 22q11 (1,2).

TREACHER COLLINS SYNDROME

Franceschetti-Zwahlen-Klein Syndrome or Mandibulofacial Dysostosis

Diagnostic criteria of Treacher Collins syndrome include microtia and malformed ears, hypoplastic midface, downslanting of the palpebral fissures, coloboma of the outer third of the lower eye lids, and micrognathia. Most patients have normal intelligence. Developmental retardation is reported in only 5% of cases. Delays are probably secondary to undetected hearing loss. The most common ocular findings are lower lid colobomas (77%) with absence of cilia medial to the coloboma (Fig. 107.13). Microphthalmia and coloboma of the iris may occasionally be seen. Other uncommon anomalies include congenital heart defects and cryptorchidism. The facies are characteristic. The supraorbital ridges are flat. The nose appears large because of the depressed malar bones. The lower nasal cartilages are underdeveloped. The bridge of the nose is often high. The auricles are malformed, and microtia is reported in 60% to 77% of the cases. The EACs are stenosed or absent. In the middle ear,



Figure 107.13 Treacher Collins syndrome.

different anomalies are described such as monopodal stapes, ankylosed foot plate, bony bridge to the fallopian canal, and malformed incus. The tympanum may be filled with connective tissue, and the epitympanum and mastoid show different degrees of hypoplasia or agenesis. The cochlea and vestibule may show abnormalities. The hearing loss is usually conductive. A sensorineural component has also been described. One-third of the patients have cleft palate or velopharyngeal insufficiency. Macrostomia and hypoplasia of the parotid glands are also seen. The coronoid process of the mandible is flat, and the condyles may be malformed. Blind fistula between the auricle and angle of the mouth, choanal atresia, and pharyngeal hypoplasia are occasional abnormalities. Five categories are described by Franceschetti, depending on the number of features present. In Tessier classification, the complete form of the syndrome manifests craniofacial clefts 6, 7, and 8. These patients have a complex craniofacial malformation involving the middle and lower parts of the face and affecting both bony structures and soft tissues. The deformity is always bilateral and nearly always symmetric. They have downward-sloping palpebral fissures, depressed cheekbones, deformed pinnas, receding chin, and wide oral commissures (macrostomia). This syndrome can be mistaken for bilateral HFM. The degree of symmetry and normal facial nerve function are important distinguishing characteristics of Treacher Collins syndrome. Plain radiographs reveal the malar hypoplasia, "tear drop"-shaped orbits, and partial or complete absence of the zygomatic arches. In severe cases, there is absence of the lateral wall and the floor of the orbits (i.e., a clefting of the inferolateral orbit extending into the sphenomaxillary [inferior orbital] fissure). Mandibular retrognathism is present, with shortening of the body and the ramus of the mandible. The chin is retruded severely, and the nasomaxillary area is relatively prominent. These children usually have normal intelligence (1,2,24,25).

The upper airway narrowing and the hearing impairment are major issues in infancy. These infants are prone to OSA and sudden infant death syndrome. The size of the nasopharynx in Treacher Collins syndrome is about 50% smaller than normal. The surgical plan for Treacher Collins syndrome must be tailored to the patient's specific deformities, taking into consideration facial growth and psychosocial impact. The surgical correction can be separated into procedures for the upper face and those for the jaws or lower face (1,25).

Treacher Collins syndrome has an AD inheritance with variable expressivity and high penetrance. A recessive form has also been described. Experimental embryologic studies using vitamin A and isotretinoin produced similar changes in rats, hamsters, and mice. Hypersensitivity of the mother to vitamin A has also been suggested. The proposed gene location is 5q11 (1). Trainor (26) explains the role of neural crest cells in the etiology and pathogenesis of Treacher Collins syndrome.

USHER SYNDROME

The incidence of Usher syndrome is estimated to be 3 to 5 per 100,000 in the general population and 1% to 10% among children who are profoundly deaf. Clinical manifestations are deafness and retinitis pigmentosa. Ocular findings include cataracts in 50% of patients by age 40 and occasionally glaucoma. Mental deficiency, psychosis, ataxia, and cataracts are sometimes associated with retinitis pigmentosa and deafness and termed "Hallgren syndrome." Abnormalities of nasal cilia and sperm axonemes have been described. The prognosis is a normal life span. Social and vocational preparation for adults who are deaf and blind is required (1,27,28).

Clinical Types

Usher, type I: Profound congenital deafness and loss of vestibular functions, onset of retinitis pigmentosa before puberty (around the age of 10 years). This constitutes 90% of the patients.

Usher, type II: Hearing loss is moderate to severe from birth, and the vestibular functions are normal. Onset of retinitis pigmentosa is in the late teens.

Usher, type III: Progressive hearing loss; retinitis pigmentosa begins at puberty.

Usher, type IV: Clinically similar to type II but with X-linked recessive inheritance.

Types III and IV constitute less than 1% of patients. The findings in the retina are described as pallor of the optic disc, "bony spicule" concretions of pigment, and arteriolar narrowing.

The changes in the temporal bone involve the cochlea. Marked atrophy of the organ of Corti in the basal turn is associated with spiral ganglion degeneration. These cochlear changes are similar to Scheibe inner ear dysplasia.

Usher syndrome has an autosomal recessive inheritance in most cases and an X-linked recessive inheritance in rare instances (1,2,27). To characterize visual function in defined genotypes including siblings with

Usher syndrome, Malm et al. (28) concluded that the evaluation of visual function comprising both the severity of the rod cone degeneration and the function in the macular region confirm phenotypical heterogeneity within siblings and between different genotypes of Usher syndrome.

WAARDENBURG SYNDROME

Along with congenital sensorineural deafness there are multiple congenital anomalies. The widely spaced medial canthi (dystopia canthorum) is characteristic of type I. Lack of penetrance of this sign occurs in no more than 1% of cases. Confluent eyebrows with hypertrichosis of their medial portions (synophrys) is present in 85% of type I and 25% of type II. White forelock (poliosis) occurs in 20% to 40% of the time in type I or II. (Fig. 107.14A and B).

Localized hypopigmentation can also be found in piebaldism and Tietz syndrome, whereas diffuse forms are typical for oculocutaneous albinism, Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, and Griscelli syndrome. Heterochromia iridis occurs in 30% of patients of both types (29).

Other findings include craniosynostosis, blepharophimosis, glaucoma, mild prognostic mandible, Hirschsprung megacolon, premature graying of hair, anophthalmia with limb malformations, ventral septal defects, meningocele, spina bifida, hypoplasia of the shoulder girdle, and axillary webbing (1,29,30).

Clinical Types

Type I: Dystopia canthorum present; this condition is 20 times more common than type II.

Type II: Dystopia canthorum not present; hearing loss (50%) as well as pigmentary disorders is more common in this type.

Type III: Klein-Waardenburg syndrome or pseudo-Waardenburg, no dystopia canthorum but with one-sided ptosis of the upper eyelid and upper limb anomalies.

A Waardenburg-Hirschsprung disease association clinical type has also been described.

Symptoms include deafness, broad nasal bridge, hypoplastic alae nasi, high-arched or cleft palate, abnormal vestibular function, and hypoplastic ear cartilage. SNHL is either unilateral (15% type I and 5% type II) or more commonly bilateral (20% type I and 55% type II). The loss is usually in the low and mid frequencies and normal hearing for 6,000 to 8,000 Hz. Abnormal vestibular functions are noted in type II but not in type I.

Temporal bone studies were described as absence of the organ of Corti with thickening of the basal membrane and degeneration of the spiral ganglion.

The mode of inheritance is AD with variable penetrance. Of all congenitally deaf children, 3% have Waardenburg syndrome. Its incidence is estimated to be 1 in 20,000 to 1 in 40,000 of the population.

Waardenburg syndrome type I (WSI) and WSIII have been mapped to a distal portion of 2q3 and found associated with PAX3 mutations.

They are considered to be allelic. WSIIis heterogeneous, with about 20% of cases caused by mutations in the human microphthalmia (microphthalmia associated transcription factor, or MITF) gene. Individuals with auditory, pigmentary, or neural crest syndromes that do not fit stringent definitions of Waardenburg syndrome are unlikely to have mutations in either PAX3 or MITF genes (1,2,30).



Figure 107.14 **A,B:** Waardenburg syndrome patients.

FETAL ALCOHOL SYNDROME

Of children born to women who suffer from alcoholism, 30% to 40% suffer from the syndrome. It is characterized by prenatal and postnatal growth deficiency, microcephaly, and an average IQ of 63. Irritability and hyperactivity are common. Seizure disorders have been identified in 10% to 20% of patients. Neural tube defects may be present. Other than the otolaryngologic anomalies, they may have hypoplasia of the optic nerve, increased tortuosity of the retinal vessels, severe microphthalmia, and colobomas. Cardiac, renal, and skeletal anomalies may be present. Malignant neoplasms of embryonal origin have been reported.

Facial dysmorphic features include a narrow forehead, short palpebral fissures, epicanthus, ptosis of the eyelids, midface hypoplasia, a short nose, a smooth philtrum, thin upper lip, and a hypoplastic mandible (Fig. 107.15A–D). A cleft palate or cleft lip may be present. Both conductive and SNHL are frequent.

Alcohol and its major metabolite, acetaldehyde, may be teratogenic. The alcohol-related developmental abnormalities can be the result of restriction of cell growth during critical periods. The amount of alcohol intake to cause the fetal alcohol syndrome is not clearly established (1,31).

Manifestations of Other Syndromes and Conditions

In this section, a few less known syndromes are briefly discussed with emphasis on their systemic and otolaryngologic manifestations.

Aarskog syndrome: The majority of patients have hypertelorism with a broad nasal bridge and forehead, with anteverted nostrils and low-set ears with thick pinnae. The eyes have large corneas, blue scleras, a variety of refractive errors, antimongoloid slants, and latent nystagmus may occur.

The syndrome is characterized by short stature and normal intelligence (90%). The hands and feet are broad. A peculiar feature is the shawl scrotum (a scrotal fold extends



Figure 107.15 **A–D:** Four patients with fetal alcohol syndrome.

dorsally to surround the penile shaft). Cryptorchidism and inguinal herniae are common (1,2,12).

Achondroplasia: This is the most common chondrodysplasia with a frequency of 1:26,000 live births. The skull is large with frontal bossing and small foramen magnum. Partial occipitalization of the atlas and early closure of the sphenooccipital suture occur in most cases. Hypoplasia of the midface with low nasal bridge and recurrent otitis media are also common. Hearing loss may be conductive or sensorineural. Acoustic neuroma and progressive otosclerosis have been described. The limb bones are short and the metacarpals and phalanges are disproportionally large. A small thoracic cage, small horizontally oriented sacrum, and kyphoscoliosis are characteristic manifestations (2,10,12).

Alport syndrome (hereditary nephropathy and deafness): The patients experience a slowly progressive, symmetrical, mild to moderately severe mid- and high-frequency SNHL. The hearing loss occurs as early as age 10. It is important to screen family members as 30% to 50% of relatives may show hearing loss. However, there may be no correlation between hearing loss and kidney function. The basal turn of the organ of Corti shows degeneration of the hair cells and the stria vascularis. Histologic sections show cyst-like vesicle formation under each utricular macule. The syndrome comprises a group of hereditary diseases characterized by progressive defect of capillaries within the glomerular basement membrane of the kidneys (glomerulonephritis). Alport syndrome is classified into six types:

- Type I: AD inheritance. Juvenile onset of end-stage renal disease (ESRD) with SNHL.
- Type II: X-linked dominant inheritance. Juvenile onset of ESRD and SNHL.
- Type III: X-linked dominant inheritance. Adult onset of ESRD and SNHL.
- Type IV: X-linked dominant inheritance. Adult onset of ESRD and normal hearing.
- Type VA: AD inheritance with nephritis, SNHL, macrothrombocytopathy and leucocyte inclusions, also known as Fechtner syndrome.
- Type VB: AD inheritance with nephritis, SNHL, and macrothrombocytopathy, also known as Epstein syndrome.
- Type VI: AD inheritance with juvenile nephritis and SNHL (1,2,12).

Antley-Bixler syndrome: The syndrome is characterized by craniosynostosis, hypoplasia of the midface, proptosis, dysplastic ears, and radiohumeral synostosis with femoral bowing or fractures. The skull is brachycephalic with frontal and biparietal bossing. The anterior fontanel is large. The nose is large and pear-shaped with low nasal bridge. Severe hypoplasia of the midface and choanal atresia or stenosis occur in 80% of the cases. The ears are low set and protruding. Stenosis of the EAC with preauricular tags is occasionally seen. Respiratory depression is the main cause of death in infancy.

Beals syndrome: This is characterized by congenital joint contractures of the knees, elbows, fingers, and ankles. The joint contractures improve spontaneously with time. Most patients are taller than average and exhibit kyphoscoliosis. Intelligence is normal. Otolaryngologic (OTL) manifestations include crumpled pinnae with ill-defined conchae, flattened antihelix, prominent crura, micrognathia, and high arched palate with relatively short neck (1,2).

Beckwith-Wiedemann syndrome: Macroglossia is evident from birth. Prognathism, infraorbital hypoplasia, and capillary nevus flammeus of the face become more obvious in the first year of life. Unusual creases of the ear lobule with indentation of the posterior rim of the helix and concha are seen. Cleft palate or submucous cleft and preauricular pits and conductive hearing loss have been reported. Macrostomia is a constant feature. Visceromegaly involving the kidneys, spleen, and liver is present in the majority of cases. Advanced bone age and widened metaphyses and cortical thickening of the long bones are important features. Intelligence is normal in most patients. Mild hydrocephaly and subdural hematomas are reported. Cardiovascular anomalies include atrial septal defect (ASD), patent ductus arteriosus (PDA), ventricular septal defect (VSD) and Fallot tetralogy. There is increased possibility of developing neoplasms especially embryonal tumors such as Wilm tumor, adrenocortical carcinoma, and hepatoblastoma (2,27).

Binder syndrome: The nose is flat and hypoplastic with absent nasofrontal angle. The nasolabial angle is acute and the nasal septum is atrophied. The sense of smell is preserved. Radiologically, the anterior nasal spine is absent with retrognathia of the maxilla and increased gonial angle. Class III malocclusion may occur. The frontal sinuses are poorly pneumatized and labiomaxillary clefts are occasionally seen. Various anomalies of the first two cervical vertebrae are described. Association of megaesophagus, dysautonomia, and Binder syndrome lead some authors to classify it as a neurocristopathy. Ocular findings include juvenile glaucoma. Cardiac anomalies, diaphragmatic herniae, and genital anomalies are uncommon (1,12).

Coffin-Lowry syndrome: The majority of patients have mental retardation. The syndrome is characterized by square forehead with prominent eyebrows, hypertelorism, and downward-slanting palpebral fissures are characteristic. The nose is short and bulbous with thick septum and flattened alae. Mild facial hypoplasia with thick lips and elongated philtrum. The tongue has a midline furrow and the ears are prominent. Occasionally, SNHL and severe speech retardation are observed. Mild to moderate growth deficiency occurs after birth. Distal muscle atrophy and hypotonia are not uncommon. Finger joints are hyperextensible. Microcephaly and thick calvaria, dilated lateral ventricles and inguinal herniae are occasional findings (1,2,27).

Cohen syndrome: Most individuals are short, obese, and hypotonic with mental retardation. Delayed puberty and downslanting palpebral fissures, and decreased visual acuity are characteristics. Optic atrophy with mottled retina has been described. Open mouth and a short philtrum with exposed upper gingival and prominent upper central incisors characterize the syndrome. Maxillary hypoplasia and micrognathia with high nasal bridge and high narrow palate are also noted. Hyperextensible joints are present in half of the patients. Heart defects may occasionally be observed and rare anomalies include microphthalmia and mild cutaneous syndactyly (2,12).

Cri-du-chat syndrome: Affected individuals exhibit microcephaly, hypotonia, and severe mental retardation. Cardiovascular defects are common, the most frequent being PDA. Diastasis recti, inguinal herniae, talipes, and dislocated hips may occur. The characteristic mewy (cat cry) is present only during infancy and disappears with age in 98% of cases. The origin of the cry is thought to be central rather than due to laryngeal anomaly. Malocclusion and high arched palate occur in most cases. The ears are posteriorly angulated with preauricular tags. The neck is short and the hair is gray in adulthood (1,2,12).

DiGeorge sequence: The sequence may present with cardiovascular and craniofacial features that may be associated with anomalies of the third and fourth pharyngeal pouches. Hypoplasia or aplasia of the thymus and the parathyroid glands result in defective cell-mediated immunity and frequent infections early in life. Patients who survive with milder manifestations are usually moderately to severely retarded. Cardiovascular and thoracic (CVT) anomalies include conotruncal defects. The incidence is 1 in 20,000 births. Craniofacial anomalies include hypertelorism, epicanthal folds, downward-slanting palpebral fissures, anomalies of the lip and palate with choanal atresia, low set ears and posteriorly angulated pinnae with middle ear defects, esophageal atresia, and speech defects are also described (1,2,27).

EEC syndrome (Ectrodactyly-ectodermal dysplasia-clefting syndrome). The majority of patients show absent lacrimal puncti and diminished tearing with dacryocystitis and blepharophimosis leading to photophobia, corneal ulcers, keratoconjunctivitis, and loss of vision. Ectrodactyly usually involves all the extremities. OTL manifestations include cleft lip/palate in the majority of patients. The maxilla is hypoplastic. Other anomalies include missing teeth, dysplastic enamel, and dental caries. Furrowed tongue, xerostomia, and atresia of Stensen ducts are reported. Thirty percent of patients have conductive hearing loss. Dysphonia and malformed auricles with absent stapes are occasionally seen (2,12,27).

Fetal rubella syndrome: The syndrome results from intrauterine rubella virus infection. Effects depend on the time of pregnancy when exposure occurs and may range from no effect to deafness only to the full spectrum of the syndrome. Fetal death may occur or the infant may be born with low birth weight, hepatosplenomegaly, large anterior fontanel, cataract, glaucoma, corneal opacity, and chorioretinitis with microphthalmia. Endocrine anomalies include insulin-dependent diabetes, parathyroid glands problem, and hypopituitarism. Other findings include renal disease, hypospadias, cryptorchidism, and CNS anomalies. Histologically, the inner ear demonstrates partial collapse of the saccule and atrophy of the otolithic membrane. The organ of Corti consists of a thin layer of flattened cells; the stria vascularis is composed of a small layer of compact cells associated with scattered cystic structures (1,2,12,27).

Fragile X syndrome: The presence of a fragile site on the long arm of the 10th chromosome in affected males and some female carriers in one family was described by Lubbs in 1969. The syndrome represents 50% of X-linked mental retardation. The incidence is 1 in 1,250 males. There is increased head circumference and a prominent forehead with broad based nose and prognathism. The ears are large with everted pinnae and absent lobules. Speech is delayed and repetitive phrases are often expressed. The palate is high arched and occasionally cleft with cross-bite or open bite. Motor development is retarded. Patients exhibit hyperactivity, clumsiness, hypotonia, autistic or aggressive behavior, and seizures. Joint laxity in the fingers, knees, and ankles as well as flat feet is described. Mitral valve prolapse with mild aortic dilatation may be associated with this condition (2,12).

Fraser syndrome: Mental retardation occurs in 80% of these patients. Cryptophthalmos is present in the majority of cases and is mostly bilateral. Upper lid coloboma with microphthalmia, symblepharon, and epibulbar dermoid may be present. Anomalies of the ear are described in the majority of patients; they include microtia, low set ears, absent pinnae, and atresia of the EAC. Ossicular anomalies may occur. No inner ear abnormalities are described. Anomalies of the nose may include beaked nose, notched or pinpoint nostrils with choanal atresia, and alar colobomas. Laryngeal atresia or stenosis, fusion of the vocal folds and laryngeal webs are documented. Abnormalities of the genitals occur in 50% to 80% of cases. They include cryptorchidism, hypoplastic penis, large clitoris/labia majora, rudimentary uterus, and vaginal atresia. Renal agenesis has been reported and gonadoblastoma may be found (2,12,27).

Gardner syndrome: The main findings of this syndrome are polyposis of the colon and rectum with tendency toward malignant degeneration, multiple osteomas of the facial bones with cutaneous epidermoid cysts (50% of cases) and fibrous hyperplasia of the skin and mesentery. Other sites of polyposis include the stomach and small intestine. Carcinoma of the ampulla of Vater has been described. Desmoid tumors occur in a high percentage of patients. Osteoma of calvaria, paranasal sinuses, and jaws is commonly seen. The rest of the skeletal system (e.g., radius, ulna, metacarpals) may also be involved. Supernumerary

teeth have also been described. Histologically, a high number of cysts resemble pilomatrixomas (2,12).

Gorlin syndrome: The syndrome is characterized by marfanoid habitus and skeletal anomalies with odontogenic dyskeratotic cysts, intracranial calcifications and predisposition toward basal cell carcinoma of the skin, medulloblastoma, ovarian fibromas, and a variety of other tumors. Calcification of the falx cerebri and cerebelli with lumbarization of the sacrum, vertebral anomalies, spina bifida occulta and pectus excavatum or carinatum may occur in 30% of the patients. Other findings include meningiomas, mesenteric cysts, iris and optic colobomas, cataract and glaucoma with nystagmus, strabismus, and hypogonadism. The nose is broad with mild hypertelorism and mild prognathism, odontogenic keratocysts of the jaws and multiple basal cell nevi that are prone to carcinomatous changes occur over the neck and trunk as well as the face and upper limbs in over 50% of cases. The nevi increase significantly in number around puberty (1,2,12).

Klippel-Feil anomaly: The only constant finding of the syndrome is fusion of the cervical vertebrae due to failure of segmentation of the somites *in utero*. Clinical types are:

- Type I: Extensive fusion of the cervical and upper thoracic vertebrae. It is more common in females.
- Type II: Fusion occurs between two intervertebral spaces. It is inherited as AD and atlanto-axial fusion is often described.
- Type III: Involves fusion of cervical and lower dorsal or lumbar vertebrae.
- Type IV: Encompasses different fusions of the cervical, upper and lower thoracic and lumbar segments. Most cases are sporadic.

Most patients have hearing loss that could be sensorineural or mixed. Inner ear anomalies, vestibular involvement, bifid tongue, cleft palate, velopharyngeal insufficiency, and laryngeal anomalies have also been reported. Other manifestations include convergent squint, nystagmus, and atrophy of the choroid plexus. Scoliosis with or without kyphosis occurs in most patients (1,2,12,27).

Larsen syndrome: It is characterized by flat facies, multiple congenital dislocations, clubfoot deformities, and short finger nails. The nose is flat with hypertelorism and depressed nasal bridge. The forehead is prominent and the palate is highly arched and often cleft. Micrognathia is usually seen. Anomalies of the upper airway include laryngomalacia or laryngotracheal stenosis. Hearing loss can be sensorineural or mixed. Temporal bone findings include dislocation of the incudomalleal joint, abnormal footplate, poorly developed mastoid system, and mesenchymal remnants in the attic and mesotympanum. Bilateral joint dislocation involving the knee, hips, and elbows occurs in the majority of patients. Pseudoclubbing of the fingers, which are cylindrical and have extra creases, occurs in 75% of cases. The eyes are wide and the cervical vertebrae may show kyphosis that could lead to quadriplegia or death. Congenital heart disease, aortic dilatation, and valvular anomalies are also seen (2,12).

LEOPARD syndrome: The acronym comes from *L*entigines, *E*lectrocardiographic abnormalities, *O*cular hypertelorism, *P*ulmonary stenosis, *A*bnormal genitalia, *R*etardation of growth, and *D*eafness (sensorineural). The onset of deafness occurs early in life. The face is triangular with hypertelorism, mild prognathism, low set ears, and mild pterygium colli. Anosmia or hyposmia may occur. Lentigines differ from freckles in being darker in color and having more melanocytes per unit of skin area and are not related to sun exposure. ECG anomalies occur in 50% of subjects and are described as prolonged PR interval, QRS and P wave abnormalities. Compete bundle branch block has also been reported. Pulmonary stenosis is the most common cardiac anomaly. Hypospadias and cryptorchidism are frequently present. Mild mental retardation occurs in 25% of cases (1,2,12).

Marfan syndrome: The syndrome is inherited as an AD trait. The palate is narrow and highly arched, and cleft palate may occur. The teeth are crowded and malocclusion is frequent. Frontal bossing and supraorbital ridges are also noted. The paranasal sinuses are enlarged. Hearing loss may occur and is usually due to recurrent otitis. Temporal bone changes include narrowing of the vestibular aqueduct, bulging round window, dilatation of the endolymphatic duct, and utriculo-ampullary space. Ocular findings include ectopia lentis (50% to 80%), myopia, flat cornea, glaucoma, and retinal detachment may occur. However, 80% of patients have good vision. The ascending aorta is progressively dilated due to cystic necrosis of the media. Mitral prolapse is often seen and musculoskeletal anomalies include arachnodactyly, pectus excavatum or carinatum, and scoliosis. Joints may be hypermobile or congenitally contracted. Pulmonary capacity is reduced and patients may develop pneumothorax. Occasional features include inguinal herniae and neuropsychological problems (1,12).

Miller syndrome: The manifestations of this syndrome include first branchial arch anomalies combined with defects of the extremities, variable degree of mandibulofacial dysostosis with lower lid colobomas, vertebral and rib defects, accessory nipples, and postaxial limb defects.

The malar bones are hypoplastic, the palpebral fissures are downslanted. Colobomas of the lower lids, micrognathia, and cleft palate do occur. The pinnae are hypoplastic and cup-shaped.

Möbius syndrome: Along with cranial nerve palsies, defect of the limbs (adactyly and or syndactyly) as well as hypoplasia or aplasia of the pectoral musculature may be seen. Poland anomaly is seen in 15% of patients. Mild mental retardation has been reported. CVT and urogenital anomalies are rare. Cranial nerve palsies of VI and VII give rise to a masked face if the palsy is bilateral. The most common ocular finding is abducens (VI CN)

paralysis. The mouth is small with drooping angles. The other cranial nerves may be affected as well, XII, IX, V, and III resulting in lingual hypoplasia, dysfunction of the palate, and ocular ophthalmoplegia with conjunctivitis or keratitis. The nose is broad and the mandible is hypoplastic and the ears lack cartilage. Hearing loss is infrequent (2,12).

Multiple mucosal melanoma syndrome (Multiple endocrine neoplasia type IIB or MEM-II): The general manifestations include failure to thrive and marfanoid habitus in the majority of patients with excessive wasting and weakness. Gastrointestinal anomalies such as megacolon with defects of autonomic innervation are also observed. Diverticula and intestinal ganglioneuromatosis have been reported. Pheochromocytoma is documented in half of the patients. Pedunculated neuromas of the palpebral conjunctiva, parathyroid hyperplasia, carcinoid tumors of the rectum, and developmental delay do occur. The multiple neuromas of the tongue and lips are associated with medullary carcinoma of the thyroid, and diagnosis usually occurs after age 12. The syndrome is of AD inheritance; however, half of the cases represent new mutations (1,2,12).

Nager acrofacial dysostosis syndrome (Mandibulofacial dysostosis limb anomalies or preaxial acrofacial dysostosis): Ocular manifestations include lower lid colobomas and a reduced number of cilia. Hypoplastic thumbs are characteristic. Deformities of the toes and radioulnar synostosis are seen in 30% of patients. Other limb deformities include shortened humerus, dislocated hips and rib anomalies. OTL anomalies include bilateral mandibular and malar hypoplasia, downward-slanting palpebral fissures, and absence of the soft palate and high arched palate. EAC anomalies and middle ear deformities are common. The external ears are posteriorly angulated in most patients and preauricular tags may occur. Absent middle ear ossicles or absence of the tympanic membrane was also described. Abnormal larynx and speech defects are known. Hearing loss is usually conductive and air-bone gap up to 50 or 60 dB is not uncommon (2,12).

Noonan syndrome (Ulrich-Noonan syndrome): In this syndrome, birth weight is usually within normal limits or may be increased due to subcutaneous tissue swelling. Prepubertal growth is slow and the pubertal spurt is reduced or absent leading to short stature. Congenital heart defects occur in 60% of patients. Congestive heart failure and pulmonary edema are not rare complications. Pectus deformities as well as cubitus valgus and vertebral anomalies are common. The iris may be blue or blue–green. von Willebrand disease, platelet dysfunction, and factor XI deficiency occur in 25% of the cases. Hypoplastic lymphatic vessels with lymphangiectasia and cystic hygromas occur in a significant number of cases. Hypertelorism, downward-slanting palpebral fissures, deep and elongated philtrum with excess nuchal skin and a low nuchal hairline are common. In infancy, the head is relatively large and the eyelids are thick and hooded. The nose is bulbous and with advanced age the face assumes a triangular shape. Malocclusion occurs in 30% of patients. Sensorineural and conductive hearing loss and language delay may occur (12,27).

Opitz (BBB/G syndrome): Also known as G syndrome or Opitz oculo-genito-laryngeal syndrome. It is characterized by hypertelorism, hypospadias of varying degrees, dysphagia, and anal anomalies. Patients have normal intelligence, mild mental retardation may exist, corpus callosum agenesis was reported. Cryptorchidism and cleft scrotum are seen; however, affected females have normal genitalia. Ectopic and imperforate anus was also documented. Other anomalies include CVT malformations, Meckel diverticulum, duodenal stricture, and agenesis of the gall bladder. The nose is flat with anteverted nostrils and flattened inapparent philtrum. Twenty five percent of patients have cleft lip/palate. Bifid uvula and ankyloglossia may also occur. The ears are posteriorly angulated and micrognathia is present. The cry is usually hoarse and infants have difficulty swallowing. Laryngotracheoesophageal cleft, vocal cord/epiglottis hypoplasia, short trachea, and absent tracheal rings as well as abnormal esophageal mobility have been described. Gastroesophageal reflux was also reported (1,12).

Orofaciodigital syndrome type I (Papillon-Léague-Psaume syndrome): This syndrome comprises oral frenula (70%) and clefts, absent lateral incisors, hypoplastic alae nasi, bifid hallux, digital asymmetry, and mental deficiency (60%). General manifestations include precocious puberty, cerebral atrophy, hydrocephalus, agenesis of the corpus callosum, and hamartoma of the hypothalamus. Webbing occurs between the alveolar ridge and buccal mucous membrane making retraction of the upper lip difficult. The tongue may be bilobed or trilobed and may display hamartomas. Absent lateral incisors and other dental anomalies usually coexist. The mandible is hypoplastic. Choanal atresia is occasionally seen and alopecia with dry scalp has been reported (12).

Orofaciodigital syndrome type II or Mohr syndrome: Characteristics include cleft or lobulated tongue, absent central incisors, polydactyly, partial duplication of the hallux, and conductive hearing loss.

Osteogenesis imperfecta: This is a group of disorders characterized by bone fragility. At least four types of OI exist. Type III is the only recessive disorder of the group. The incidence of all types is 0.5 per 10,000 births. General manifestations include blue sclera that is the hallmark of OI. It is due to an increase in the noncollagenous matrix and molecular disorganization. In type III the blue color fades away after the first year of life. Patients with type IV OI usually have normal sclera. Other ocular anomalies seen in type I are embryotoxon (circular anomalies in the periphery of the cornea), keratoconus, and megalocornea. Long bones display bowing and angulation due to the sparse trabeculae and thin cortex. Type I patients have kyphosis and/or scoliosis in 20% of cases. Macrocephaly and wormian bones are also reported.

Higher incidence of fractures occurs between age 5 and 20. Fifty percent of type III patients demonstrate fractures at birth. OTL manifestations include conductive deafness. By the seventh decade, most patients are deaf, hearing loss may be sensorineural or mixed. The stapes is the most affected ossicle. The footplate is thickened and the crura demonstrate abnormal ossification pattern with thinning or fractures. The temporal bone also exhibits deficient ossification in the facial canal and cochlea. The IAC is grossly widened. Histologically, the stria vascularis may show calcified deposits and the utricle displays abnormal structures. Deafness is more prominent in type I. Type IV patients experience hearing loss 30% of the time. Deafness has not been well documented in types II and III. Dental anomalies include opalescent teeth due to hypoplastic dentin and pulp. Dental caries and malocclusion occur (1,2,12).

Otopalatodigital syndrome type I (Taybi syndrome): This syndrome is characterized by cleft palate, moderate conductive deafness, short stature, short terminal phalanges, and characteristic pugilistic facies (prominent supraorbital ridges, hypertelorism, and broad nasal root). The hearing loss varies between 30 and 90 dB. A variety of ossicular anomalies have been described such as thickened incus, unstable incudostapedial joint, short anterior crus, and wide head of the stapes. Retarded speech occurs due to the hearing loss. The paranasal sinuses and mastoids are poorly pneumatized and the mandibular angle is more obtuse than normal (2,12,27).

Otopalatodigital syndrome type II: The syndrome is characterized by cleft palate, broad forehead, unusual facies, low set ears, short stature, and multiple skeletal anomalies. Death may occur during early life due to feeding and respiratory difficulties. The forehead is prominent with large anterior fontanel, a flat nasal bridge, and cleft palate. Hearing loss is conductive; ossicular deformities include malformed ankylosed stapes and abnormal incus. The mandible is hypoplastic and the facial bones are small and the skull base is thickened (2,12,27).

Smith-Lemli-Opitz syndrome: It is characterized by growth and mental retardation, microcephaly, cleft palate, facial and genital anomalies associated with syndactyly of the second and third toes with postaxial polydactyly of the hands. Failure to thrive occurs in 90% of patients with poor sucking and gastroesophageal reflux. Hypotonia during the newborn period with resultant bronchopneumonia is a frequent feature. Seventy percent of male patients have abnormal external genitalia including hypospadias, cryptorchidism, and microphallus. Various cardiac defects have been reported such as PDA, Fallot tetralogy, and aberrant subclavian artery. Renal defects and incomplete lobation of the lungs have also been described (1,2,12).

Stickler syndrome or hereditary arthroophthalmopathy: Ocular anomalies occur in the majority of patients and include high myopia presenting before age 10, retinal detachment, and cataract. Other eye manifestations include vitreous degeneration, astigmatism, strabismus, and glaucoma. It is important to schedule all patients diagnosed with Robin sequence for ophthalmologic periodic visits since a high percentage of them have Stickler syndrome and may have eye complications. Midfacial hypoplasia with short maxilla and depressed nasal bridge and elongated philtrum are characteristics. Hearing loss (progressive sensorineural or conductive) has been reported in 10% to 80% of patients (2,12).

Sturge-Weber syndrome: The syndrome is characterized by port-wine facial angiomas taking the course of the trigeminal nerve. This is accompanied by intracranial calcifications and seizures in over 90% of cases. Mental deficiency occurs in 30% of patients. Venous angiomas of the leptomeninges are quite characteristic and occur in the temporal, occipital, or parietal regions. With age, the intracranial calcifications mature and detection of vascular angiomas becomes difficult radiologically. Ocular findings include angiomas of the choroid, congenital glaucoma, and hemianopsia. Capillary angiomas of a pink to purplish-red color are seen in almost all the patients. Angiomatosis occurs also on the buccal mucosa or lips and hypertrophy of the tongue may develop. The gingiva may show enlargement and the teeth may display irregular positioning, premature eruptions, and malocclusion. Blue nevus around the trigeminal territory (Ota's nevus) and blue nevus around the shoulder girdle (Ito's nevus) may also be observed (1,12).

Turner syndrome: In this syndrome, growth is stunted and the birth weight is lower than normal. Patients tend to be obese. Cubitus valgus occurs in 70% of patients. Medial exostosis of the knees, short metatarsals, and metacarpals occur (50%). A coarse trabecular pattern is observed on x-ray of the long bones and osteoporosis is observed in older patients. The chest is usually broad with widely spaced nipples. Coarctation of the aorta, hypertension, VSD, and other CVT anomalies occur in 25% of cases. Cochlear anomalies include epicanthal folds, ptosis, and myopia. Ovarian dysgenesis with absent germinal elements is the characteristic of the syndrome. Renal anomalies such as horse-shoe kidney, duplicated renal pelvis, duplicated ureter or unilateral renal aplasia may exist. Anomalies of the ear are common in 80% of patients. They include prominent auricles, abnormal EAC, underdeveloped mastoids, and abnormal stapes. Otitis media is frequent (80%) and conductive or SNHL is documented. The neck is short and webbed with excessive skin in 80% of cases; cystic hygroma has also been reported. Micrognathia with high-arched palate, abnormal dentition, and premature eruptions are frequent occurrences (2,12,27).

van der Woude syndrome: Congenital lip pits are described in this syndrome. They are usually paramedian and bilateral. Occasionally they are asymmetric. They vary in depth from a few millimeters to a few centimeters. They usually occur on the vermillion border of the lower lip.

Hypodontia and missing second premolars and/or bicuspids may occur. The association of cleft lip/palate with lip pits is estimated to be 65%. Submucous cleft is not rare. Adhesions between the maxilla and mandible have been described (2,12).

Whistling face syndrome: Also known as Freeman-Sheldon syndrome. The facies are immobile with microstomia and hypertelorism. An H- or V-shaped crease is usually seen extending from the lower lip to the chin in 30% of cases. The eyes are sunken and strabismus or epicanthus may be seen. The palate is high-arched. The tongue and mandible are hypoplastic. The nose and nostrils are small. Speech is usually nasal. The philtrum is elongated and the cheeks are bulging. Radiologically, the anterior cranial fossa is steep. Conductive and SNHL have been described (1,12).

Williams syndrome: Williams syndrome is a neurodevelopmental disorder of genetic origin, characterized by relative proficiency in language in the face of serious impairment in several other domains. Individuals with this syndrome display an unusual sensitivity to noise, known as hyperacusis. Alterations in sensitivity to input mediate atypical pathways for language development, where hyperacusis exerts an important influence together with other nonauditory factors. Other manifestations include mental retardation (IQ 40–80), reduced motor and perceptual functions, moderate growth deficiency and during childhood, most patients are described as friendly. The nasal bridge is depressed with periorbital fullness, prominent lips and anteverted nares are characteristic. The voice is often brassy and hoarse. Abnormal teeth (microdontia, hypoplastic deciduous second molars, and permanent first molars), delayed dental mineralization, and accessory labial frenula were reported. CVT anomalies include supravalvular stenosis as well as hypoplasia of the aorta, coronary artery stenosis, bicuspid aortic valve, and coarctation. Hypercalcemia, nephrocalcinosis, and renal failure are not uncommon. Blue eyes with stellate pattern of the iris, strabismus, fifth finger clinodactyly, and small penis are other anomalies (12,32).

HIGHLIGHTS

- The presence of three unrelated minor anomalies is associated with 20% risk of major structural defects, and most of these infants will, in fact, have a dysmorphic syndrome.
- The spectrum of dysmorphic phenotypes is broad and includes malformations, deformations, disruptions, sequences, associations, and syndromes.
- The major diagnostic criteria of Apert syndrome are craniosynostosis and syndactyly of the hands and feet.
- The components of CHARGE association are as follows: C (*c*oloboma of the eye), H (*h*eart disease), A (*a*tresia of the choanae), R (*r*etarded development and growth), G (*g*enital anomalies), and E (*e*ar anomalies and/or deafness).
- Down syndrome is the most common of the chromosomal abnormality syndromes. The diagnosis of the syndrome can be made in the early newborn period. Four out of ten signs are needed to make a clinical diagnosis. However, a final diagnosis may be made only after having the results of the chromosomal pattern.
- In Goldenhar syndrome or HMS, the mandibular deformity is graded according to the size of the mandible. "Mandibular distraction" is a new method for ramus elongation for type I, type IIA, and some Type IIB mandibles.
- Most patients with Treacher Collins syndrome have normal intelligence. The manifestations of the syndrome include malformed ears, hypoplastic midface, downslanting of the palpebral fissures, coloboma of the eye lids, and micrognathia.
- The incidence of Usher syndrome is estimated to be 3 to 5 per 100,000 in the general population and up to 10% among the profoundly deaf children. Clinical manifestations are deafness and retinitis pigmentosa.
- Of all congenitally deaf children, 3% have Waardenburg syndrome. Its incidence is estimated to be 1 in 20,000 to 1 in 40,000 of the population. Four clinical types of the syndrome are recognized; type I is the most common.

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